

Understanding the local reactivity in polar organic reactions through electrophilic and nucleophilic Parr functions†‡

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Building upon our recent studies devoted to the bonding changes in polar reactions [*RSC Advances*, 2012, **2**, 1334 and *Org. Biomol. Chem.*, 2012, **10**, 3841], we propose herein two new electrophilic, P_k^+ , and nucleophilic, P_k^- , Parr functions based on the spin density distribution at the radical anion and at the radical cation of a neutral molecule. These local functions allow for the characterisation of the most electrophilic and nucleophilic centres of molecules, and for the establishment of the regio- and chemoselectivity in polar reactions. The proposed Parr functions are compared with both, the Parr–Yang Fukui functions [*J. Am. Chem. Soc.* 1984, **106**, 4049] based on frontier molecular orbitals, and Yang–Mortier condensed Fukui functions [*J. Am. Chem. Soc.* 1986, **108**, 5708] based on Mulliken charges.

Introduction

Organic reactions can be classified as non-polar or polar depending on the overall electronic character of the bond formation and/or bond breaking along the reaction. Most organic molecules with polarised functional groups present a polar reactivity, which is characterised by a nucleophilic/electrophilic interaction. While electrophiles are molecules able to accept an amount of electron density along the reaction, nucleophiles are molecules able to donate an amount of electron density during the reaction. The electrophilic or nucleophilic power of a molecule is related to its ability to exchange electron density along a reaction.

From a theoretical point of view, the electrophilic and nucleophilic behaviours of organic molecules can be characterised by using the reactivity indices defined within the conceptual density functional theory (DFT) framework.¹ Thus, Parr and coworkers² introduced the following definition of the electrophilicity index ω as:

$$\omega = \frac{\mu^2}{2\eta} \quad (1)$$

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where μ is the chemical potential, and η is the absolute hardness. The electrophilicity index ω is a measure of the energy stabilisation of a given molecule when it gains an amount of electron density.

Since the electron density donation process from a neutral molecule is thermodynamically unfavourable, we can assert that the best nucleophiles are those having low ionization potentials. Based on this idea, we have introduced an empirical (relative) nucleophilicity index^{3,4} (N) based on the HOMO energies obtained within the Kohn–Sham scheme,⁵ and defined as:³

$$N = E_{\text{HOMO}(\text{Nu})} (\text{eV}) - E_{\text{HOMO}(\text{TCE})} (\text{eV}) \quad (2)$$

Nucleophilicity is referred to tetracyanoethylene (TCE) because it presents the lowest HOMO energy in a large series of molecules already investigated in the context of polar cycloadditions. This choice allows us to conveniently handle a nucleophilicity scale of positive values.

Along a polar reaction, the bond breaking and bond formation takes place at a specific position of a molecule, and if a molecule has several positions with similar reactivity, we can talk of regio- or chemoselectivity. This situation is common in cycloaddition reactions, in which the different approach modes of a reagent towards the other can yield two competitive isomers named regioisomers. Recent studies devoted to polar cycloaddition reactions have shown that the most favourable regioisomeric channel is that involving the bond formation between the most electrophilic and the most nucleophilic centre of the reagents. Consequently, it is desirable to have local reactivity indices able to characterise these relevant centres in organic molecules.

In 1984 in a short communication entitled “*Density Functional Approach to the Frontier-Electron Theory of Chemical Reactivity*”, Parr and Yang⁶ proposed within the DFT the $f(\mathbf{r})$ function named frontier function or Fukui function for a molecule, which was defined as,

$$f(\mathbf{r}) = \left[\frac{\partial \rho(\mathbf{r})}{\partial N} \right]_{v(\mathbf{r})} \quad (3)$$

Parr and Yang assumed that the preferred direction for an approach of a reagent over the other is the one for which the initial variation of the chemical potential μ for a species is a maximum, and that the preferred direction is the one with largest f at the reaction site.⁶ Using a frozen core approximation in which $\partial \rho = \partial \rho_{\text{valence}}$ they proposed:

$$f^-(\mathbf{r}) \approx \rho_{\text{HOMO}}(\mathbf{r}) \text{ for electrophilic attacks} \quad (4)$$

and

$$f^+(\mathbf{r}) \approx \rho_{\text{LUMO}}(\mathbf{r}) \text{ for nucleophilic attacks} \quad (5)$$

They assumed that the preferred direction of a chemical process is that in which the incoming reagent will produce the biggest change in the system's electronic chemical potential.⁶

In 1984, Yang and Mortier,⁷ proposed a different approach to the Fukui functions based on the variation of the Mulliken gross charges, $q(\mathbf{r})$, of an atom in a molecule. In a finite-difference approximation, the condensed Fukui functions are given by,⁷

$$f_k^- = q_k(N) - q_k(N - 1) \quad (6)$$

$$f_k^+ = q_k(N + 1) - q_k(N) \quad (7)$$

Fukui functions enable the distribution of some relevant global reactivity indices, such as the electrophilicity and the nucleophilicity indices, along the atoms of a molecule, and therefore to characterise the most electrophilic and nucleophilic centres of a reagent, allowing for the characterisation of the local reactivity. Thus, we defined the local electrophilicity⁸ ω_k as:

$$\omega_k = \omega f_k^+ \quad (8)$$

and the local nucleophilicity⁹ N_k as:

$$N_k = N f_k^- \quad (9)$$

These local indices have been shown to be useful tools in the study of the regioselectivity in cycloaddition reactions.

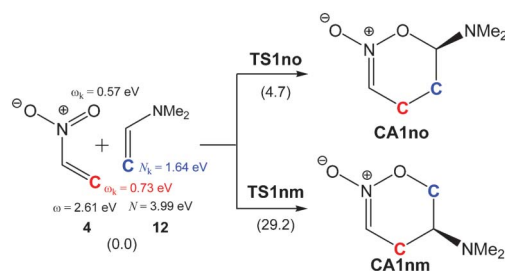
Polar Diels–Alder (P-DA) reactions involving asymmetrically substituted reagents take place through high asymmetric transition state structures (TSS).¹⁰ Several studies have established that the most favourable regioisomeric reactive channel is that involving the most favourable local electrophilic and nucleophilic interactions. This behaviour is well predicted by the analysis of the local electrophilicity ω_k and

the nucleophilicity N_k indices derived from the Fukui functions.

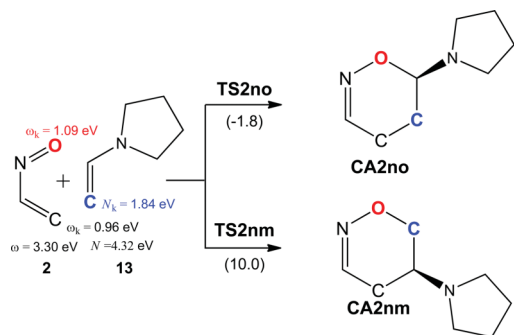
In this sense, we studied the P-DA reaction between nitroethylene **4** and dimethylvinylamine (DMVA) **12** (see Scheme 1).¹¹ This cycloaddition showed a very high regioselectivity, the most unfavourable **TS1nm** being 24.5 kcal mol⁻¹ higher in energy than **TS1no**.¹¹ The most favourable **TS1no** was characterised by the initial C–C σ bond formation between the most electrophilic centre of nitroethylene **4**, the β conjugated carbon, and the most nucleophilic centre of DMVA **12**, the β conjugated carbon, which displayed the maximum ω_k and N_k values, 0.73 and 1.64 eV, respectively (see Scheme 1).¹² The large charge transfer (CT) found at **TS1no**, 0.41e, was in agreement with the high electrophilicity of nitroethylene **4**, $\omega = 2.61$ eV, and nucleophilicity of DMVA **12**, $N = 3.99$ eV.

Electron localization function (ELF)¹³ analysis of the structures involved in the intrinsic reaction coordinate (IRC) of a reaction has been used to study bonding changes along organic reactions.^{12,14–16} These analyses stress that in a polar cycloaddition the bond formation takes place through a *centre-to-centre pseudoradical* coupling at the most electrophilic and nucleophilic centres of the reagents.¹⁵ In addition, the zwitterionic character of the *pseudodiradical* species involved in the IRC increases with the electrophilic and nucleophilic character of the reagents. In the extreme case in which the transferred electron density is *ca.* one electron, the nucleophile becomes a radical cation and the electrophile a radical anion. Atomic spin density (ASD) analysis of these radical species provides an electron density distribution similar to that found in the LUMO and HOMO of the reagents.^{12,16,17} However, in spite of this similarity, the reactivity model based on electron-density changes is opposed to that proposed by the frontier molecular orbital (FMO) theory,¹⁸ in which the HOMO of the nucleophile interacts with the LUMO of the electrophile.

Thus, the P-DA reaction between nitrosoethylene **2** and 1-vinylpyrrolidine **13** was studied as an extreme case of P-DAs, nitrosoethylene **2** being one of the most electrophilic monosubstituted ethylenes, $\omega = 3.30$ eV, and 1-vinylpyrrolidine **13** one of the most nucleophilic monosubstituted ethylenes, $N = 4.32$ eV (see Scheme 2). This cycloaddition also presented a total *meta* regioselectivity.¹⁹ However, in this case the analysis of the local electrophilicity index failed to predict that the O4 oxygen would be the most electrophilic centre of nitrosoethy-



Scheme 1



Scheme 2

lene 2. An even less favorable result was obtained by analysis of the local reactivity based on Yang and Mortier's condensed Fukui functions. However, ASD analysis of the radical anion of the electrophile and the radical cation of the nucleophile allows for the correct evaluation of the most electrophilic centre of nitrosoethylene 2.²⁰

Taking into account the observations obtained from the ASD analysis performed in polar reactions,^{12,16,17,20} we propose herein a new local reactivity index, named Parr function $P(\mathbf{r})$, which is obtained from the ASD at the radical cation and at the radical anion of the corresponding reagents, which is given by the following equations,

$$P^-(\mathbf{r}) = \rho_S^{rc}(\mathbf{r}) \text{ for electrophilic attacks} \quad (10)$$

and

$$P^+(\mathbf{r}) = \rho_S^{ra}(\mathbf{r}) \text{ for nucleophilic attacks} \quad (11)$$

where $\rho_S^{rc}(\mathbf{r})$ is the ASD of the radical cation, and $\rho_S^{ra}(\mathbf{r})$ is the ASD of the radical anion. Each ASD condensed at the different atoms of the radical cation and radical anion provides our local nucleophilic P_k^- and electrophilic P_k^+ Parr functions of the neutral system.

With these electrophilic and nucleophilic Parr functions at hand, we can redefine the local electrophilicity ω_k and the local nucleophilicity N_k indices as follows:

$$\omega_k = \omega P_k^+ \quad (12)$$

and

$$N_k = N P_k^- \quad (13)$$

Therefore, one can easily find the ω_{\max} and N_{\max} , which are associated with the most electrophilic and most nucleophilic centres in a molecule, respectively, and correspond to the centres with the highest electron density developed along the CT process.¹⁷

Herein, electrophilic and nucleophilic Parr functions are compared with the Fukui functions computed from both Parr and Yang (PY) and Yang and Mortier (YM) approaches for a series of twelve organic molecules involved in polar reactions (see Chart 1).

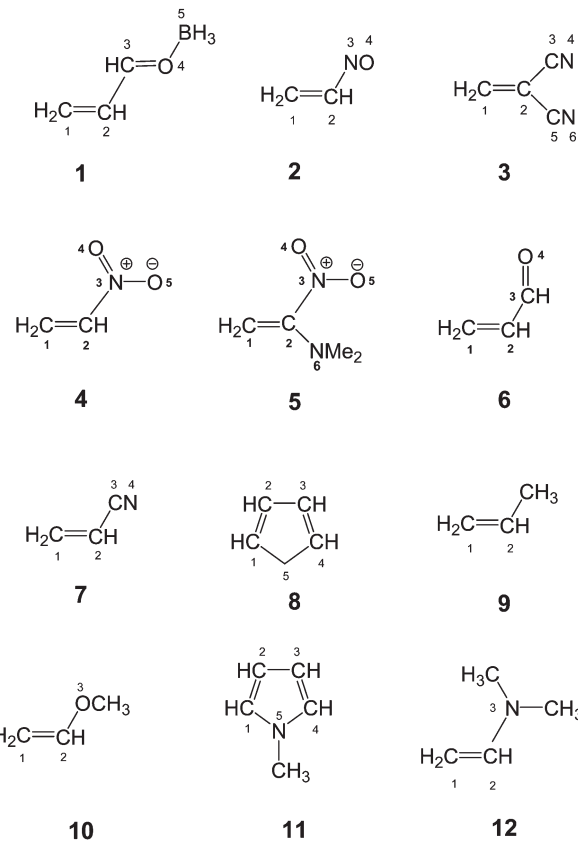


Chart 1

Computational details

DFT calculations were carried out using the B3LYP²¹ exchange–correlation functionals, together with the standard 6-31G* basis set.²² Optimisations were carried out using the Bery analytical gradient optimisation method.²³ The stationary points were characterised by frequency calculations in order to verify that TSs have one and only one imaginary frequency. All calculations were carried out with the Gaussian 09 suite of programs.²⁴

The electrophilic, P_k^+ , and nucleophilic, P_k^- , Parr functions, were obtained through the analysis of the Mulliken ASD of the radical anion and the radical cation by single-point energy calculations over the optimised neutral geometries using the unrestricted UB3LYP formalism for radical species. PY and YM Fukui functions were computed using the eqn (4)–(7), respectively.

Results and discussion

First, the Parr functions computed for a series of substituted reagents involved in P-DA reactions will be compared with the Fukui functions computed from both PY and YM methods. Then, the regioselectivity of the P-DA reaction between the captodative (CD) ethylene 5 and enamine 12 will be analysed using the activation energies associated with the *meta* and

ortho reactive channels, and the corresponding Parr and Fukui functions. Finally, a study of the local electrophilic/nucleophilic reactivity in the intramolecular Michael type addition in Breslow intermediate **13** will be performed.

(i) Comparative analysis of the local indices for a series of substituted reagents involved in P-DA reactions

In order to analyse the proposed Parr functions and compare them with the Fukui functions computed from the PY and YM methods, the corresponding local electrophilic and nucleophilic functions for a series of twelve reagents involved in P-DA reactions were computed. Note that some of these compounds participate in several polar reactions, such as Michael additions or aromatic electrophilic substitutions. The structures and atomic numbering of the twelve compounds are given in Chart 1. These compounds are ordered by decreasing global electrophilic character. The corresponding values for both electrophilic and nucleophilic functions are given in Table 1. To facilitate the analysis of the results presented in Table 1, the electrophilic indices greater than 0.1 are given in red, while the nucleophilic indices greater than 0.1 are given in blue. The corresponding values for the hydrogen atoms are not given, since the Parr functions and the Fukui functions computed from the PY method are closer to zero.

A preliminary analysis of the data given in Table 1 indicates that all three models show similar patterns for the local reactivity of these molecules. However, a detailed analysis shows that the YM Fukui functions present some relevant deficiencies. In spite of the fact that the three local functions are normalised, the sum of the YM Fukui functions corresponding to the heavy atoms is below 1.0, in discrepancy with the sum of the Parr and the PY Fukui functions, which is closer to 1.0.

The poor results given by the YM Fukui functions can be understood when considering that all these molecules can present a hyperconjugation effect between the π system and the substituents on the C–C double bond, which are enhanced at the corresponding radical anion and radical cation. Since the hyperconjugation effect is stronger in the charged species than in the neutral species, the charge differences can be significant in the substituents. Note that for simplicity the local functions corresponding to the hydrogen atoms are not reported.

A prototypical example of hyperconjugative effects is shown in propene **9**. While the sum of the Parr and PY Fukui functions for the three carbon atoms is 0.95 for P_k^+ , 0.99 for P_k^- , 0.91 for f_k^+ , and 0.94 for f_k^- , the sum of the YM Fukui functions are 0.15 for f_k^+ and 0.22 for f_k^- . This is a serious problem when computing the local electrophilicity and nucleophilicity indices using eqn (8) and (9), because the YM Fukui functions render small values. A similar result is observed for cyclopentadiene **8** for which the sum of the YM Fukui functions are 0.16 for f_k^+ and 0.29 for f_k^- .

In addition, there are serious problems when characterising the most nucleophilic centre in some well known molecules. It is widely known that α,β -unsaturated carbonyl compounds present the most electrophilic centre at the β conjugated position, a behaviour that is well reproduced by the Parr and

Table 1 Electrophilic and nucleophilic Parr functions, and electrophilic and nucleophilic PY and YM Fukui functions

			PY		YM			
			P_k^+	P_k^-	f_k^+	f_k^-	f_k^+	f_k^-
1	1	C	0.54	0.18	0.36	0.06	0.11	0.08
	2	C	-0.08	0.07	0.08	0.01	0.00	0.01
	3	C	0.42	-0.05	0.33	0.04	0.12	0.02
	4	O	0.20	0.10	0.20	0.02	0.12	0.01
	5	B	-0.01	0.22	0.01	0.37	-0.09	0.00
2	1	C	0.41	-0.09	0.29	0.01	0.11	0.10
	2	C	-0.06	0.08	0.04	0.09	-0.01	0.01
	3	N	0.31	0.30	0.35	0.34	0.21	0.20
	4	O	0.38	0.68	0.33	0.54	0.26	0.34
3	1	C	0.74	0.44	0.50	0.34	0.14	0.13
	2	C	0.10	0.16	0.21	0.20	0.10	0.07
	3	C	0.00	-0.05	0.04	0.05	0.11	0.14
	4	N	0.12	0.27	0.11	0.18	0.14	0.15
	5	C	0.00	-0.05	0.04	0.05	0.11	0.14
	6	N	0.12	0.27	0.11	0.18	0.14	0.15
4	1	C	0.44	-0.01	0.28	0.01	0.11	0.07
	2	C	0.01	0.01	0.08	0.01	0.03	0.02
	3	N	0.23	-0.05	0.23	0.02	0.07	0.04
	4	O	0.22	0.83	0.22	0.52	0.22	0.37
	5	O	0.16	0.20	0.19	0.43	0.20	0.21
5	1	C	0.34	0.42	0.19	0.29	0.09	0.13
	2	C	0.01	-0.10	0.05	0.06	0.04	0.02
	3	N	0.28	0.01	0.29	0.01	0.01	-0.01
	4	O	0.20	0.04	0.23	0.01	0.21	0.08
	5	O	0.20	0.03	0.23	0.01	0.21	0.06
	6	N	0.00	0.60	0.01	0.47	-0.02	0.14
6	1	C	0.52	-0.04	0.37	0.01	0.11	0.08
	2	C	0.04	0.13	0.14	0.10	0.01	0.00
	3	C	0.27	-0.07	0.27	0.05	0.11	0.02
	4	O	0.24	0.83	0.22	0.71	0.19	0.37
7	1	C	0.63	0.44	0.47	0.37	0.13	0.14
	2	C	0.20	0.27	0.27	0.27	0.11	0.11
	3	C	0.03	-0.07	0.09	0.09	0.14	0.18
	4	N	0.22	0.41	0.18	0.28	0.17	0.19
8	1	C	0.40	0.47	0.29	0.34	0.09	0.11
	2	C	0.10	0.08	0.15	0.16	0.03	0.05
	3	C	0.10	0.08	0.15	0.16	0.03	0.05
	4	C	0.40	0.47	0.29	0.34	0.09	0.11
	5	C	-0.08	-0.06	0.01	0.00	-0.09	-0.05
9	1	C	0.51	0.59	0.46	0.50	0.15	0.16
	2	C	0.46	0.38	0.44	0.41	0.06	0.10
	3	C	-0.02	0.02	0.02	0.03	-0.05	-0.05
10	1	C	0.48	0.58	0.44	0.47	0.13	0.16
	2	C	0.50	0.07	0.46	0.20	0.16	0.06
	3	O	0.00	0.36	0.05	0.28	0.03	0.17
11	1	C	0.39	0.52	0.30	0.37	0.11	0.15
	2	C	0.01	0.07	0.08	0.13	0.02	0.04
	3	C	0.39	0.52	0.30	0.37	0.11	0.15
	4	C	0.01	0.07	0.08	0.13	0.02	0.04
	5	N	0.14	-0.12	0.16	0.01	-0.02	-0.02
	6	C	-0.01	0.00	0.01	0.00	-0.06	-0.04
12	1	C	0.40	0.56	0.40	0.41	0.10	0.14
	2	C	0.42	-0.11	0.44	0.09	0.12	0.01
	3	N	0.00	0.53	0.06	0.39	-0.02	0.12

the PY Fukui functions. For instance, in acrolein **6** and BH_3 -acrolein complex **1**, the β conjugated C1 atom, $P_k^+ = 0.52$ and $f_k^+ = 0.37$ (**6**) and $P_k^+ = 0.54$ and $f_k^+ = 0.36$ (**1**), is more

electrophilically activated than the C3, $P_k^+ = 0.27$ and $f_k^+ = 0.27$ (6) and $P_k^+ = 0.42$ and $f_k^+ = 0.33$ (1), and O4, $P_k^+ = 0.24$ and $f_k^+ = 0.22$ (6) and $P_k^+ = 0.20$ and $f_k^+ = 0.20$ (1), atoms. However, YM condensed Fukui functions fail since they predict that the O4 atom, $f_k^+ = 0.19$ (6) and $f_k^+ = 0.12$ (1), is more electrophilically activated than the C1 one, $f_k^+ = 0.11$ (6) and $f_k^+ = 0.11$ (1). Similarly, the YM Fukui functions also fail in 1,1-dicyanoethylene 3 since they consider that the C1, N4 and N5 centres have the same electrophilic activation, $f_k^+ = 0.14$. An even less favourable result is obtained in the carbonyl compounds, where YM Fukui functions suggest that the carbonyl oxygen atom is more electrophilically activated than the carbon one (for dimethyl ketone, the electrophilic YM condensed Fukui functions are $f_k^+ = 0.16$ at the carbonyl carbon and $f_k^+ = 0.22$ at the carbonyl oxygen).

Interesting cases are found in compounds 4 and 5. While for nitroethylene 4 the YM Fukui functions suggest a higher electrophilic activation at the O4 and O5 oxygen atoms, $f_k^+ = 0.22$ and $f_k^+ = 0.20$, than at the β conjugated C1 atom $f_k^+ = 0.11$, for CD ethylene 5, YM Fukui functions give a negligible electrophilic activation at the β conjugated C1 atom, $f_k^+ = 0.09$. However, it is known that these electron-deficient ethylenes experience nucleophilic attacks on the β conjugated C1 position (see later).²⁵ Note that the electrophilic Parr function at C1 is $P_k^+ = 0.34$. Consequently, this first analysis allows us to reject the Fukui functions based on the YM approach for the study of local reactivity in organic reactions.

A comparative analysis of the Parr functions proposed herein with the PY Fukui ones for the compounds given in Table 1 indicates that, in general, both provide similar patterns for the electrophilic and nucleophilic activations for this series of molecules. In general, Parr functions provide larger electrophilic and nucleophilic activations than the PY ones. In this way, the analysis of the electrophilic activation at the β conjugated C1 position of the electron-deficient ethylenes 2 to 5 shows that the electrophilic Parr function, P_k^+ , ranges from 0.34–0.74, presenting larger values than the PY one, f_k^+ , which ranges from 0.19–0.50.

Interestingly, two opposite results should be commented on. As we indicated in the Introduction, for nitrosoethylene 2, the electrophilic Parr function shows that the C1 carbon, $P_k^+ = 0.41$, is slightly more electrophilically activated than the O4 oxygen, $P_k^+ = 0.38$, while the electrophilic PY Fukui function shows that the O4 oxygen, $f_k^+ = 0.33$, is slightly more electrophilically activated than the C1 carbon, $f_k^+ = 0.29$. Both experimental²⁶ and theoretical¹⁹ results indicate that the C1 carbon is the most electrophilic centre of nitrosoethylenes.

Another remarkable difference is found in CD ethylene 5, in which the electrophilic Parr function suggests that the C1 carbon, $P_k^+ = 0.34$, is more electrophilically activated than the O4 oxygen, $P_k^+ = 0.20$, while the electrophilic PY Fukui function suggests that the O4 oxygen, $f_k^+ = 0.23$, is more electrophilically activated than the C1 carbon, $f_k^+ = 0.19$. Note that CD ethylenes experience nucleophilic attacks at the β conjugated C1 position (see below).

For nucleophilic species, a similar trend is observed for the nucleophilic Parr and PY Fukui functions, the former providing also a larger resolution (see compounds 10 and 12 in Table 1).

Finally, the electrophilic Parr function P_k^+ for the electron-deficient ethylenes 3 and 6, and the nucleophilic Parr function P_k^- for the electron-rich ethylenes 9 and 10 were computed using the natural spin density obtained through NBO calculations²⁷ in order to explore the stability of the Parr functions computed by Mulliken ASD. The corresponding data are given in Table 2.

A comparison of the Mulliken and NBO electrophilic and nucleophilic Parr functions given in Table 2 indicates that there is no substantial difference.

Despite the similarity of the electrophilic and nucleophilic local activations given for the Parr and PY Fukui functions for the series of compounds given in Table 1, there are two considerations that recommend the use of the Parr functions instead of the PY ones: (i) as stated in the Introduction, both functions are conceptually different. The electrophilic PY condensed Fukui function f_k^+ is obtained from the LUMO electron density (see eqn (5)) as an approximation of the FMO theory, in which the bond formation takes place through HOMO_{nucleophile}–LUMO_{electrophile} interactions. Our recent ELF bonding analyses concerning polar reactions suggest that the new σ bonds are formed by a *centre-to-centre* coupling of two *pseudoradical centres* instead of a HOMO–LUMO donation process as suggested by the FMO theory.¹⁸ Consequently, the LUMO of electrophiles does not participate in the bond formation (see later); and ii) the Parr functions obtained by performing simple unrestricted calculations at the radical anion and radical cation of a molecule are easier to obtain than the PY condensed Fukui functions obtained from the HOMO and LUMO coefficients and the corresponding overlapping integrals using specific programs.²⁸

ii) Study of the regioselectivity of the P-DA reaction between CD ethylene 5 and enamine 12

As indicated above, the Parr and the PY Fukui functions yield a different local electrophilic activation in CD ethylene 5. CD ethylenes present a concurrent electrophilic and nucleophilic activation at the β conjugated C1 carbon.³ Although both local functions predict an electrophilic and nucleophilic activation at the C1 carbon, the PY Fukui function indicates that the O4 oxygen is the most electrophilically activated centre of this molecule, whereas the Parr function suggests that the C1

Table 2 Electrophilic Parr function P_k^+ for the electron-deficient ethylenes 3 and 6, and nucleophilic Parr function P_k^- for the electron-rich ethylenes 9 and 10 computed by Mulliken and NBO ASD analyses

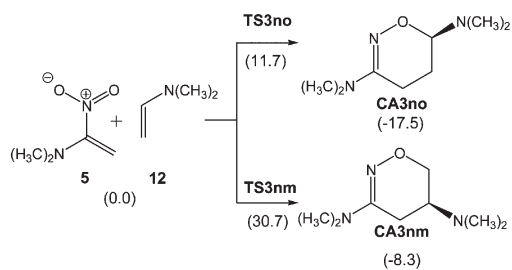
		P_k^+ (Mulliken)	P_k^+ (NBO)			P_k^+ (Mulliken)	P_k^+ (NBO)	
3	C 1	0.74	0.67	6	C 1	0.52	0.48	
	C 2	0.10	0.11		C 2	0.04	0.06	
	C 3	0.00	0.01		C 3	0.27	0.25	
	N 4	0.12	0.12		4 O	0.24	0.25	
	C 5	0.00	0.01					
	N 6	0.12	0.12					
		P_k^- (Mulliken)	P_k^- (NBO)			P_k^- (Mulliken)	P_k^- (NBO)	
9	C 1	0.59	0.56	10	C 1	0.58	0.54	
	C 2	0.38	0.38		C 2	0.07	0.08	
	C 3	0.02	0.04		O 3	0.36	0.37	

carbon is more electrophilically activated than the O4 oxygen (see Table 1). Consequently, the Parr and the PY Fukui functions predict a different regioselectivity in this case. In order to test these local functions, the *meta* and *ortho endo* regioisomeric TSs associated with the P-DA reaction between CD ethylene **5** and enamine **12** were studied to establish the regioselectivity in this hetero-Diels–Alder reaction, and thus, to characterise the most electrophilic centre of CD ethylene **5** (see Scheme 3). The stationary points associated with this P-DA reaction, including their relative energies, are given in Scheme 3. The geometries of the TSs are presented in Fig. 1.

The activation energies associated with the two regioisomeric channels are 11.7 (**TS3no**) and 30.7 (**TS3nm**) kcal mol⁻¹. Therefore, this P-DA reaction is completely regioselective. Note that **TS3nm** is 19.0 kcal mol⁻¹ in energy higher than **TS3no**. On the other hand, the activation energy associated with **TS3no** is 7.0 kcal mol⁻¹ higher in energy than that associated with the P-DA reactions between nitroethylene **4** and enamine **12**,¹¹ in clear agreement with the higher electrophilic character of nitroethylene **4**, $\omega = 2.61$ eV, than that of CD ethylene **5**, $\omega = 2.17$ eV. The energy difference between the two regioisomeric TSs associated with the P-DA reaction of CD ethylene **5** is lower than that associated with the P-DA reaction of nitroethylene **4**, where the *meta* **TS1nm** is 24.5 kcal mol⁻¹ above the *ortho* **TS1no** (see Scheme 1).¹¹ These energy results are in complete agreement with the larger electrophilic local activation at the C1 carbon of nitroethylene **4** than that at the C1 carbon of CD ethylene **5**. However, while the electrophilic Parr function shows the C1 carbon to be the most electrophilic centre of nitroethylenes **4** and **5**, the electrophilic PY Fukui function displays the O4 and O5 oxygen as the most electrophilic centres of CD ethylene **5**, in clear disagreement with the computed regioselectivity.

The geometries of the TSs of the P-DA reaction between CD ethylene **5** and enamine **12** are given in Fig. 1. The lengths of the two forming bonds at the regioisomeric TSs indicate that they correspond to highly asynchronous bond-formation processes. At the most favourable **TS3no**, the σ bond formation begins at the most electrophilic centre of CD ethylene **5** and the most nucleophilic centre of enamine **12**,³ in clear agreement with the analysis of the Parr functions of the reagents.

CT analysis at these TSs indicates that this DA reaction has a large polar character as a consequence of the high electrophilicity of CD ethylene **5** ($\omega = 2.17$ eV) and the high



Scheme 3 Stationary points involved in the P-DA reaction of CD ethylene **5** with enamine **12**. Relative energies, in kcal mol⁻¹, are given in parentheses.

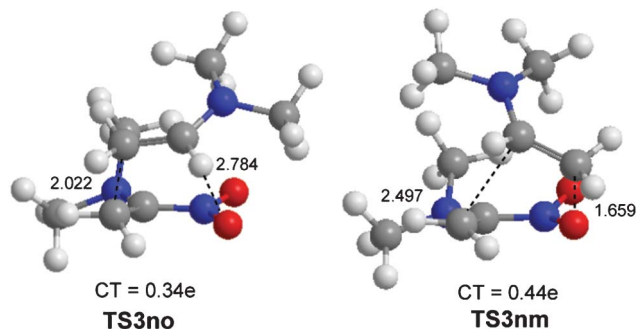


Fig. 1 B3LYP/6-31G⁺ geometries and CT of the *endo* regioisomeric TSs associated with the P-DA reaction between CD ethylene **5** and enamine **12**.

nucleophilicity of enamine **12** ($N = 3.99$ eV) (see Fig. 1). It is noteworthy that the CT at the most unfavourable **TS3nm** is larger than that at **TS3no** as a consequence of the more advanced character of the latter. This behaviour, which has also been observed in other P-DA reactions, allows to establish that along a polar reaction, the CT that takes place globally from nucleophile to the electrophile does not depend on the approach mode of either reagent,^{12,20} as proposed by the FMO theory.

In Fig. 2 it can be seen that a comparison of the ASD of the radical anion (b) with the LUMO (d), and the ASD of the radical cation (c) with the HOMO (e) of CD ethylene **5** indicates that there are no significant differences. Both, the nucleophilic Parr function and the nucleophilic PY condensed Fukui functions predict that the N6 nitrogen is more nucleophilically activated than the C1 carbon. However, a different behaviour is found between the electrophilic Parr function and the electrophilic PY condensed Fukui function. While the Parr function states that the C1 carbon of CD ethylene **5** is more electrophilically activated than the oxygen atoms, the Fukui function predicts that the oxygen atoms are more electrophilically activated than the C1 carbon, in clear disagreement with the computed regioselectivity.

Finally, an analysis of the HOMO_{nucleophile}–LUMO_{electrophile} energy gap for the P-DA reaction between CD ethylene **5** and enamine **12** indicates that, despite its relatively low value (2.96 eV, see Fig. 3), it represents a huge barrier, 68.2 kcal mol⁻¹, unachievable under the usual thermal reaction conditions. Note that the activation energy associated with **TS3no** is 11.7 kcal mol⁻¹. Consequently, no HOMO_{nucleophile}–LUMO_{electrophile} interactions are expected at this stage of the reaction.

iii) Study of the local reactivity in the intramolecular Michael-type addition in Breslow intermediate **14**

Finally, in order to test the Parr functions with more complex molecules, we have analysed the local reactivity in the intramolecular Michael-type addition in Breslow intermediate **14**, which is the key step of Stetter reactions.²⁹ In this kind of reaction, a new C–C bond is formed between a nucleophilic Breslow intermediate and an electrophilically activated double bond. In its intramolecular mode, both nucleophilic and electrophilic frameworks are present in the same molecule.³⁰

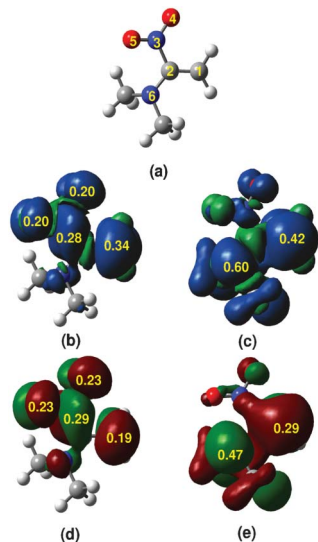


Fig. 2 Maps of (b) ASD of the radical anion and the local electrophilic Parr function values, (c) ASD of the radical cation and the local nucleophilic Parr function values, (d) LUMO and local electrophilic PY condensed Fukui function values, and (e) HOMO and the corresponding local nucleophilic PY condensed Fukui function values of CD ethylene **5** (a).

Very recently, we have theoretically studied the mechanism of the intramolecular Stetter reaction involving Breslow intermediate **14** (see Scheme 4).³¹ Our recently proposed reactivity difference index R_x ,³² which is based on the local electrophilicity/nucleophilicity difference, was used to explain the formation of the C–C bond in the Michael-type addition step. Since both local electrophilicity and nucleophilicity indices were originated from PY Fukui functions, herein we analysed the Parr functions for this complex intermediate. In

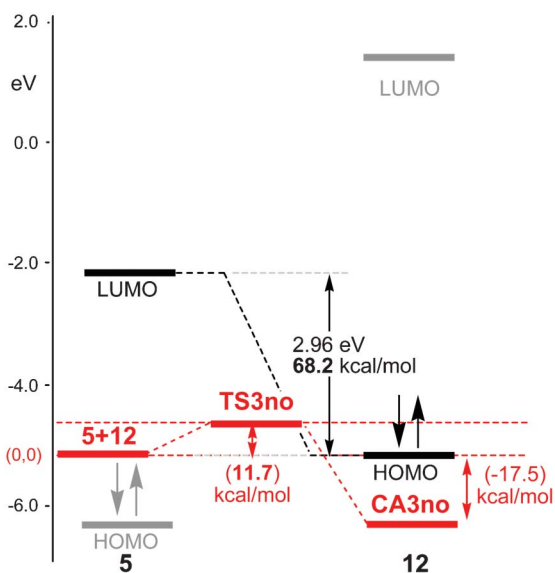


Fig. 3 A schematic representation of the HOMO (**12**)–LUMO (**5**) interaction as proposed by the FMO theory, and the energy profile for the P-DA reaction between CD ethylene **5** and the enamine **12**.

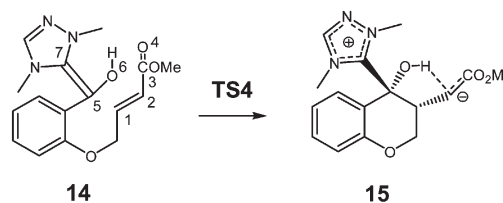
Table 3, the electrophilic and nucleophilic Parr functions, together with the electrophilic and nucleophilic PY and YM Fukui functions for the most relevant heavy atoms of Breslow intermediate **14** are presented.

Table 3 shows that the YM Fukui functions do not agree with the Parr functions nor with the PY Fukui functions as the observed electrophilic/nucleophilic behaviour does not correspond to changes in charge distribution, as proposed by the YM Fukui functions. On the other hand, the Parr functions yield the same pattern for the electrophilic and nucleophilic local activation as the PY Fukui functions. Thus, the Parr functions correctly suggested that the C5 carbon is the most nucleophilic centre of Breslow intermediate **14**, $P_k^- = 0.49$, and that the C1 carbon corresponds to the most electrophilic centre, $P_k^+ = 0.37$. Consequently, the most favourable reactive channel for this intramolecular Michael-type addition will correspond to that associated to the C1–C5 bond formation, in clear agreement with the experimental results. Similar results are obtained with the PY Fukui functions.

However, the HOMO–LUMO energy gap in the Breslow intermediate **14** is 2.64 eV (61.0 kcal mol⁻¹), a value that increases to 3.89 eV (89.65 kcal mol⁻¹) at **TS4**. Moreover, the gas-phase activation energy associated to the C–C bond formation at **TS4** of this Michael-type addition is only 5.55 kcal mol⁻¹.³¹ Consequently, as in the P-DA reaction of CD ethylene **5** with enamine **12**, the LUMO is too high to be reached by the HOMO electrons under the reaction conditions, as proposed by the FMO theory.

ELF bonding analysis along the C–C bond formation step *via* **TS4** suggests that it takes place by a *C-to-C coupling* of two *pseudoradical* centres located at the most electrophilic centre of Breslow intermediate **14** (see monosynaptic basin V(C1), integrating 0.34 e, in Fig. 4a), and the most nucleophilic centre (see monosynaptic basin V(C5), integrating 0.54 e, in Fig. 4a),³¹ in complete agreement with the analysis of the atomic spin density at the radical anion and radical cation of Breslow intermediate **14** (see Fig. 4b and 4c).

In summary, although the Parr and PY Fukui functions give a similar local reactivity pattern in most cases, PY Fukui functions fail in cases of molecules having a concurrent electrophilic and nucleophilic activation. Besides, we have shown that the LUMO of the electrophiles can not be reached under thermal conditions. Therefore, Parr functions allow for a more practical approach to the local reactivity pattern of organic molecules.



Scheme 4 C–C bond formation step in Breslow intermediate **14** in the intramolecular Stetter reaction.

Table 3 Electrophilic and nucleophilic Parr functions, and electrophilic and nucleophilic PY and YM Fukui functions for the most relevant heavy atoms of Breslow intermediate **14** (see atom numbering in Scheme 4)

	P_k^+	P_k^-	PY		YM	
			f_k^+	f_k^-	f_k^+	f_k^-
1	0.37	0.00	0.36	0.00	0.08	-0.03
2	0.10	0.01	0.18	0.01	0.03	0.01
3	0.16	0.00	0.19	0.00	0.09	0.00
4	0.13	0.00	0.15	0.00	0.01	-0.01
5	-0.03	0.49	0.01	0.32	-0.03	0.11
6	0.00	0.05	0.00	0.06	0.02	0.05
7	0.07	-0.07	0.00	0.06	0.01	0.03

Conclusions

Building upon recent studies devoted to bonding changes along a polar reaction, we propose herein two new electrophilic and nucleophilic Parr indices based on the atomic spin density distribution in the radical anion and radical cation of neutral molecules. These indices are based on the observed bond formation along polar reactions, which take place by *centre-to-centre* coupling of two *zwitterionic pseudoradical* species. These studies suggested that the bonding changes demanded for the σ bond formation are favoured by the global CT that takes place in polar reactions. ASD analysis at the radical anion and at the radical cation of the reagents provides the characterisation of the most electrophilic and nucleophilic centres of the molecules, and thus makes it possible to establish the regio- and chemoselectivity in polar reactions.

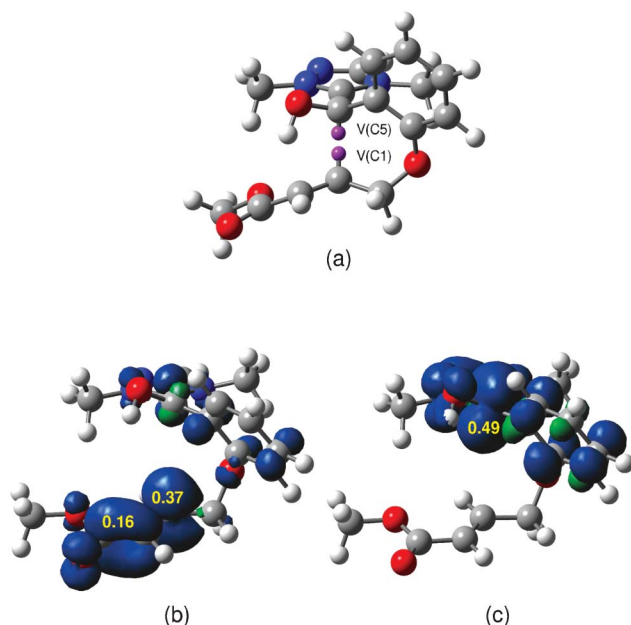


Fig. 4 (a) ELF attractors of the monosynaptic basins V(C1) and V(C5) present at the *zwitterionic pseudodiradical* **TS4**. Maps of (b) ASD of the radical anion and the local electrophilic Parr functions, and (c) ASD of the radical cation and the local nucleophilic Parr functions of Breslow intermediate **14**.

Although the proposed Parr functions give a similar local reactivity as the PY Fukui functions, both are derived from conceptually different reactivity models. We have also demonstrated that PY Fukui functions fail in cases of molecules with concurrent electrophilic and nucleophilic activation.

We have also tested the Parr functions in another more complex system such as the Breslow intermediate in the intramolecular Stetter reaction. The local reactivity given by the Parr electrophilic and nucleophilic functions is in agreement with experimental results.

Finally, our comparative analysis enables us to rule out the use of the YM condensed Fukui functions when computing the local electrophilicity and nucleophilicity indices as they tend to introduce some severe errors.

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