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A redefinition of global conceptual density functional theory reactivity indexes by means of the cubic expansions of the energy†

Luis Rincón,*[a] Wendy M. Rodríguez,[a] Jose R. Mora,[a] Cesar Zambrano,[a] Luis E. Seijas,[b] Andres Reyes[c] and F. Javier Torres*[a]

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In the present work, a new definition of the conceptual density functional theory reactivity indexes is proposed, based on a cubic interpolation of the energy as function of number of electrons as well as a generalization of the net electrophilicity index. This new proposal takes into account both the influence of hyperhardness on the reactivity and a weighted average of the electrodonating and electroacepting powers. Thus, the presented redefinition incorporates corrections and additional degrees of freedom to the prior CDFT indexes. Numerical support for global descriptors is presented for 30 benzhydrylium ions (*i.e.*, charged electrophiles) and 15 alkyl and aryl nucleophiles taken as reference cases from the Mayr Database of Reactivity Parameters. In the best-case scenario, the descriptors correlated better with the electrophilicity parameter (r^2 = 0.981) than with the nucleophilicity parameter (r^2 = 0.827).

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1 Introduction

The classical principles of modern organic chemistry are built around the concepts of electrophilicity and nucleophilicity.[1,2] Since their introduction, it was clear that electrophilicity and nucleophilicity are closely related to Lewis acidity and Lewis basicity, respectively. However, it is interesting to note that, while Lewis acidity and basicity are thermodynamic properties typically measured by means of equilibrium constants, electrophilicity and nucleophilicity are instead kinetic properties commonly quantified through rate constants determined for reactions between given electrophiles and nucleophiles. By employing the aforementioned, chemists can: (i) predict the outcome of organic reactions, and (ii) design new synthetic routes, both of which are critical for the advancement of chemical science.

In view of the previous, extensive research has been devoted to establish appropriate electrophilicity and nucleophilicity scales. Among the most notable cases, the early proposals of Swain and Scott,[3] Edwards,[4–6] and Ritchie[7] are to be mentioned. These pioneering works ultimately led to the Mayr–Patz equation,[8] which is recognized as the workhorse of reactivity scales in organic chemistry and is defined as follows:

$$\log_{10}(k) = s_N(E + N). \quad (1)$$

In eqn (1), k is the second-order rate constant for a combination of an electrophile with a nucleophile at 20 °C, s_N is a nucleophile-specific sensitivity factor, and E and N are the electrophilicity and nucleophilicity scales, respectively. Concerning the parameter s_N, it is equal to 1 when 2-methyl-1-pentene acts as the nucleophile. Although the Mayr–Patz equation was created considering a set of specific experimental data obtained for π-nucleophiles (*i.e.*, alkenes, arenes and allylsilanes) reacting with benzhydrylium ions as electrophiles,[9–12] the applicability of eqn (1) has been confirmed for a wide diversity of nucleophiles, including amines, enamines, alcohols, ethers, ylides, phosphines, hydride donors and even organometallic compounds, as well as for many types of electrophiles such as carbocations and Michael acceptors (*i.e.*, compounds with α, β unsaturated carbonyl groups).[9–12] Noteworthy, Mayr's scale has also been used to critically examine the HSAB principle.[13] Moreover, a particularity of Mayr's scale is that electrophilicity is exclusively related to electronic effects, whereas nucleophilicity can bear, in some cases, contributions of solvent[14] and steric effects.[15] In spite of its success, a complete theoretical

[a] *Grupo de Química Computacional y Teórica, Departamento de Ingeniería Química, Colegio Politecnico de Ciencias e Ingeniería, Diego de Robles y Vía Interoceanica, Universidad San Francisco de Quito, Quito 17-1200-841, Ecuador. E-mail: lrincon@usfq.edu.ec, jtorres@usfq.edu.ec*
[b] *Escuela de Ingeniería Ciencia y Tecnología, Universidad del Rosario, Bogota 111711, Colombia*
[c] *Departamento de Química, Universidad Nacional de Colombia, Bogota 111321, Colombia*

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understanding of the applicability of eqn (1) is still lacking, and the existence of a unique and universal nucleophilicity scale is still doubtful.[16] Nonetheless, the Mayr's Database of Reactivity Parameters[17] is considered the main source of numerical information on the reactivity of organic species. In July 2024, this data bank held numerous entries: 355 for electrophiles (E) and 1300 for nucleophiles (N, s_N). In Mayr's database, a star rating system qualitatively accounts for the experimental uncertainty in the correlations used for the determination of each reactivity scale. In this vein, each compound, belonging to the database, is rated from one to five stars, depending on the experimental conditions used to determine the molecule's parameters and the reliability of the results. Consequently, the larger the number of stars, the greater the confidence in the correlation-related reactivity parameter. In this way, for reactions of reference electrophiles with reference nucleophiles, the most accurate predictions of the rate constants resulting from eqn (1) can be expected. Finally, although rate constants for reactions involving reference electrophiles are commonly reproduced with variances of less than a factor of two, errors of 10 to 100 must be expected when both reactants are not from the reference set.[15,18] For this reason, in this work, only reference species from the Mayr's Database of Reactivity Parameters[17] are considered.

Beyond reactivity scales, such as Mayr's one, theoretical and computational methodologies have been developed with the purpose of quantifying nucleophilicities and electrophilicities by employing electron-based descriptors. In fact, one of the main objectives in computational organic chemistry is to reach accurate predictions of the Mayr's reactivity scale,[18] and at the same time, use these theoretical descriptors to gain a deeper knowledge of the factors that control the reactivity of organic compounds in general. As chemical reactivity is not an observable in a strict sense (something that happens with many basic chemical concepts[19]), global indexes intend to capture in a single number the 'propensity' of a molecule to donate an electron (nucleophile) to an electron-deficient molecule (electrophile). In this context, we cannot expect experimental scales and theoretical indexes to be identical because, in most cases, these two approaches consider different effects (or the same effect in a different way). Experimental scales are clearly based on rate constants; however, theoretical indexes depend on the energy change as a result of electron transfer in a molecule. Although in the latter case, we believe that a solid theoretical index should reflect, at least, the main trends observed in eqn (1). At the end of the day, the reactivity scales and reactivity indexes must be complementary rather than similar.

In the framework of the conceptual density functional theory, (CDFT)[20–26] attempts have been made towards the definition of global and local electrophilic indexes.[27–35] In the next section, we critically review some classical global CDFT electrophilicity indexes as they provide an appropriate framework for the present work, which focuses on defining global quantities designed to characterize reactivity by assigning a unique value to each molecule in a similar way to the E and N of eqn (1) originate electrophilicity and nucleophilicity scales. It is important to underline that, classical CDFT indexes are based on the quadratic expansion of the energy, and, although such approximation results are adequate for the context, an important flaw emerges from it as the leading term results to be directly proportional to the ionization potential rather than the electron affinity, as expected for an electrophilicity index. A solution to this problem is proposed at the end of the next section as part of the present contribution. In contrast to the proliferation of electrophilic indices for CDFT, the definition of a nucleophilicity index is undoubtedly a more difficult task. One reason is the withdrawal of electrons from a molecule always increases its energy. In these regards, many authors have conducted research on nucleophilicity models in the CDFT framework, but a definitive recipe that accounts for all important phenomena remains elusive.[36–38] To take one step further, we define the electrophilicity index through a cubic expansion of the energy (Section 3). Through our approach, we consider the effect of incorporating the hyperhardness in the expansion (the third derivative of the energy with respect to the number of electrons).[39–46] This idea has been recently explored by Hoffmann, Chermette and Morell,[47] and also by Figueredo and Quintero.[48] In this work, we complement previous studies by demostrating that the cubic expansion introduces some corrections to the classical CDFT electrophilicity indexes. In addition to these corrections, these cubic indexes can incorporate new degrees of freedom that are simple to interpret. This approach provides further insight into the factors that determine electrophilicity and nucleophilicity. To test the performance of cubic reactivity indices, in Section 4, we correlated the CDFT indexes with the experimental Mayr reactivity parameters for two reference cases: benzhydrylium ions (charge electrophiles) and alkyl nucleophiles. We note, that quantitative correlations of classical electrophilicity measurements with Mayr's reactivity parameters have previously been reported.[49] Since the cubic indices introduce additional degrees of freedom, compared with the classical ones, a better numerical correlation is obtained, in particular when nucleophiles are employed. The concluding remarks and future directions are presented in the final section.

2 CDFT reactivity indexes

One of the most important objectives of CDFT is to capture information on the reactivity of molecular systems through the partial derivatives of the electronic energy with respect to the number of electrons N_e and the external potential. From the latter, two global reactivity descriptors can be defined as the first and second derivatives of the energy with respect to N_e, at constant external potential.[20,21,25,50] Parr defined the first derivative of the energy with respect to the number of electrons as the electronic chemical potential (μ),[51] which in turn is the negative of the electronegativity (χ),

$$\mu = -\chi = \left(\frac{\partial E}{\partial N_e}\right)_v, \tag{2}$$

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while the second derivative correspond to the chemical hardness (η),[52] with its reciprocal being the softness (S),

$$\eta = \frac{1}{S} = \left(\frac{\partial^2 E}{\partial N_e^2}\right)_v = \left(\frac{\partial \mu}{\partial N_e}\right)_v. \quad (3)$$

These derivatives are commonly interpreted as the molecule's sensitivity to electron transfer processes (expressed as a change in the number of electrons) and thus indicate the molecule's susceptibility to chemical processes that involve electron transfer. The evaluation of eqn (2) and (3) require an expression of the energy as a function of N_e at a constant external potential (*e.g.*, molecular geometry). At this point, it is worth noting that (at zero-temperature) the energy as a function of the number of electrons consists of a series of straight lines connecting the ground state energies of integer numbers of particles.[53,54] Despite the challenges associated with energy discontinuities of the exact interpolation, from a chemical standpoint, it makes sense to assume a smooth expansion energy with a change in the number of electrons; in fact, various flavors of these expansions are described in the literature.[55] The simplest and most common approach to define the energy as a function of the number of electrons is the use of a quadratic expansion around a reference number of electrons (N_0),[50,52,55,56]

$$\Delta E_{\text{quadratic}} = E[N_0 + \Delta N_e] - E[N_0] = \mu \Delta N_e + \frac{1}{2}\eta \Delta N_e^2. \quad (4)$$

This expansion is reasonable because a fragment of a reacting system can have fractional charge, and the dependence of the energy on the amount of fractional charge is, based on both computational evidence and theoretical arguments,[34,57,58] expected to be smooth. It is also common to consider the interpolation of eqn (4) between integer values around N_0 using the ionization potential ($I = E[N_0 - 1] - E[N_0]$) and the electron affinity ($A = E[N_0] - E[N_0 + 1]$). Assuming that the quadratic expansion is valid, it is possible to obtain both μ and η from I and A as

$$\mu = -\frac{I + A}{2}, \quad (5)$$

$$\eta = I - A. \quad (6)$$

eqn (5) and (6) are finite-difference approximations to the first and second derivatives of eqn (2) and (3), respectively. Further, approximations to eqn (5) and (6) can be obtained based on Koopmans' theorem in terms of the highest occupied ($\varepsilon_{\text{HOMO}}$) and lowest unoccupied ($\varepsilon_{\text{LUMO}}$) molecular orbital energies assuming that $I = -\varepsilon_{\text{HOMO}}$ and $A = -\varepsilon_{\text{LUMO}}$. This approach is justified within the framework of the Hatree–Fock approximation; however, DFT is a theory of the total energy, and while the Kohn–Sham auxiliary system is a powerful construct, the energies of the Kohn–Sham orbitals are not necessarily related to the energy of the charge excitations. The Janak theorem established the equality of orbital energies with the derivatives of total energy with respect to the orbital occupation numbers.[59] For the exact Kohn–Sham potential, it has been proven that the highest occupied Kohn–Sham orbital energy (HOMO) is negative of the first ionization energy.[60] Additionally, the ground state chemical potential theorem proves that in any ground-state Kohn–Sham calculation with an exchange–correlation functional that is a continuous functional of the density or the Kohn–Sham density matrix, the energy of the HOMO is the chemical potential of the electron removal and the energy of the lowest unoccupied molecular orbital (LUMO) is the chemical potential of electron addition.[61,62] The ground-state chemical potential theorem justifies using the Kohn–Sham orbital energies to approximate experimental I and A. Throughout this study, all ionization potentials and electron affinities refer to vertical rather than adiabatic quantities.

Based on kinetic data, in 1998, Maynard empirically proposed that the ratio between the square of the electronegativity and the hardness measures the electrophilic power of a molecule, that is, its tendency to accept electrons.[63] This work, inspired by Parr, von Szentpaly, and Liu, defined the electrophilicity index as the energy change of an electrophile when it becomes saturated with electrons,[27] considering the case where an electrophilic species is immersed in an idealized zero temperature electron sea with zero chemical potential. In such a situation, the electrophile becomes saturated with electrons when its chemical potential becomes equal to that of the electron sea. Using the quadratic expansion, the system reaches saturation when $\partial \Delta E_{\text{quadratic}}/\partial \Delta N_e = 0$, and this occurs when

$$\Delta N_{\max} = -\frac{\mu}{\eta}. \quad (7)$$

By inserting eqn (7) in the quadratic expansion, we obtain the electrophilicity index of a molecule, just as was suggested by Maynard,[63]

$$\omega_{\text{quadratic}} = \frac{\chi^2}{2\eta} = \frac{\mu^2}{2\eta}. \quad (8)$$

In the previous equation, we explicitly indicate that this expression is based on the quadratic expansion, eqn (4). Eventually, it is possible to generalize this expression for the spin-polarized case.[64–66] Clearly, the electrophilicity index corresponds to the minimum energy in the quadratic interpolation. The electron affinity of a chemical system is assessed by its ability to accept one electron from a donor, but the maximum amount of electron flow is determined by the electrophilicity, which depends on the chemical potential and hardness as described above. From eqn (5) and (6), it is also clear that as long as the quadratic expansion is valid, the electrophilicity depends not only on the electron affinity, A, but also on the ionization potential, I,

$$\omega_{\text{quadratic}} = \frac{(I + A)^2}{8(I - A)}. \quad (9)$$

The electrophilicity index sounds appealing because it is based on the stabilization energy produced by electron transfer. Several comprehensive reviews on the usefulness of the electrophilic index are available in the literature.[67–72] We encourage

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readers to refer to these reviews to assess the significance of the electrophilicity index in many chemical contexts. As shown in these reviews, this index has been quite successful in comparing electrophilicity differences among molecules. The minimum electrophilicity principle and the electrophilicity equalization principle have provided some insights into the possible underlying rules governing this quantity.[73–75] The influence of dynamical effects on the electrophilicity was investigated by Hoffmann, Tognetti and Joubert.[35] The authors discovered substantial differences when compared to static reactivity descriptors. Recently, Miranda-Quintana raised some concerns about the definition of the electrophilicity index,[33] and redefined the electrophilicity index in terms of the electronic Helmholtz free energy, focusing on the zero-temperature limit. This new definition, referred to as thermodynamic electrophilicity, addresses two key issues present in the quadratic electrophilicity index: the use of a truncated second-order Taylor expansion to estimate energy changes and the assumption of a zero-temperature environment. These approaches often lead to inconsistencies, particularly when applied to systems with very low electron affinities or multicharged cations. By focusing on thermodynamic electrophilicity, these challenges are mitigated, offering a more reliable framework for such systems. Furthermore, an electrophilicity index has been defined for the electronic Helmholtz free energy, and it is observed that, for some temperature values, this index corresponds to the electrophilicity index defined within the quadratic interpolation.[34]

One big issue of eqn (9) is related to the fact that $I > A$ (sometimes much larger). Therefore, it is convenient to expand this equation in powers of $x = \frac{A}{I}$. The result is as follows,

$$\omega_{\text{quadratic}} = \frac{I + 2A + Ax}{8(1-x)} \approx \frac{1}{8}(I + 2A) + \frac{1}{8}(I + 3A)x + \cdots. \tag{10}$$

This equation establishes that the leading term of $\omega_{\text{quadratic}}$ goes as $\frac{1}{8}(I + 2A)$, therefore in general, the electrophilic index follows the ionization potential, not the electron affinity as expected.[33] The success of $\omega_{\text{quadratic}}$ comes from the significant correlation between I and A.

In 2007, Gázquez, Cedillo, and Vela distinguished between charge-donating and charge-accepting scenarios by minimizing the change in the grand potential with respect to the amount of transferred charge.[28] In the grand canonical ensemble, chemical reactivity is characterized in terms of derivatives of the grand potential. In this context, changes in the grand potential due to electron transfer between a molecular system and an electron sea, with chemical potential μ^0, are defined as

$$\Delta\Omega = \Delta E - \mu^0 \Delta N. \tag{11}$$

Using the quadratic expansion for ΔE, the number of electrons transferred that minimize the grand potential is

$$\Delta N_{\max} = -\frac{\mu - \mu^0}{\eta} = -\frac{\Delta\mu}{\eta}. \tag{12}$$

In contrast with eqn (7) where $\mu^0 = 0$, this equation states that the number of electrons transferred is determined solely by the difference between the chemical potential of the molecular system and that of the environment. Thus, depending on this difference, the number of electrons in the molecule can be increased or decreased. In principle, this approach may provide a way to define electrophilicity and nucleophilicity at the same time.

Consider, for example, the situations where μ^0 is close to μ, and therefore $\Delta\mu = \mu - \mu^0$ is small. One may assume that $\mu^0 = s\mu$, where if $s > 1$ we obtain that the number of electrons in the molecule decreases, while if $s < 1$ the system increases the number of electrons. Of course, if $s = 1$, electron transfer does not occur. Thus, the energy change in the molecular system is given by,

$$\Delta E = \frac{(s^2 - 1)\mu^2}{\eta}. \tag{13}$$

In addition to including the change in the grand potential, eqn (13), Gázquez, Cedillo and Vela consider that, in contrast to the finite differences approximation to μ, eqn (5), the derivative of the energy evaluated at some integral value of N generally has one result when evaluated from the left and a different result when evaluated from the right.[28] That is, from the left is the negative of the ionization potential,

$$\mu^- = \left(\frac{\partial E}{\partial N_e}\right)_v^- = E[N_0] - E[N_0 - 1] = -I, \tag{14}$$

and from the right, is the negative of the electron affinity,

$$\mu^+ = \left(\frac{\partial E}{\partial N_e}\right)_v^+ = E[N_0 + 1] - E[N_0] = -A. \tag{15}$$

The use of different values of chemical potential for the electron donation and withdrawal cases is equivalent to the use of two quadratic interpolations: one for $\Delta N_e < 0$ and a different one for $\Delta N_e > 0$. Because s in eqn (13) is a constant that characterizes the environment; one can define for the charge donating process the electrodonating power as,

$$\omega_{\text{GCV}}{}^- = \frac{(\mu^-)^2}{2\eta^-} \approx \frac{(3I + A)^2}{16(I - A)}, \tag{16}$$

while for the charge accepting process, the electroaccepting power is defined as,

$$\omega_{\text{GCV}}{}^+ = \frac{(\mu^+)^2}{2\eta^+} \approx \frac{(I + 3A)^2}{16(I - A)}. \tag{17}$$

The right-hand side of eqn (16) and (17) are based on an interpolation in which the chemical hardness for the electron donation and electron accepting process is equal. In contrast to $\omega_{\text{quadratic}}$, ω^-_{GCV} gives more emphasis to the ionization potential than to the electron affinity, while ω^+_{GCV} shows the opposite behavior. Using the reasoning presented in the expansion of eqn (10), we obtain the leading term of eqn (16) and (17), $\omega^-_{\text{GCV}} \approx \frac{3}{16}(3I + 2A)$ and $\omega^+_{\text{GCV}} \approx \frac{1}{16}(I + 6A)$. The electrodonating and electroacepting power is closely related to the nucleofugality and electrofugality that is used to predict the quality of

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leaving groups in organic reactions.[76] Alternatively, Chamorro, Duque-Noreña and Perez approximated the electrodonating and electroaccepting powers using the chemical potentials given by eqn (14) and (15),[29,30] that is,

$$\omega^{-}_{\mathrm{CDP}} \approx \frac{(I)^2}{2(I-A)}, \tag{18}$$

and

$$\omega^{+}_{\mathrm{CDP}} \approx \frac{(A)^2}{2(I-A)}. \tag{19}$$

where the leading term of eqn (19) depend directly on $x = \frac{A}{I}$.

In 2009, Chattaraj, Chakraborty, and Giri introduced the concept of net electrophilicity as the electron accepting ability of a species relative to its electron donating ability,[31] which is defined from the electrodonating and electroaccepting power in the form,

$$\Delta\omega^{\pm} = \omega^{+} + \omega^{-}, \tag{20}$$

an alternative manner of defining this quantity and while maintaining the same idea is as follows,

$$\Delta\omega^{\pm} = \left(\omega^{+} - \frac{1}{\omega^{-}}\right). \tag{21}$$

The idea of combining ω^{+} and ω^{-} appears to be interesting based on the fact that a good electrophile is, in some way, a bad nucleophile, and *vice versa*. However, eqn (21) has the disadvantage of having two quantities with different units. As a result, eqn (20) can be regarded as a more adequate expression for theoretical developments because it presents units consistency. Moreover, eqn (20), divided by 2, can be seen as the arithmetic mean of ω^{-} and ω^{+}. In the following, these descriptors are referred to as $\Delta\omega^{\pm}_{\mathrm{arithmetic}} = 0.5(\omega^{+} + \omega^{-})$. The geometric mean can be used as an alternative to the arithmetic mean of eqn (20),

$$\Delta\omega^{\pm}_{\mathrm{geometric}} = \sqrt{\omega^{+}\omega^{-}}. \tag{22}$$

The last equation contains the same ingredients as eqn (20), but the leading term, in this case, is the electron affinity.

As commented earlier, previous indexes emphasized electrophilicity rather than nucleophilicity. Therefore, the final part of this section is devoted to the less explored nucleophilicity index. Regarding this, Partihar and Roy have proposed, with limited success, the inverse of the electrodonating power as the nucleophilicity index.[37,77] Later, Domingo, Chamorro, and Perez connected nucleophilicity to the highest occupied Kohn–Sham orbital energy, which was a partially successful approach.[37,78] Some additional attempts were made towards the definition of a relative measure of nucleophilicity.[36,38] Finally, Liu and co-workers have proposed a method to simultaneously determine electrophilicity and nucleophilicity values through the use of information-theoretic quantities, resulting in good correlations with experimental scales.[79–82] Notwithstanding, as we mentioned in the introduction, a descriptor that accounts for all major trends in the experimental nucleophilic index is still missing.

3 Beyond the quadratic model: revision of the electrophilicity index

The energy expansion in all the descriptors introduced so far assumes a quadratic form.[50,52] In this work, we instead consider a cubic interpolation as follows (see for intance the work of Hoffmann, Chermette and Morell[47] and also Figueredo and Quintero[48]),

$$\Delta E_{\mathrm{cubic}} = \mu\Delta N_{\mathrm{e}} + \frac{1}{2}\eta\Delta N_{\mathrm{e}}^{2} + \frac{1}{6}\gamma\Delta N_{\mathrm{e}}^{3}. \tag{23}$$

Due to the greater order of the expression, a better description of the chemical reactivity can be expected. Considering eqn (23), the dependence of μ, η and γ on the ionization potential ($I = E[N_0 - 1] - E[N_0]$) and electron affinity ($A = E[N_0] - E[N_0 + 1]$) of an N_0 electron reference system can be defined in the same way as in the case of the quadratic interpolation. In fact, it is straightforward to demonstrate that the hardness formula of the cubic expression coincides with the one obtained from the quadratic model; that is, $\eta = I - A$. On the other hand, it follows that the chemical potential and the hyperhardness (γ) satisfy the relation,

$$-3(I + A) = 6\mu + \gamma \tag{24}$$

Therefore, based on this constrains, γ depends on the chemical potential in the cubic interpolation. At this point, to establish a connection with the previous elaborations of reactivity parameters, we introduce an α-dependent μ in the form,

$$\mu = -(\alpha I + (1 - \alpha)A). \tag{25}$$

Now, eqn (23) results in,

$$\begin{aligned}\Delta E_{\mathrm{cubic}} \;=\; & -(\alpha I + (1-\alpha)A)\Delta N_{\mathrm{e}} + \frac{1}{2}(I - A)\Delta N_{\mathrm{e}}^{2} \\ & + \frac{1}{2}(2\alpha - 1)(I - A)\Delta N_{\mathrm{e}}^{3}.\end{aligned} \tag{26}$$

Clearly, if $\alpha = 1/2$, eqn (26) reduces to the quadratic interpolation. This equation shows that α represents the weighted contribution of both the ionization potential and the electron affinity to the chemical potential. We notice that based on the constrains imposed in the present work, in eqn (26), $\Delta E_{\mathrm{cubic}} = I$ if $\Delta N = -1$ and $\Delta E_{\mathrm{cubic}} = A$ if $\Delta N = +1$, for any value of the parameter α. Recently, Miranda-Quintana interpreted eqn (25) as a perturbed chemical potential that incorporates the effect of the molecular environment.[83–87] Moreover, as shown in the work of Heidar-Zadeh *et al.*,[55] eqn (26) incorporates the correct interpolated electron density and the Fukui function in the hyperhardness. Eventually, the parameter α can be adjusted based on additional constrains, or alternatively, α can be envisaged as the propensity of a given chemical species to donate or accept fractional amounts of charge and can be treated as an adjustable parameter for correlations with experimental data.

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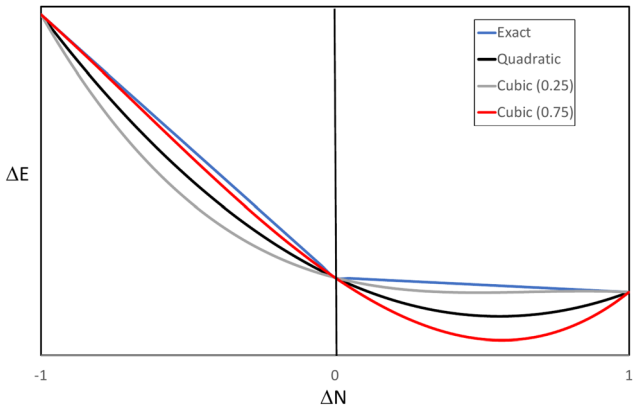

Fig. 1 Plot of the total energy as a function of the number of electrons. Straight lines correspond to the exact behaviour (blue line), black line correspond to the quadratic model (eqn (4)), gray line correspond to the cubic interpolation (eqn (26)) for α = 0.25 and red line for α = 0.75.

In Fig. 1 we compare the exact behaviour (blue line), the quadratic interpolation (black line) and the cubic interpolation with $\alpha = 0.25$ (grey line) and $\alpha = 0.75$ (red line). Compared to the quadratic interpolation, the cubic interpolation with $\alpha = 0.25$ is closer to the straight lines connecting the integer ΔN values for electron gain, that is when $\Delta N > 0$; in contrast, the cubic interpolation with $\alpha = 0.75$ resembles the blue line for electron loss.

The global electrophilicity is defined as the stabilization energy when the system is saturated with the maximum allowed number of electrons.[27] Using this definition, the maximum number of electrons transferred is obtained by minimizing the eqn (23). Since the global minimum of eqn (23) is at $\Delta N = -\infty$, the number of electrons transferred in the local minima is,

$$\Delta N_{\max} = -\frac{\eta}{\gamma}\phi, \tag{27}$$

where,

$$\phi = 1 - \sqrt{1 - \frac{2\mu\gamma}{\eta^2}}. \tag{28}$$

Since $\eta > 0$, $\Delta N_{\max}$ is negative when γ is positive, that is for $\alpha > 0.5$; whereas $\Delta N_{\max}$ is positive for γ negative ($\alpha < 0.5$). Thus by changing the value of α we can describe both electron accepting and electron donation process. This number of electrons results in the following stabilization energy when inserting in eqn (23),

$$\omega_{\text{cubic}} = \frac{\eta\mu}{\gamma}\phi - \frac{\eta^3}{2\gamma^2}\phi^2\left(1 - \frac{\phi}{3}\right). \tag{29}$$

At first glance, eqn (29) seems different from the previous expressions of the electrophilic index. To connect ω_{cubic} to its quadratic model counterpart, we use the power expansion of the square root in eqn (28), that is $\sqrt{1 - \frac{2\mu\gamma}{\eta^2}} \approx 1 - \frac{\mu\gamma}{\eta^2}$. The number of electrons transferred is then approximately given by

$$\Delta N_{\max} \approx -\frac{\mu}{\eta}, \tag{30}$$

which is the same as eqn (7). Eqn (29) can be approximated as

$$\begin{aligned}\bar{\omega}_{\text{cubic}} &= \frac{\mu^2}{2\eta}\left[1 + \frac{\mu\gamma}{3\eta^2}\right] \\ &= \frac{(\alpha I + (1-\alpha)A)^2}{2(I-A)}\left[1 - (2\alpha - 1)\frac{(\alpha I + (1-\alpha)A)}{(I-A)}\right].\end{aligned} \tag{31}$$

The first term in this equation resembles the previous elaborations of the electrophilicity index (the electrophilicity index and the electrodonating power). This equation is similar to that found by Hoffmann, Chermette, and Morell[47] by taking the local maxima rather than the local minima of the cubic energy expansion. Since, eqn (31) is an approximation of eqn (29), it is instructive to determine the conditions under which this approximation holds. In Fig. 2, we plot ω_{cubic} *versus* $\bar{\omega}_{\text{cubic}}$ using the values of I and A for the 61 atoms and 55 molecules reported in the work of Parr, von Szentpaly, and Liu.[27] In both indexes we assume that $\mu = -(\alpha I + (1-\alpha)A)$, $\eta = I - A$ and $\gamma = 3(2\alpha - 1)(I - A)$. We include different values of α in the range between {0.0, 1.0}. The straight blue line corresponds to the value of $\alpha = 0.5$ for which both equations are identical, and corresponds to the case of $\omega_{\text{quadratic}}$. An important observation in this figure is that for $\alpha \neq 0.5$ the values of eqn (29) always tend to be larger than eqn (31), for this reason, the points are in the inferior quadrant of the figure. In the range, {0.40, 0.60} a good correlation is observed, and the approximation is safe. For $\alpha < 0.5$ the values of $\omega_{\text{quadratic}}$ are lower than for $\alpha > 0.5$, indicating that the range of values of ω tends to increase with α. For $\alpha = 0.0$ the ω is in the range [0.05, 0.60], but for $\alpha = 1.0$ in [3.9, 1.1], and this is observed for eqn (29) and (31). Therefore, as α increases, the electrophilicity also grows. The difference between the two equations is greater for

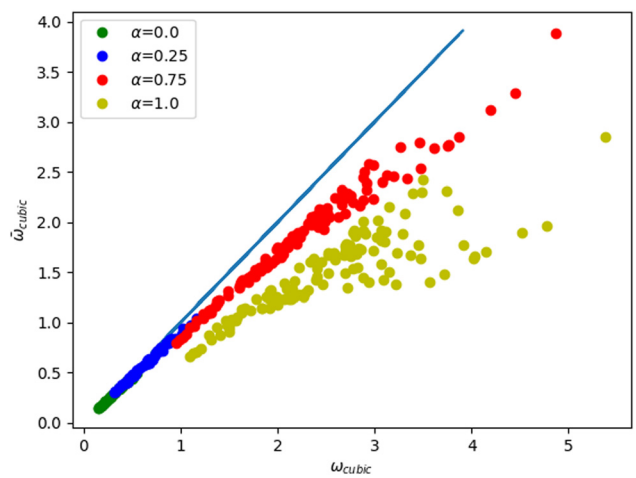

Fig. 2 Correlation between ω_{cubic} eqn (31) and $\bar{\omega}_{\text{cubic}}$ eqn (33) for 61 neutral atoms and 55 molecules taken from ref. 27. The blue straight line corresponds to $\alpha = 0.5$.

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$\alpha > 0.5$ than for $\alpha < 0.5$. For $\alpha = 0.0$ the mean deviation is 2.2%, but for $\alpha = 1.0$ is 37.4%. For $\alpha < 0.5$ the term $\frac{2\mu\gamma}{\eta^2}$ is positive, since $\mu < 0$ and $\gamma < 0$. It is important to notice that for small values of α, the term $\frac{2\mu\gamma}{\eta^2}$ is often larger than 1, and the square root of eqn (28) is undetermined. This implies that for low values of α, the cubic interpolation do not present a local minimum for certain combinations of I and A.

Since the differentiation of a molecule's response to donation and acceptance of charge is important from a chemical perspective, it is plausible to use different values of α depending on the sign of ΔN. For instance, we assume that for the charge donation process ($\Delta N < 0$) $\alpha > 0.5$, while for $\Delta N > 0$ we employ an $\alpha < 0.5$. Using two α values not only distinguishes between charge receiving and donating processes, as also observed in Fig. 1, it also provides a better approximation of energy. Using the previous approximations, one can define for the charge donating process the electrodonating power as

$$\bar{\omega}_{\alpha^-}^{-} = \frac{(\alpha^- I + (1-\alpha^-)A)^2}{2(I-A)}\left[1 - (2\alpha^- - 1)\frac{(\alpha^- I + (1-\alpha^-)A)}{(I-A)}\right], \tag{32}$$

while for the charge accepting process, the electroaccepting power is defined as,

$$\bar{\omega}_{\alpha^+}^{+} = \frac{(\alpha^+ I + (1-\alpha^+)A)^2}{2(I-A)}\left[1 - (2\alpha^+ - 1)\frac{(\alpha^+ I + (1-\alpha^+)A)}{(I-A)}\right]. \tag{33}$$

Finally, in the same spirit of the net electrophilicity index, a general net nucleophilicity and electrophilicity index can be defined as a weighted average between $\bar{\omega}_{\alpha^-}^{-}$ and $\bar{\omega}_{\alpha^+}^{+}$. Thus, we define the net nucleophilicity as a weighted arithmetic mean,

$$\Delta\bar{\omega}_{\beta^-,\,\text{arithmetic}}^{\pm} = (1-\beta^-)\bar{\omega}_{\alpha^+}^{+} + \beta^-\bar{\omega}_{\alpha^-}^{-}. \tag{34}$$

and the general net electrophilicity index,

$$\Delta\bar{\omega}_{\beta^+,\,\text{arithmetic}}^{\pm} = (1-\beta^+)\bar{\omega}_{\alpha^-}^{-} + \beta^+\bar{\omega}_{\alpha^+}^{+}. \tag{35}$$

Alternatively, a geometrical index can be defined as

$$\Delta\bar{\omega}_{\beta^-,\text{geometric}}^{\pm} = \left(\bar{\omega}_{\alpha^+}^{+}\right)^{1-\beta^-}\left(\bar{\omega}_{\alpha^-}^{-}\right)^{\beta^-}, \tag{36}$$

$$\Delta\bar{\omega}_{\beta^+,\text{geometric}}^{\pm} = \left(\bar{\omega}_{\alpha^-}^{-}\right)^{1-\beta^+}\left(\bar{\omega}_{\alpha^+}^{+}\right)^{\beta^+}. \tag{37}$$

These formulations incorporate a correction to the classical index as well as new degrees of freedom in the parameters α^-, α^+, and β. As commented before, the α parameters can be interpreted as the weighted contribution of the ionization potential and electron affinity to the chemical potential. Likewise, β can be envisaged as the weighted contribution of $\bar{\omega}^-$ and $\bar{\omega}^+$ to the net nucleophilicity or electrophilicity. In the following, we will analyze how the previously discussed electrophilicity and nucleophilicity correlate with the Mayr's scale.

4 Correlations between reactivity scales and global CDFT reactivity index

To compare the reactivity indices, we correlated the CDFT index presented in Sections 2 and 3, with the Mayr's reactivity parameters for a set of reference systems. It is important to mention that, the goal of this section is not to propose a novel way for estimating the experimental parameters using the theoretical ones; for this, machine learning approaches that use additional descriptors, in addition to CDFT ones, are a far superior option.[88–90] Here, the question is whether these descriptors follow the same general patterns or are they distinct, and if so, why? In addition, correlations provide a way to estimate the values of the parameters α^+, α^- and β introduced in the cubic expansion. In the case of electrophiles, we employ 30 benzhydrylium ions (charge electrophiles) and for nucleophiles, we employ 15 neutral compounds that include alkenes and arenes. Since these two sets of compounds contain similar electrophiles and nucleophiles, it is logical to conclude that the cubic expansion parameters are likewise similar. The most important aspect of this comparison is the determination of the vertical ionization potential and the electron affinity to evaluate the various CDFT indexes. For the determination of the values of I and A, we have performed DFT-ωB97XD/6-311++G(2df,2pd) calculations. The geometries of the compounds were fully optimized, and the coordinates are presented as ESI.† All calculations were performed using the Gaussian 16 suite of programs.[91] The vertical ionization potential (I) and the vertical electron affinities (A) are calculated in two forms: from the highest occupied (HO) and lowest unoccupied (LU) molecular orbital (MO) energies, $I \approx -\varepsilon_{\text{HOMO}}$ and $A \approx -\varepsilon_{\text{LUMO}}$, and upon the addition or removal of one electron while keeping the geometry frozen. It is important to notice that in the absence of a derivative discontinuity, $\varepsilon_{\text{LUMO}}$ is a better approximation for the excitation energy.[92,93] However, it is important to point out that other methodologies have also been proposed to compute the chemical hardness.[94,95] The experimental vertical ionization potential is positive for electrophiles and nucleophiles, and it can be reproduced to within a few tenths of an electron volt using standard DFT calculations with the removal of electrons. For nucleophiles, the electron affinity is negative rather than positive, even as measured by electron transmission spectroscopy methods.[96–98] Thus, such systems pose a fundamental problem because the anion is unstable with respect to electron loss and is difficult to describe by a standard DFT ground-state total energy calculation. In practice, medium-sized basis-set DFT calculations with diffuse orbitals on the anion do give energies above that of the neutral species, so reasonable estimates for the negative affinity can be obtained. Say that, it is an open issue as to whether it is appropriate to use negative electron affinities, instead of zero electron affinity, to compute the chemical hardness.[99] For this problem, Vibert and Tozer propose a simple DFT scheme based on a consideration of the integer discontinuity and density scaling.[100] Because nucleophiles electron affinity levels are very small (but negative), their inclusion or exclusion has no significant effect on the final

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nucleophilicity parameter that depend heavily on the ionization potential.

Linear regression models were used to test the correlation between the experimental reactivity scale and the CDFT reactivity indexes. The following metrics were used to assess the model performance: root mean square error (RMSE), mean absolute error (MAE), maximum error, the coefficient of determination (r^2) and Kendall rank correlation coefficient (τ_{Kendall}). In contrast to the coefficient of determination, τ_{Kendall} is used to measure the strength and direction of the association between two variables, even if the correlation is not linear. If $\tau_{\text{Kendall}} \sim r^2$, the linear correlation is reliable. Statistical analysis was performed using Scikit-learn (version 1.6.1) and τ_{Kendall} is obtained from the *stats* library of Scipy (version 1.11.4). The parameters α and β of eqn (34)–(37) are optimized using the Levenberg–Marquardt algorithm as implemented in the least-square library of Scikit. The parameters α and β are limited to being between 0 and 1, and the computed indexes of eqn (34)–(37) must be positives. A total of 12 CDFT indexes are used in the correlations:

• The ionization potential (1) and the electron affinity (2). As previously described, these descriptors are calculated in two forms.

• The electrophilicity index obtained from the quadratic expansion (3), $\omega_{\text{quadratic}}$ (eqn (8)). Even though this descriptor was originally proposed as an electrophilic measure, we tested it also in the case of nucleophilic compounds based on the (not necessarily erroneous) premise that a good electrophile is a bad nucleophile. Furthermore, as shown in eqn (9), the leading term of this descriptor is dependent on the ionization potential and may describe electron loss.

• The electrodonating and electroaccepting power. We used the electrodonating power to correlate nucleophilicity and the electroacepting power to correlate electrophilicity. Two definitions are used, depending on the form of μ^+ and μ^-: ω^+_{GCV} and ω^-_{GCV} correspond to descriptor (4) and ω^+_{CDP} and ω^-_{CDP} to descriptor (5).

• The net electrophilicity. We employ the value taken from the arithmetic mean, eqn (20), and the geometric mean introduced in this work, eqn (22). For each of these two net electrophilicity definitions, the electrodonating and electroacepting power can be calculated using the two definitions previously mentioned. Thus, for the arithmetic mean, when using ω^+_{GCV} and ω^-_{GCV}, the descriptor is denoted as $\Delta\omega^{\pm}_{\text{arithmetic,GCV}}$ (6), and for ω^+_{CDP} and ω^-_{CDP} the descriptor is denoted as $\Delta\omega^{\pm}_{\text{arithmetic,CDP}}$ (7). For the geometric mean, when using ω^+_{GCV} and ω^-_{GCV}, the descriptor is $\Delta\omega^{\pm}_{\text{geometric,GCV}}$ (8), and for ω^+_{CDP} and ω^-_{CDP} the descriptor is $\Delta\omega^{\pm}_{\text{geometric,CDP}}$ (9).

• The approximated electrophilic index obtained from the cubic expansion, eqn (31), by considering α as an optimized parameter. This descriptor is (10).

• The generalized net arithmetic nucleophilicity of eqn (34) or electrophilicity of eqn (35), (11), and the generalized net geometric nucleophilicity eqn (36) or electrophilicity of eqn (37), (12).

Table 1 presents the data obtained for the reference benzhydrylium ions, where the names of the compounds are taken from Mayr's database.[17] This set of carbocations represents the most precise estimate of the electrophilicity parameter, E, which covers almost 18 orders of magnitude on the rate constant; that is: from −10.04 to 7.52 (in log scale). Using the data in Table 1, we perform linear correlations of E with each one of the 12 descriptors mentioned previously. The ESI,† provides the value of each descriptor for the entire collection of electrophiles. The statistics of the correlations are presented in Table 2, where some relevant aspects can be highlighted: the first point is that the correlation is very similar for the two definitions used of I and A. Removing or adding an electron does not significantly alter the numbers obtained from the HOMO and LUMO energies. This is because even if $I_{\text{HOMO}} > I^+$ and $A_{\text{LUMO}} < A^-$, both descriptors are strongly correlated. The second point to mention is the fact that both I and A strongly correlate with E, in fact, their correlation is better than most of the classical descriptors. We anticipate the correlation of A, but not of I. This is a consequence of the high correlation between I and A for this set. For the classical descriptors (3–9) the RMSE are around 1.2 and the MAE is close to 1, this mean that an error in an order of magnitude is expected for rate constant. We can improve the correlation in the case of cubic descriptors introduced in this work (10–12) by including additional degrees of freedom. By using an optimized value of $\alpha^+ = 0.65(0.62)$ in 10 the correlation improves to $r^2 = 0.973(0.976)$ and the MAE decrease to 0.735(0.728). This is a 25% reduction in MAE

Table 1 Data of electrophiles molecules. Name of the benzhydrylium ions, electrophilicity parameter (E), I and A from HOMO and LUMO energies (I_{HOMO} and A_{LUMO}), I and A by removing and adding one electron (I^+ and A^-). All energies are in eV

Molecule	E	I_{HOMO}	A_{LUMO}	I^+	A^-
(ani)2CH+	0.00	11.52	5.36	11.34	5.60
(dfp)(mfp)CH+	7.52	13.42	6.88	13.29	7.05
(dfp)PhCH+	6.74	13.30	6.67	13.15	6.84
(dma)2CH+	−7.02	10.20	4.55	9.89	4.84
(dpa)2CH+	−4.72	9.75	4.42	9.27	4.87
(ftol)2CH+	5.24	12.56	6.23	12.39	6.46
(fur)(ani)CH+	−0.81	11.35	5.27	11.15	5.52
(fur)2CH+	−1.36	11.22	5.21	11.01	5.47
(ind)2CH+	−8.76	9.88	4.36	9.54	4.67
(jul)2CH+	−9.45	9.62	4.17	9.20	4.54
(lil)2CH+	−10.04	9.71	4.19	9.36	4.52
(mfa)2CH+	−3.85	10.64	4.92	10.31	5.23
(mfp)2CH+	6.87	13.21	6.69	13.13	6.86
(mfp)PhCH+	6.23	13.10	6.47	13.01	6.64
(mor)2CH+	−5.53	10.21	4.63	9.83	4.97
(mpa)2CH+	−5.89	10.08	4.40	9.66	4.77
(pcp)2CH+	5.48	12.55	6.36	12.44	6.60
(pfa)2CH+	−3.14	10.48	4.77	10.07	5.16
(pfp)2CH+	5.01	12.92	6.32	12.85	6.48
(pyr)2CH+	−7.69	9.98	4.36	9.60	4.69
(tfm)PhCH+	6.70	13.36	6.59	13.53	6.78
(thq)2CH+	−8.22	9.87	4.32	9.50	4.65
(tol)2CH+	3.63	12.36	5.86	12.19	6.09
(ani)(Ph)CH+	2.11	12.24	5.74	12.10	5.94
(ani)(pop)CH+	0.61	11.48	5.33	11.25	5.61
(ani)(tol)CH+	1.48	11.94	5.59	11.77	5.82
Benzhydrilium ion	5.47	13.05	6.27	12.95	6.44
(pfp)(Ph)CH+	5.20	12.98	6.29	12.89	6.46
(pop)(Ph)CH+	2.90	11.96	5.66	11.93	5.91
(tol)(Ph)CH+	4.43	12.69	6.05	12.56	6.25

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Table 2 Root mean square error (RMSE), mean absolute error (MEA), maximum error, coefficient of determination (r^2) and Kendall rank correlation coefficient (τ_{Kendall}) for electrophilicity descriptors. The values in parenthesis are obtained using I^+ and A^-, the others correspond to I_{HOMO} and A_{LUMO}

Descriptors	RMSE	MAE	Max error	r^2	τ_{Kendall}
1 I	1.041 (1.133)	0.803 (0.830)	3.137 (3.412)	0.967 (0.961)	0.894 (0.885)
2 A	0.997 (0.919)	0.835 (0.802)	2.002 (1.697)	0.969 (0.974)	0.936 (0.949)
3 $\omega_{\text{quadratic}}$	1.161 (1.222)	1.006 (1.048)	2.174 (2.665)	0.959 (0.954)	0.936 (0.959)
4 ω^{+}_{GCV}	1.274 (1.505)	1.106 (1.342)	2.501 (3.140)	0.950 (0.931)	0.940 (0.949)
5 ω^{+}_{CDP}	1.434 (1.910)	1.242 (1.735)	2.878 (3.590)	0.937 (0.888)	0.940 (0.917)
6 $\Delta\omega^{\pm}_{\text{arithmetic,GCV}}$	1.147 (1.187)	0.992 (1.011)	2.128 (2.593)	0.960 (0.957)	0.936 (0.959)
7 $\Delta\omega^{\pm}_{\text{arithmetic,CDP}}$	1.111 (1.096)	0.953 (0.937)	1.997 (2.379)	0.962 (0.963)	0.931 (0.954)
8 $\Delta\omega^{\pm}_{\text{geometric,GCV}}$	1.282 (1.260)	1.110 (1.087)	2.720 (2.739)	0.946 (0.951)	0.931 (0.959)
9 $\Delta\omega^{\pm}_{\text{geometric,CDP}}$	1.224 (1.391)	1.064 (1.224)	2.366 (2.961)	0.954 (0.941)	0.936 (0.959)
[a]10 $\bar{\omega}^{*}_{\text{cubic},\,\alpha}$	0.930 (0.883)	0.735 (0.728)	2.645 (1.960)	0.973 (0.976)	0.913 (0.931)
[b]11 $\Delta\bar{\omega}^{\pm}_{\beta^{+},\,\text{arithmetic}}$	0.929 (0.882)	0.740 (0.733)	2.574 (1.886)	0.974 (0.976)	0.917 (0.931)
[c]12 $\Delta\bar{\omega}^{\pm}_{\beta^{+},\,\text{geometric}}$	0.784 (0.830)	0.632 (0.734)	1.732 (1.844)	0.981 (0.979)	0.894 (0.922)

[a] $\alpha^+ = 0.65(0.62)$. [b] $\beta^+ = 1.00(0.98)$, $\alpha^+ = 0.65(0.62)$, $\alpha^- = 0.49(0.48)$. [c] $\beta^+ = 0.73(0.66)$, $\alpha^+ = 0.00(0.00)$, $\alpha^- = 0.76(0.74)$.

Table 3 Data of nucleophiles molecules. Name of the nucleophile, nucleophilicity parameter (N), I and A from HOMO and LUMO energies (I_{HOMO} and A_{LUMO}), I and A by removing and adding one electron (I^+ and A^-). All energies are in eV

Molecule	N	I_{HOMO}	A_{LUMO}	I^+	A^-
1-Hexene	−2.77	9.21	−1.17	9.53	−1.01
1-Methyl-4-vinyl-benzene	1.70	8.10	−0.67	8.14	−0.67
1-Methylcyclopentene	1.18	8.38	−1.16	8.59	−0.99
1,3-Dimethoxybenzene	2.48	8.07	−1.05	8.13	−0.85
2-Chloropropene	−3.65	9.24	−1.10	9.64	−0.88
2-Methyl-pent-1-ene	0.84	8.87	−1.11	9.10	−0.95
2-Methyl-furan	3.61	8.13	−1.12	8.41	−0.93
2,3-Dimethyl-but-1-ene	0.65	8.89	−1.09	9.10	−0.93
2,3,3-Trimethyl-but-1-ene	0.06	8.91	−1.08	9.07	−0.92
2,4,4-Trimethyl-pent-1-ene	0.79	8.82	−1.07	8.95	−0.92
Furan	1.33	8.55	−1.21	8.94	−1.00
Isobutylene	1.11	8.91	−1.13	9.27	−0.97
N-Methylpyrrole	5.85	7.86	−1.04	8.09	−0.80
Norbornene	−0.25	8.68	−1.09	8.86	−0.93
Styrene	0.78	8.33	−0.54	8.42	−0.58

respect the classical descriptors. Notice that an α^+ value greater than 0.5 ($\alpha^+ > 0.5$) in the descriptor 10 is counterintuitive, because it suggests that the contribution of the ionization potential is more significant than the electron affinity in the estimation of the chemical potential. However, this specific value of α^+ guarantees the existence of a minimum in the cubic interpolation, being, this behavior, in line with the existing correlation between I and A quantities of the database. Notwithstanding, it must be indicated that its interpretation deserves some caution. Inclusion of the parameter β^+ in eqn (34) and (36) improve much more the correlation only in the case of the geometric average. The best fitting is to use the geometric average with $\beta^+ = 0.73(0.76)$, $\alpha^+ = 0.00(0.00)$ and $\alpha^- = 0.76(0.74)$. The improvements in correlation due to the descriptors 10 and 12, even at the cost of introducing new degrees of freedom, open the doors to comprehending similar set of electrophiles with an attempt to understand the variability of the parameters α and β. Additional studies in this direction is now underway.

Table 3 presents the data for a set of 15 references nucleophiles (11 Alkenes and 4 Arenes). In all cases, the solvent employed in determining the N scale is dichloromethane; thus, no solvent influence is expected in this dataset. N spans nine orders of magnitude, from −3.65 (2-chloropropene) to 5.85 (*N*-methylpyrrole). The electron affinity in all cases is negative

Table 4 Root mean square error (RMSE), mean absolute error (MEA), maximum error, coefficient of determination (r^2) and Kendall rank correlation coefficient (τ_{Kendall}) for nucleophilicity descriptors. The values in parentheses are obtained using I^+ and A^-, the others correspond to I_{HOMO} and A_{LUMO}

Descriptors	RMSE	MAE	Max error	r^2	τ_{Kendall}
1 I	1.108 (1.257)	1.024 (1.128)	1.660 (2.229)	0.743 (0.669)	−0.657 (−0.600)
2 A	2.166 (2.120)	1.472 (1.502)	4.933 (4.614)	0.017 (0.058)	0.086 (0.048)
3 $\omega_{\text{quadratic}}$	1.644 (1.225)	1.269 (0.964)	3.004 (2.563)	0.434 (0.686)	−0.600 (−0.657)
4 ω^{-}_{GCV}	1.185 (1.089)	1.063 (0.920)	1.919 (2.132)	0.706 (0.751)	−0.752 (−0.638)
5 ω^{-}_{CDP}	0.998 (1.124)	0.903 (1.011)	1.545 (2.096)	0.791 (0.735)	−0.714 (−0.619)
6 $\Delta\omega^{\pm}_{\text{arithmetic,GCV}}$	1.335 (1.102)	1.144 (0.923)	2.420 (2.210)	0.627 (0.746)	−0.714 (−0.657)
7 $\Delta\omega^{\pm}_{\text{arithmetic,CDP}}$	0.979 (1.143)	0.884 (1.036)	1.506 (2.098)	0.799 (0.726)	−0.714 (−0.619)
8 $\Delta\omega^{\pm}_{\text{geometric,GCV}}$	1.946 (1.573)	1.428 (1.206)	3.864 (3.459)	0.206 (0.482)	−0.505 (−0.543)
9 $\Delta\omega^{\pm}_{\text{geometric,CDP}}$	2.158 (2.107)	1.471 (1.509)	4.917 (4.577)	0.024 (0.070)	−0.086 (−0.086)
[a]10 $\bar{\omega}^{*}_{\text{cubic},\,\alpha}$	0.983 (1.090)	0.880 (0.920)	1.511 (2.135)	0.798 (0.751)	−0.733 (−0.638)
[b]11 $\Delta\bar{\omega}^{\pm}_{\beta^{+},\,\text{arithmetic}}$	0.969 (1.064)	0.873 (0.938)	1.555 (1.796)	0.803 (0.763)	−0.714 (−0.657)
[c]12 $\Delta\bar{\omega}^{\pm}_{\beta^{-},\,\text{geometric}}$	0.909 (0.831)	0.751 (0.792)	1.867 (1.705)	0.827 (0.831)	−0.581 (−0.543)

[a] $\alpha^- = 0.79(0.67)$. [b] $\beta^- = 0.25(0.11)$, $\alpha^+ = 0.23(0.14)$, $\alpha^- = 1.00(0.99)$. [c] $\beta^- = 0.99(0.99)$, $\alpha^+ = 0.11(0.09)$, $\alpha^- = 0.85(0.72)$.

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and very small, as computed by both approaches. In contrast to the electrophile data set, in nucleophiles the correlation between I and A is very small, $r^2 < 0.1$. Since $I \gg A$ in this case, the CDFT descriptors are strongly dependent on the values of I. Using the data in Table 3 we perform linear correlations of N with each one of the 12 descriptors previously mentioned. The ESI,† provides the value of each descriptor for the entire collection of nucleophiles. The statistical data is presented in Table 4, where it is observed that the correlations are lower than in the case of electrophiles, sometimes remarkably low for the descriptors A 2, $\Delta\omega^{\pm}_{\text{geometric,GCV}}$ 8 and $\Delta\omega^{\pm}_{\text{geometric,CDP}}$ 9. These three descriptors are strongly dependent on A, and this last descriptor is almost constant and close to −1.1 eV in all cases, except for 1-methyl-4-vinyl-benzene and styrene. Notice that even if the regression is not as good for this case, when compared with the electrophilic case, the errors in RMSE, MAE, and Max Error are not significant. τ_{Kendall} shows that for most cases, the correlation is negative, which means that the larger descriptors are the poor nucleophiles. As in the case of the electrophilic index, the generalized net nucleophilicity based on the cubic interpolation outperforms the classical descriptors, in particular the geometric mean. In the case of the arithmetic mean 11, $\beta^- = 0.25(0.11)$, $\alpha^+ = 0.23(0.14)$ and $\alpha^- = 1.00(0.99)$, the $r^2 = 0.803(0.763)$ and a MAE of 0.873(0.938), taking the geometric mean with $\beta^- = 0.99(0.99)$, $\alpha^+ = 0.11(0.09)$ and $\alpha^- = 0.85(0.72)$, increase the fit to $r^2 = 0.827(0.831)$ and the MAE decrease to 0.751(0.792). In the last descriptor β^- is close to 1 indicating the importance of I in the correlation.

5 Conclusions

We reformulate some classical electrophilicity descriptors using the cubic interpolation of energy as a function of number of electrons. The analysis presented in this work leads to two observations about the elaboration of the electrophilicity and nucleophilicity concepts. The first one is related to the connection between the electrophilicity index based on the quadratic interpolation and the based on a cubic interpolation. Our analysis shows that after the appropriate inclusion of an α-dependent chemical potential, the new index can incorporate the effect of the environment in which the species is immersed, leading to the possibility of defining both the electrodonating and the electroaccepting powers using different values for the α parameter. The parameter α have been used as additional degrees of freedom, whose values have been fixed to impose specific conditions that characterize an interaction or to improve the correlation with the empirical reactivity index. The second conclusion is related to the new net electrophilicity introduced in Section 2. The classical net electrophilicity, eqn (20), can be interpreted as the arithmetic mean between the electrodonating and electroaccepting powers, based on the idea that both quantities enclose the same property. At the end of Section 2 we suggest the use of the geometric mean, instead of the arithmetic one. Since the classical definition assumes that in net electrophilicity the electrodonating and electroacepting power have the same weight, at the end of Section 3 we introduce a parameter β that weighs the contribution of these two parameters. The generalized net electrophilic and nucleophilic index, eqn (34)–(37), are based on this philosophy. The correlations presented in Section 4 allow us to assert that the generalized net nucleophilicity and electrophilicity index displays concurrently electrophilic and nucleophilic behaviors. It is important to emphasize that the present descriptors depend on the quality of the vertical ionization potential and electron affinity. Work along these lines is ongoing. The results presented here, even taken as a starting point, are quite satisfactory, and they encourage further work in the use of generalized net electrophilicity and nucleophilicity.

Electrophilicity and nucleophilicity are widely used throughout organic and inorganic chemistry. Despite their impressive popularity, no satisfactory quantitative definition exists, neither as an experimental reactivity scale nor as a theoretical reactive index (or descriptor). All methods for describing the reactivity have some limitations. Perhaps one of the most common errors is attempting to separate electrophile and nucleophile reactivity to establish an universal scale. In some way, a nucleophile's reactivity is determined by the electrophile with which it reacts. Therefore, at best, an average scale can be obtained. In many parts of the text we insist that reactivity scales, like the Mayr's ones, and CDFT reactivity index may not necessarily be equal. In general, they are constructed from different perspectives. Reactivity scales are based on correlations obtained from the logarithm of the experimental rate constants (or the activation energy), the basis idea in eqn (1) is that nucleophilicity and electrophilicity are separable and additive. CDFT reactivity index is intended to capture how the energy of a molecular system changes as a result of electrons transfer. Its main idea is to treat chemical processes as molecular perturbations with respect to the total number of electrons and the external potential. These two points of view are similar but not equivalent, and in the case of the nucleophilicity a problem arises because the minima of the energy always occur for electron attachment, not for electron donation. To bring together of these two visions is not always possible because a large part of the activation energy in an electrophile–nucleophile reaction is due to geometric distortions, rather than electron transfer. For this reason, we consider both visions complementary, not equivalent.

Author contributions

LR, FJT and JRM contributed to the initial conception of the work. Design and formal analysis was performed by LR, FJT, JRM, AR, LES and CZ. The first draft of the manuscript was written by LR and FJT, and all authors commented on previous versions of the manuscript. WMR performed the calculations. All authors read and approved the final manuscript.

Data availability

The data supporting this article have been included as part of the ESI.†

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Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 C. K. Ingold, *J. Chem. Soc.*, 1933, 1120–1127.
2 C. K. Ingold, *Chem. Rev.*, 1934, **15**, 225–274.
3 C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, 1953, **75**, 141–147.
4 J. O. Edwards, *J. Am. Chem. Soc.*, 1954, **76**, 1540–1547.
5 J. O. Edwards, *J. Am. Chem. Soc.*, 1956, **78**, 1819–1820.
6 J. O. Edwards and R. Pearson, *J. Am. Chem. Soc.*, 1962, **84**, 16–24.
7 C. D. Ritchie, *Acc. Chem. Res.*, 1972, **5**, 348–354.
8 H. Mayr and M. Patz, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 938–957.
9 H. Mayr and A. R. Ofial, *Pure Appl. Chem.*, 2005, **77**, 1807–1821.
10 H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov and H. Schimmel, *J. Am. Chem. Soc.*, 2001, **123**, 9500–9512.
11 R. Lucius, R. Loos and H. Mayr, *Angew. Chem., Int. Ed.*, 2002, **41**, 91–95.
12 F. Brotzel, Y. C. Chu and H. Mayr, *J. Org. Chem.*, 2007, **72**, 3679–3688.
13 A. A. Tishkov and H. Mayr, *Angew. Chem., Int. Ed.*, 2005, **44**, 142.
14 S. Minegishi, S. Kobayashi and H. Mayr, *J. Am. Chem. Soc.*, 2004, **126**, 5174–5181.
15 H. Mayr and A. R. Ofial, *SAR QSAR Environ. Res.*, 2015, **26**, 619–646.
16 H. Mayr and A. R. Ofial, *J. Phys. Org. Chem.*, 2008, **21**, 584–595.
17 Mayr's Database Of Reactivity Parameters (**https://www.cup.lmu.de/oc/mayr/reaktionsdatenbank2/**).
18 M. Vahl and J. Proppe, *Phys. Chem. Chem. Phys.*, 2023, **25**, 2717.
19 G. Frenking and A. Krapp, *J. Comput. Chem.*, 2006, **28**, 15–24.
20 H. Chermette, *J. Comput. Chem.*, 1998, **20**, 129–154.
21 P. Geerlings, F. De Proft and W. Langenaeker, *Chem. Rev.*, 2003, **103**, 1793.
22 P. W. Ayers, J. Anderson and L. J. Bartoloti, *Int. J. Quantum Chem.*, 2005, **101**, 520–534.
23 J. L. Gázquez, *J. Mex. Chem. Soc.*, 2008, **52**, 3–10.
24 S. Liu, *Acta Phys. Chem. Sin.*, 2009, **25**, 590–600.
25 in *Conceptual Density Functional Theory: Towards a New Chemical Reactivity Theory*, ed. S. Liu, Wiley, 2022.
26 P. Geerlings, E. Chamorro, P. K. Chattaraj, F. De Proft, J. L. Gázquez, S. Liu, C. Morell, A. Toro-Labbe, A. Vela and P. W. Ayers, *Theor. Chem. Acc.*, 2020, **139**, 36.
27 R. G. Parr, L. G. von Szentpaly and S. Liu, *J. Am. Chem. Soc.*, 1999, **1922**, 121.
28 J. L. Gázquez, A. Cedillo and A. Vela, *J. Phys. Chem. A*, 2007, **111**, 1966–1970.
29 E. Chamorro, M. Duque-Noreña and P. Pérez, *THEOCHEM*, 2009, **986**, 73–79.
30 E. Chamorro, M. Duque-Noreña and P. Pérez, *THEOCHEM*, 2009, **901**, 145–152.
31 P. K. Chattaraj, A. Chakraborty and S. Giri, *J. Phys. Chem. A*, 2009, **113**, 10068–10074.
32 C. Morell, J. L. Gázquez, A. Vela, F. Guegan and H. Chermette, *Phys. Chem. Chem. Phys.*, 2014, **16**, 26832–26842.
33 R. A. Miranda-Quintana, *J. Chem. Phys.*, 2017, **146**, 214113.
34 M. Franco-Perez, J. L. Gazquez, P. W. Ayers and A. Vela, *J. Chem. Theory Comput.*, 2018, **14**, 597–606.
35 G. Hoffmann, V. Tognetti and L. Joubert, *Chem. Phys. Lett.*, 2019, **724**, 24–28.
36 P. Jaramillo, P. Perez, R. Contreras, W. Tiznado and P. Fuentealba, *J. Phys. Chem. A*, 2006, **110**, 8181–8187.
37 L. R. Domingo and P. Perez, *Org. Biomol. Chem.*, 2011, **9**, 7168.
38 E. Chamorro, M. Duque-Noreña, R. Notario and P. Perez, *J. Phys. Chem. A*, 2013, **117**, 2636–2643.
39 P. Fuentealba and R. G. Parr, *J. Chem. Phys.*, 1991, **94**, 5559–5564.
40 P. Senet, *J. Chem. Phys.*, 1996, **105**, 6471–6489.
41 P. Geerlings and F. De Proft, *Phys. Chem. Chem. Phys.*, 2008, **10**, 3028–3042.
42 P. W. Ayers and R. G. Parr, *J. Chem. Phys.*, 2008, **129**, 054111.
43 C. Cardenas, E. Echegaray, D. Chakraborty, J. S. Anderson and P. W. Ayers, *J. Chem. Phys.*, 2009, **130**, 244105.
44 C. Morell, A. Grand, A. Toro-Labbe and H. Chermette, *J. Mol. Model.*, 2013, **19**, 2893–2900.
45 G. Hoffmann, V. Tognetti and L. Joubert, *J. Phys. Chem. A*, 2020, **124**, 2090.
46 R. A. Miranda-Quintana, P. W. Ayers and F. Heidar-Zadeh, *ChemistrySelect*, 2021, **6**, 96–100.
47 G. Hoffmann, H. Chemette and C. Morell, *J. Mol. Model.*, 2024, **30**, 232.
48 S. F. Figueredo and M. A. Quintero, *Int. J. Quantum Chem.*, 2024, **214**, e27366.
49 M. E. Gonzalez, C. Cardenas, J. I. Rodriguez, S. Liu, F. Heidar-Zadeh, R. A. Miranda-Quintana and P. W. Ayers, *Acta Phys.-Chim. Sin.*, 2018, **34**, 662–674.
50 R. G. Parr and W. Yang, *Density Functional Theory of Atoms and Molecules*, Oxford University Press, 1989.
51 R. G. Parr, R. A. Donelly, M. Levy and W. E. Palke, *J. Chem. Phys.*, 1978, **68**, 3801–3807.
52 R. G. Parr and R. Pearson, *J. Am. Chem. Soc.*, 1983, **105**, 7512–7516.
53 J. P. Perdew, R. G. Parr, M. Levy and J. L. Balduz, *Phys. Rev. Lett.*, 1982, **49**, 1691–1694.

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54 W. T. Yang, Y. K. Zhang and P. W. Ayers, *Phys. Rev. Lett.*, 2000, **84**, 5172–5175.
55 F. Heidar-Zadeh, R. A. Miranda-Quintana, T. Verstraelen, P. Bultinck and P. W. Ayers, *J. Chem. Theory Comput.*, 2016, **12**, 5777–5787.
56 R. A. Miranda-Quintana and P. W. Ayers, *J. Chem. Phys.*, 2016, **144**, 244112.
57 R. G. Parr and R. Pariser in *Concepts and Methods in Modern Theoretical Chemistry*, ed. S. K. Ghosh and P. K. Chattaraj, CRC Press, 2013, pp. 431–440.
58 P. W. Ayers and R. G. Parr, *J. Chem. Phys.*, 2008, **128**, 184108.
59 J. F. Janak, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1978, **18**, 7165.
60 J. P. Perdew and M. Levy, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1997, **56**, 16021.
61 A. J. Cohen, P. Mori-Sánchez and W. Yang, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 2008, **77**, 115123.
62 W. Yang, A. J. Cohen and P. Mori-Sánchez, *J. Chem. Phys.*, 2012, **136**, 204111.
63 A. T. Maynard, M. Huang, W. G. Rice and D. G. Covell, *Proc. Natl. Acad. Sci. U. S. A.*, 1998, **95**, 11578–11583.
64 E. Chamorro, P. Perez, F. De Proft and P. Geerlings, *J. Phys. Chem.*, 2006, **124**, 044105.
65 P. Perez, J. Andres, V. S. Safont, O. Tapia and R. Contreras, *J. Phys. Chem. A*, 2002, **106**, 5353.
66 P. Perez, E. Chamorro and P. W. Ayers, *J. Chem. Phys.*, 2006, **128**, 204108.
67 P. K. Chattaraj, U. Sarkar and D. R. Roy, *Chem. Rev.*, 2006, **106**, 2065–2091.
68 P. K. Chattaraj and D. R. Roy, *Chem. Rev.*, 2007, **107**, PR46–PR74.
69 P. K. Chattaraj, S. Giri and S. Duley, *Chem. Rev.*, 2011, **111**, PR43–PR73.
70 S. Liu, in *Chemical Reactivity Theory: A density Functional view*, ed. P. K. Chattaraj, Taylor and Francis, 2009, p. 179.
71 L. R. Domingo, M. Ríos-Gutiérrez and P. Pérez, *Molecules*, 2016, **16**, 748.
72 R. Pal and P. K. Chattaraj, *J. Comput. Chem.*, 2023, **44**, 278.
73 P. K. Chattaraj, *Indian J. Phys.*, 2007, **81**, 871–879.
74 C. Morell, V. Labet, A. Grand and H. Chermette, *Phys. Chem. Chem. Phys.*, 2009, **11**, 3417–3423.
75 P. K. Chattaraj, S. Giri and S. Duley, *J. Phys. Chem. Lett.*, 2010, **1**, 1064–1067.
76 P. W. Ayers, J. S. M. Anderson, J. I. Rodriguez and Z. Jawed, *Phys. Chem. Chem. Phys.*, 2005, **7**, 1918–1925.
77 S. Pratihar and S. Roy, *J. Org. Chem.*, 2010, **75**, 4957.
78 L. R. Domingo, E. Chamorro and P. Perez, *J. Org. Chem.*, 2008, **73**, 4615–4624.
79 S. Liu, C. Y. Rong and T. Lu, *J. Phys. Chem. A*, 2014, **118**, 3698–3704.
80 X. Y. Zhou, C. Y. Rong, L. U. Tian and S. Liu, *Acta Phys.-Chim. Sin.*, 2014, **30**, 2055–2062.
81 J. Fu, M. Li, C. Rong, D. Zhao and S. Liu, *J. Mol. Model.*, 2024, **30**, 341.
82 B. Wang, S. Liu, M. Lei and F. De Proft, *Chem. – Eur. J.*, 2024, **54**, e202401295.
83 R. A. Miranda-Quintana and P. W. Ayers, *Phys. Chem. Chem. Phys.*, 2016, **18**, 15070–15080.
84 R. A. Miranda-Quintana, *Theor. Chem. Acc.*, 2017, **136**, 76.
85 R. A. Miranda-Quintana and P. W. Ayers, *Theor. Chem. Acc.*, 2016, **135**, 172.
86 R. A. Miranda-Quintana, *Theor. Chem. Acc.*, 2016, **135**, 189.
87 R. A. Miranda-Quintana, M. M. Gonzalez and P. W. Ayers, *Phys. Chem. Chem. Phys.*, 2016, **18**, 22235–22243.
88 M. Orlandi, M. Escudero-Casao and G. Licini, *J. Org. Chem.*, 2021, **86**, 3555–3564.
89 G. Hoffmann, M. Balcilar, V. Tognetti, P. Heroux, B. Gaüzere, S. Adam and L. Joubert, *J. Comput. Chem.*, 2020, **41**, 2124–2136.
90 S. A. Cuesta, M. Moreno, R. A. Lopez, J. R. Mora, J. L. Paz and E. Marquez, *J. Chem. Inf. Model.*, 2023, **63**, 507–521.
91 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman and D. J. Fox, *Gaussian 16, Revision C.01*, Gaussian, Inc., Wallingford CT, 2016.
92 C. Filippi, C. J. Umrigar and X. Gonze, *J. Chem. Phys.*, 1997, **107**, 9994–10002.
93 P. W. Ayers, R. C. Morrison and R. G. Parr, *Mol. Phys.*, 2005, **103**, 2061–2072.
94 M. V. Putz, N. Russo and E. Sicilia, *J. Comput. Chem.*, 2004, **95**, 994.
95 R. Mineva and T. Heine, *J. Phys. Chem. A*, 2004, **108**, 11086.
96 K. D. Jordan and P. D. Burrow, *Chem. Rev.*, 1987, **87**, 557.
97 M. Guerra, *Chem. Phys. Lett.*, 1990, **167**, 315.
98 D. J. Tozer and F. De Proft, *J. Phys. Chem. A*, 2005, **109**, 8923–8929.
99 C. Cardenas, P. Ayers, F. De Proft, D. J. Tozer and P. Geerlings, *Phys. Chem. Chem. Phys.*, 2011, **13**, 2285–2293.
100 C. P. Vibert and D. J. Tozer, *J. Chem. Theor. Comput.*, 2019, **15**, 241–248.