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Invariance of electrophilicity of independent fragments. Application to intramolecular Diels–Alder reactions

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ABSTRACT

We herein demonstrate that the global electrophilicity may be distributed into fragments within a single molecule by using an empirical partitioning scheme of the electronic chemical potential framed on the chemical potential inequality principle. Group electrophilicity for several fragments may thereby be defined. Their values show a remarkable stability, independent of the chemical environment they are attached to. The model is applied to asses the chemical reactivity of a series of fragments involved in intramolecular Diels–Alder reactions.

1. Introduction

The distribution of global electronic properties into fragments or functional groups within a single molecule is a powerful tool to discuss reactivity patterns in intramolecular processes. However, partitioning schemes are in general arbitrary in nature and they may or may not have a chemical meaning. Parr, Ayers, and Nalewajski [1] persuasively argued that concepts like atoms in molecules are ambiguous, in the sense that there is not a unique partition scheme of molecules into atoms which may become consistent with observed chemical trends or experimental data. Gazquez et al. [2] proposed later that while some definitions may be useful in certain cases, there is no unique partitioning that could be experimentally verified or defined. Nevertheless, they have shown that the distribution of local properties, like the Fukui function or the local softness, using a density-based distribution function provides support for the calculation of these fragment properties. This is the case of the Hirshfeld stockholders partitioning [3], which leads to very reliable values of the condensed Fukui function. This result is in agreement with the work of Ayers, Morrison, and Roy [4], in the sense that the same distribution function may be used for several local properties. We add to this argument, that any extensive global property as for instance the global electrophilicity may be conveniently distributed onto fragments or functional groups within a molecule by using the condensed to atom Fukui function as a distribution function [5].

The availability of group properties is particularly relevant for intramolecular processes because there are a significant number of cases where a single molecule may present more than one different reactivity pattern.

For instance, the global electrophilicity index [6]:

$$\omega = \frac{\mu^2}{2\eta} \tag{1}$$

expressed in terms of the electronic chemical potential μ and chemical hardness η has been proposed as a suitable reactivity index to rationalize reactions mechanism in intermolecular Diels–Alder (DA) reactions [7] and 1,3 dipolar cycloadditions [8]. A big difference in electrophilicity of the diene (D)-dienophile (Dp) interacting pair has been interpreted as a measure of the polarity of the process with high charge transfer (CT) at the transition state (TS). A small difference in global electrophilicity on the other hand has been associated with a non-polar mechanism with a vanishing CT at the TS [7,8]. For intramolecular DA (IMDA) processes, these useful reactivity rules may not be immediately transferred, because the presence of two reactivity patterns (i.e., electrophilicity and nucleophilicity of the Dp and D fragments) hampers a clean separation of both properties within the single molecule [9]. There may be cases where this problem dramatically increases, namely, those cases where the frontier molecular orbitals HOMO and LUMO become localized in the same fragment of the molecule. In these cases the frontier molecular orbital (FMO) reactivity theory [10] will certainly fail to describe the reactivity on IMDA processes [9,11]. The present approach is very similar to dual descriptors of reactivity proposed earlier to deal with cycloaddition reactions [12,13].

The availability of stable group properties that are transferable along a set of varying chemical environments is therefore of funda-

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mental importance when discussing reactivity patterns in intramolecular processes. In this work, we present an empirical fragmentation scheme allowing the group electrophilicity of a series of D and Dp fragments present in IMDA processes to be defined from a simple model framed on the electronic chemical potential inequality principle [14]. The resulting model shows that the global electrophilicity of simple molecules may be cleanly partitioned to their corresponding values in their valence state, and that these values are reasonably stable when these fragments are embedded in different chemical environments.

2. Model equations and computational details

Let consider a molecule **M** which may be arbitrarily partitioned into two fragments **A** and **B** say and the corresponding chain of union ($(CH_2)_n$) as shown below (Scheme 1).

For an IMDA process, what we need is the group electrophilicity of fragments **A** and **B** embedded within the framework of the IMDA reagent **M.** For this purpose, we rely on a previous anzats introduced by Meneses et al. [15] to represent a local hardness condensed to atom k in terms of the electrophilic and nucleophilic Fukui functions and the one electron energies of the frontier molecular orbitals HOMO and LUMO, ε_H and ε_L, respectively. It is worth mentioning that this local hardness is defined not derived. This anzats may be used to build up a group hardness associated to the fragments Ω = A, B as:

$$\eta_\Omega = \sum_{k\in\Omega} \eta_k \tag{2}$$

Where

$$\eta_k = If_k^- - Af_k^+ \approx \varepsilon_L f_k^+ - \varepsilon_H f_k^- \tag{3}$$

I and A are the vertical ionization potential and electron affinity, respectively.

We make now the hypothesis that a similar anzats may hold for the electronic chemical potential, which is defined in a finite difference scheme as:

$$\mu = -\left[\frac{I+A}{2}\right] \tag{4}$$

We now write for a fragment:

$$\mu_\Omega = -\sum_{k\in\Omega}\frac{I}{2}f_k^- - \sum_{k\in\Omega}\frac{A}{2}f_k^+ \tag{5}$$

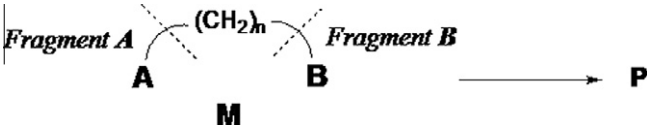
A further simplification to evaluate the group electronic chemical potential of fragments **A** and **B** may be done by using again Koopmans theorem. There results:

$$\mu_A = \sum_{k\in A}\frac{\varepsilon_H}{2}f_k^- + \sum_{k\in A}\frac{\varepsilon_L}{2}f_k^+ \tag{6}$$

and

$$\mu_B = \sum_{k\in B}\frac{\varepsilon_H}{2}f_k^- + \sum_{k\in B}\frac{\varepsilon_L}{2}f_k^+ \tag{7}$$

We propose that in our systems, both **A** and **B** regions may be considered as a non homogeneous electron gas with $\mu_A \neq \mu_B$. This hypothesis is framed on Tachibana et al. model [14,16,17], suggesting that regions A and B may exchange heat, work, and electrons within the whole molecule **M**. Specifically, the chemical potential inequality principle [14] states that *'The constancy of the chemical potential is perturbed if we put an object between a pair of regions, when the transfer of particles is rather inhibited through the interface, bringing about a finite difference in regional chemical potentials even after chemical equilibrium is attained globally'*. In the present case, with reference to Scheme 1, the perturbing body is the methylene chain that bridges fragment A and B within the molecule M. It is worth mentioning that partitions similar to that shown in Scheme 1 revealed that the contribution of the methylene chain to the intramolecular reactivity is negligible [9], thereby suggesting that the chain of union plays the role of the perturbing agent in Tachibanás model. Note that the unperturbed system becomes naturally the intermolecular interaction between A and B.



Scheme 1. Independent fragments partitioning scheme.

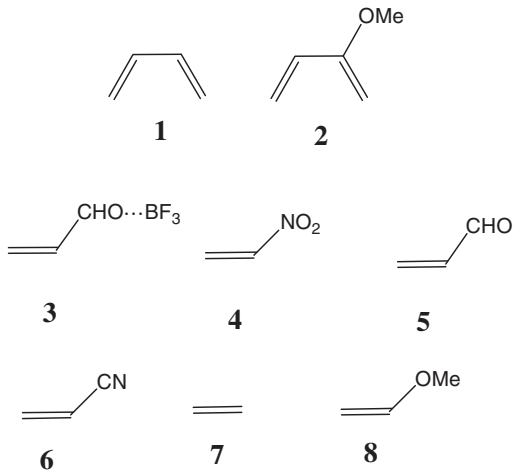
The group electrophilicities of fragments or region **A** and **B**, may therefore be calculated ignoring the contribution of the methylene chain as:

$$\omega_\Omega = \frac{\mu_\Omega^2}{2\eta_\Omega} \tag{8}$$

Therefore the group electrophilicity of fragments **A** and **B** in the molecule **M** may be directly evaluated from Eq. (8), using Eq. (2) to obtain η_A and η_B and Eqs. (6 and 7) to obtain μ_A and μ_B, respectively. The global electrophilicity of the reference isolated fragments was evaluated using Eq. (1).

All structures were optimized using B3LYP/6–31G(d) level of theory using the Gaussian 03 suite of programs[18]. The stationary points were characterized by frequency calculations in order to verify that the TS structures had one and only one imaginary frequency. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method [19] to asses the CT patterns at the TS. Regional Fukui function for electrophilic (f_k^+) and nucleophilic (f_k^-) attacks were obtained from single point

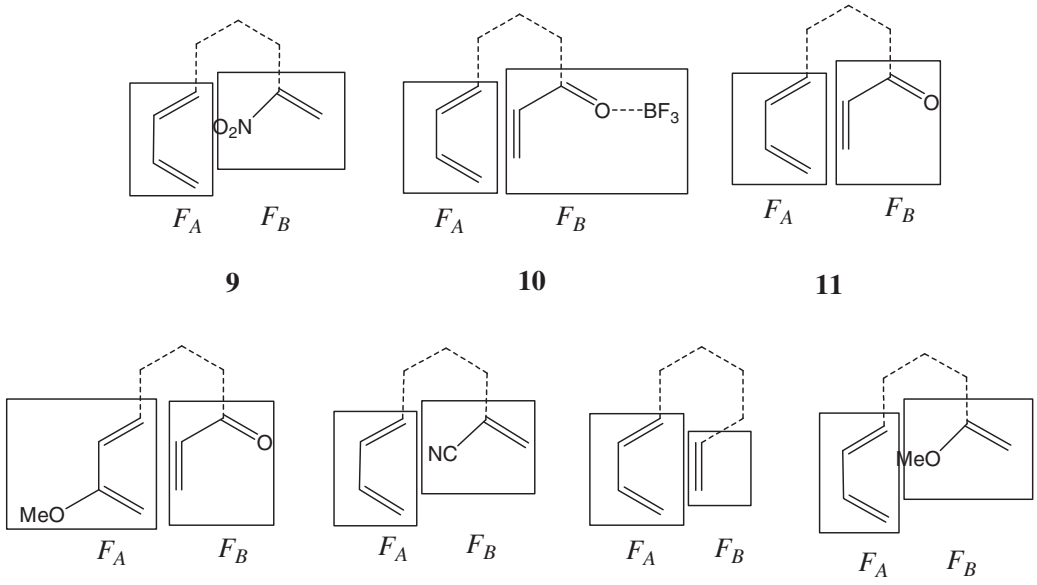
Table 1
Global properties of some isolated molecules present in IMDA processes, as fragments. Electronic chemical potential μ chemical hardness η in a.u. and electrophilicity ω in eV units.



	μ	η	ω
(a) Dienes (D)			
1	−0.1270	0.2083	1.05
2	−0.1154	0.1991	0.91
(b) Dienophiles (Dp)			
3	−0.1837	0.1516	3.20
4	−0.1958	0.2001	2.61
5	−0.1611	0.1921	1.84
6	−0.1726	0.2329	1.74
7	−0.1239	0.2855	0.73
8	−0.0894	0.2564	0.42

Table 2
Global properties of fragments embedded in different chemical environments present in IMDA processes. Electronic chemical potential μ and chemical hardness η in a.u. and electrophilicity ω in eV units.

Molecular fragment



9 **10** **11** **12** **13** **14** **15**

	A			B			$\Delta\omega_\Omega = \lvert\omega_B - \omega_A\rvert$
	μ_A	η_A	ω_A	μ_B	η_B	ω_B	
9	−0.1161	0.1893	0.97	−0.1859	0.1942	2.47	1.50
10	−0.1252	0.1919	1.11	−0.1781	0.1599	2.70	1.59
11	−0.1221	0.1991	1.01	−0.1653	0.2178	1.70	0.69
12	−0.1078	0.1928	0.82	−0.1269	0.1504	1.52	0.70
13	−0.1164	0.1897	0.97	−0.1475	0.2068	1.43	0.46
14	−0.1225	0.1991	0.96	−0.1109	0.2699	0.61	0.35
15	−0.1118	0.1874	0.91	−0.1117	0.2955	0.64	0.27

calculations at the optimized structures of the ground state of molecules by a method described elsewhere [20,21]. The condensation process in the present case is however a little bit different compared to the intermolecular reaction, since the molecular orbitals used are those centred at each molecular fragment and not necessarily the frontier molecular orbitals HOMO and LUMO.

3. Results and discussion

In order to test the reliability and usefulness of the fragmentation scheme for the molecular electrophilicity we evaluated the global electrophilicity ω for a series of simple molecules, present as common reagents in intermolecular DA reactions that are also involved in IMDA processes as fragments. They are compiled in Table 1. Included in this set of molecules are the marginal, **2**, **7** and **8**, and moderate**, 1,** electrophiles, and the strong electrophiles **3**–**6**. The ranking of increasing electrophilicity was reported in a previous work [7]. In Table 2, the electrophilicity of these molecules embedded within more complex molecules that correspond to IMDA reagents **9**–**15** are depicted. Molecule **1** in Table 1 when embedded into IMDA reagents **9**, **10**, **11**, **13**, **14** and **15** shows a remarkable transferability $((\omega_A/\omega)^*100)$ from 1.05 to 0.97 eV (92.3%) in compound **9**, 1.11 eV (105%) in compound **10,** 1.01 eV (96.1%) in compound **11,** 0.97 eV (92.3%) in compound **13,** 0.96 eV (91.4%) in compound **14** and 0.91 eV (86.7%) in compound **15**. The slight electrophilicity excess in compound **10** may be traced to an activating effect promoted by the presence of the Lewis acid (LA) catalyst BF_3 that seems to affect the whole IMDA structure. Note that in those cases where the reference electrophilicity of molecule **1** diminishes: compounds **9**, **11**, **13**–**15**, the slight electrophilic deactivation may be traced to an inductive effect promoted by the chain of union which may be regarded as an electron releasing methylene substitution.

Molecule **2** in Table 1 which presents a global elecrophilicity of 0.91 eV, reduces its electrophilicity to 0.82 eV (*c.a.* 90.1% of transferability) when embedded in the IMDA reagent **12**, a marginal electrophilic deactivation probably due to an electron-releasing effect promoted by the methylene chain. Other good comparisons between isolated molecules and the embedded fragments may be deduced from the comparison of Tables 1 and 2.

A summary of these comparisons is shown in Figure 1a where a remarkable correlation ($R = 0.993$) is observed. The observed slope, 1.18, implies a maximum deviation of approximately 18%. On the other hand, the same trend is observed for the differences in electrophilicity index for both molecular fragments (see Figure 1b). Also included in Table 2 are the values of fragment electrophilicity difference $\Delta\omega_\Omega = |\omega_B - \omega_A|$ which may be used to test, whether or not the empirical reactivity rules derived for intermolecular DA reactions are transferable to IMDA processes [7]. For instance, while the IMDA processes involving compounds **9** and **10** are expected to follow a polar mechanism with significant CT at the TS, $\Delta\omega_\Omega > 1.50$, compounds **11** and **12** are predicted to undergo a polar mechanism with marginal CT at the TS, $0.5 \geqslant \Delta\omega_\Omega \geqslant 1.50$. Compounds **14** and **15** on the other hand are expected to react via a non-polar mechanism with negligible CT at the TS, $\Delta\omega_\Omega < 0.5$ [22].

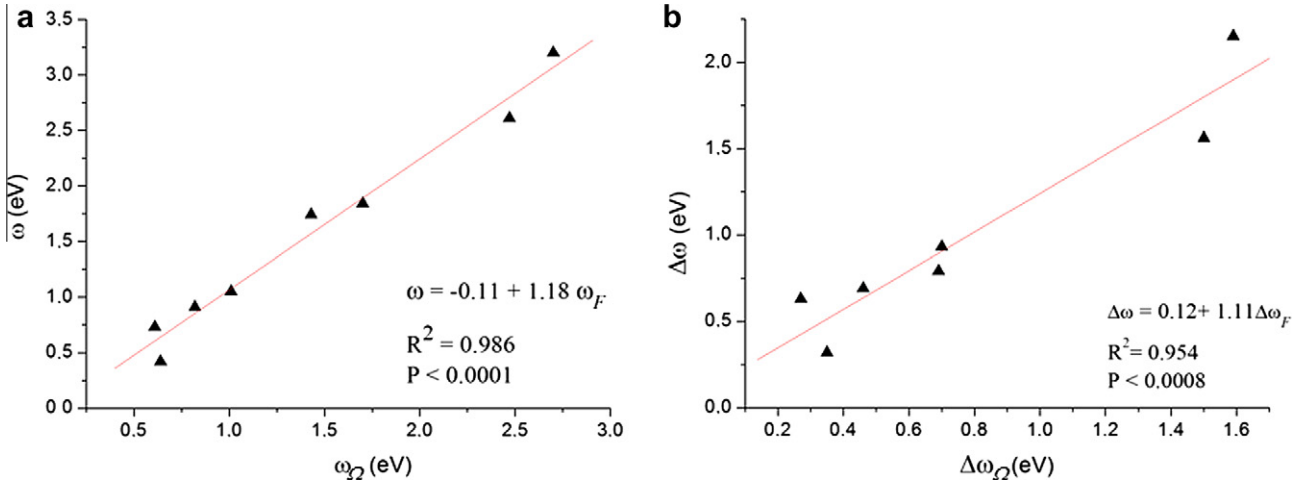


Figure 1. (a) Relationship between global electrophilicity of simple molecules (ω) and group electrophilicity of fragments (ω_Ω; Ω = A,B) embedded in different chemical environments. (b) Electrophilicity difference between global electrophilicity of simple molecules ($\Delta\omega$) and group electrophilicity difference of fragments ($\Delta\omega_\Omega$; Ω = A,B) embedded in different chemical environments.

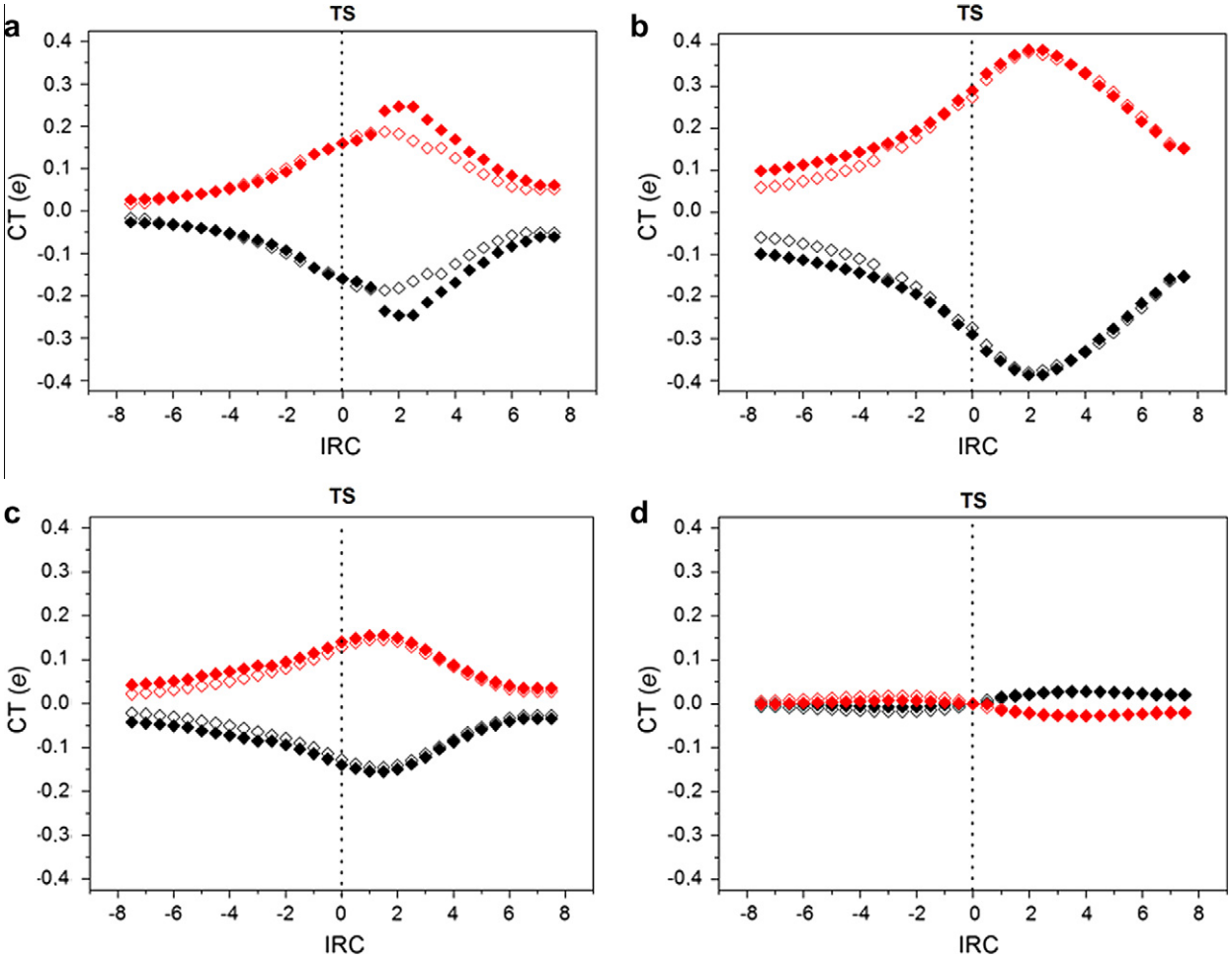
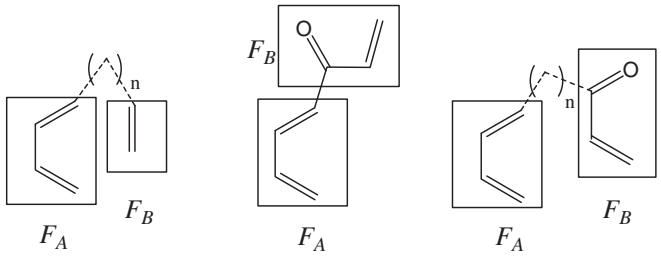


Figure 2. Charge transfer along the intrinsic reaction coordinates (IRC) for intermolecular DA (empty red circles for D moieties and empty black circles for Dp moieties) and IMDA reactions (filled red circles for D moieties and filled black circles for Dp ends). The selected systems for NBO analysis are (a) intermolecular nitroethylene/butadiene; (b) acrolein-BF3 /butadiene complex; (c) acrolein/butadiene and (d) ethylene/butadiene interactions.

In order to check the reliability and usefulness of the empirical reactivity rules derived herein for IMDA processes let us consider the series of compounds **10**, **11** and **14** for which experimental data are available in the literature. Compound **10** has been reported to undergo IMDA reaction within 5 h with a 80% yield with a high selectivity for the *cis* cycloadducts [23]. Compound **11** on the other hand has been reported to undergo an IMDA process within 24 h-5 days to yield about 80% of product with a product distribution

Table 3
Group properties of fragments embedded in different chemical environments. Electronic chemical potential μ and chemical hardness η in a.u. and electrophilicity ω in eV units.

Molecular fragments



16 n=1
17 n=2
18 n=3

19

20 n=1
21 n=2

	A			B			$\Delta\omega_\Omega = \lvert\omega_B - \omega_A\rvert$
	μ_A	η_A	ω_A	μ_B	η_B	ω_B	
16	−0.1146	0.1920	0.93	−0.1028	0.2506	0.57	0.36
17	−0.1170	0.1958	0.95	−0.1110	0.2650	0.63	0.32
18	−0.1163	0.1965	0.94	−0.1117	0.2694	0.63	0.31
19	−0.1132	0.2015	0.87	−0.1621	0.2186	1.64	0.77
20	−0.1110	0.1831	0.92	−0.1678	0.2241	1.71	0.79
21	−0.1130	0.1804	0.96	−0.1660	0.2221	1.69	0.73

consistent with lower *cis–trans* selectivity as compared to compound **10** [23,24]. Compound **14** has been has been reported to undergo IMDA reactions in harsh conditions (340 °C) with an even lower selectivity [25,26].

We have selected these representative molecules plus compound **9** to evaluate the CT pattern along the intrinsic reaction coordinate (IRC) using a NBO population analysis that includes the IMDA processes compared to their intermolecular counterparts. The TS structure used corresponds to the favored *endo-boat* stereoselective channel [9,27]. Figure 2 illustrates the variations in CT along the IRC profile for all four compounds, **9**, **10**, **11** and **14**. This information is a key piece to discuss the useful relationship between CT and $\Delta\omega$. For instance Figure 2a shows the CT/IRC profile for the nitro ethylene/butadiene inter and intramolecular DA reactions. It may be seen that the CT pattern is essentially the same for the intermolecular and intramolecular processes. A substantial CT is observed in the vicinity of the corresponding TS structure. Note that most of the DA reactions have a *one-step two-stage* mechanism through high asynchronous TSs. Along the first stage of the reaction the CT increases to reach the formation of the first C–C sigma bond. At the second stage of the reaction there is a decrease of the CT as a consequence of a back-donation along the formation of the second C–C sigma bond [22]. This result consistently reinforces the transferability of the empirical reactivity rules incorporating the $\Delta\omega$ index, namely a significant $\Delta\omega$ value may be associated with a polar process. Figure 2b for the DA and IMDA reaction of compound **10**, emphasizes this effect. Note that in this case the enhanced CT and polarity of the reaction mechanism may be explained on the basis of the presence of a Lewis acid (LA) catalyst that increases both the $\Delta\omega$ values and the CT. Figure 2c, for the case of compound **11** illustrates the same reaction in the absence of LA catalysts, and it is included for comparison. Finally, Figure 2d, for the case of compound **14**, shows the CT/IRC profile for the non-polar inter and intra DA reactions. It may be seen that a marginal CT is observed along the IRC. This last case consistently matches the small electrophilicity difference shown in Table 2.

Finally, some words regarding the role of the chain of union are worth mentioning. The information required for this analysis is given in Table 3 for $n = 1, 2, 3$. For instance, compounds **16**, **17** and **18** include the ethylene/ butadiene Dp/D pair. It may be seen that the group electrophilicity of these fragments shows a negligible variation with the length of the chain of union. This result may be traced to the fact that the chain of union acts as an efficient spacer for both fragments, even for n small, and those negligible values of electrophilicity are accumulated on it, probable due to the saturated nature of the methylene chain union. Shortening the chain only affects the activation energy [26]. This result is of relevance for it probes the quality of the fragment independent approximation made on our working Eq. (8). The same result is valid for the more polar cases represented by compounds **19**, **20** and **21**. A reviewer called our attention to the fact that in many synthetically useful transformations the linkers (aliphatic chains) include sigma acceptors or donors not considered in this study that may influence the electrophilicity of the fragments. We have performed a quick calculation of a series of alpha-substituted propenes to address the effect of sigma donors and acceptors on electrophilicity. The results show that even in the case of a strong electron donor (OH) the change in electrophilicity with reference to ethene is marginal: it changes from 0,73 eV in ethene to 0,78 eV in 3-hydroxi-1-propene.

In summary, the proposed fragment independent model allows to quantitatively separate the molecular electrophilicity of the D and Dp moieties in IMDA reagents, thereby permitting the empirical reactivity rules derived for intermolecular DA reactions to be almost completely transferred to IMDA processes. In this way we may establish that IMDA processes showing small $\Delta\omega_\Omega$ values will follow a non-polar mechanism with negligible CT at the TS with high activation energy. IMDA processes exhibiting big $\Delta\omega_\Omega$ values will take place via a polar mechanism with substantial CT at the TS with lower activation energy [22].

4. Concluding remarks

We have found that the global electrophilicity of a molecule may be distributed into fragments by using a suitable empirical partitioning scheme. Group electrophilicity for several fragments have been thereby constructed. The fragment elecrophilicity shows a remarkable stability, independent of the chemical environment they are attached to. The model has been applied to asses the

chemical reactivity of a series of fragments involved in IMDA reactions. The empirical reactivity rules derived for intermolecular DA reactions are thereby almost completely transferred to IMDA processes. We therefore establish that IMDA processes showing small $\Delta\omega_{\Omega}$ values will follow a non-polar mechanism channel with negligible CT at the TS with high activation energy, whereas IMDA process exhibiting big $\Delta\omega_{\Omega}$ values will proceed via a polar mechanism with substantial CT at the TS with lower activation energy.

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