Quantitative characterization of group electrophilicity and nucleophilicity for intramolecular Diels–Alder reactions†

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In a previous work (L. R. Domingo, M. J. Aurell, P. Perez and R. Contreras, *Tetrahedron* 2002, **58**, 4417) we proposed that the difference in global electrophilicity index be taken as a measure of the polarity at the transition state in intermolecular Diels–Alder reactions. We herein extend this model to deal with intramolecular Diels–Alder (IMDA) processes. The transferability of the empirical reactivity rules established for the intermolecular DA reactions to the IMDA reactions is discussed. The analysis based on group electrophilicity and nucleophilicity in general fails because having two different reactivity patterns within the same molecule hampers a clean classification of electrophilicity and nucleophilicity of the interacting fragments. We introduce dual philicity indexes *E*1 and *E*2 that solve this problem by separating a series of 30 IMDA reactions into two families, namely the diene to dienophile electron flow (DDpF) and the dienophile to diene electron flow (DpDF) processes. The new indexes correctly describe the charge transfer at the transition state and the reaction mechanism expected for the title reactions.

Introduction

The Diels–Alder (DA) reaction is one of the most useful synthetic reactions in organic chemistry. It corresponds to one of a general class of cycloaddition reactions. By varying the nature of the diene (D) and dienophile (Dp) many different types of six-membered carbocyclic structures can be built up. The intramolecular Diels–Alder (IMDA) reaction is widely used for the construction of contiguous cycles in only one synthetic step. This reaction has been used in the construction of many biological and pharmacological systems and also as a route in the total synthesis of natural products.[1] The reaction generates two new carbon–carbon bonds to produce polycyclic compounds from reactants bearing the D and Dp frameworks in the same molecule.

In a previous article[2] we proposed that the global electrophilicity index[3] introduced by Parr *et al.* could be used as a reliable quantity to classify the electrophilicity of a series of dienes and dienophiles involved in intermolecular DA reactions within a unique relative scale.

Useful information about the polarity at the transition state (TS) structure expected for a given reaction was obtained from the difference in global electrophilicity $\Delta\omega$ of the D/Dp interacting pair. While small electrophilicity differences were related to non-polar mechanisms, big electrophilicity differences were associated with polar mechanisms.[2]

In this work, we extend the model to deal with IMDA reactions with the aim of testing whether or not these empirical rules of reactivity derived for intermolecular DA reactions are transferable for IMDA processes. The focus is put on two main aspects: first of all we establish the degree of transferability of these empirical rules, and secondly, we introduce dual philicity indices that solve the problem of having two different reactivity patterns within a single molecule. The dual philicity indexes permit the transferability of the empirical rules of reactivity derived for intermolecular DA reactions to IMDA processes.

Model equation and computational details

The global electrophilicity index ω introduced by Parr *et al.*[3] is a measure of the stabilization energy when the system acquires an additional electronic charge ΔN from the environment. It was given the following expression:

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

This index incorporates two main contributions that are determinant to establish the quality of an atom or a molecule to behave as a good electron acceptor within a universal scale defined in terms of the electronegativity of the molecule represented by the square of the electronic chemical potential μ, and the chemical hardness η representing the resistance of the system to exchange electrons or fraction of electronic charge with the environment. The global electrophilicity is an extrinsic property of the system, in the sense that it may be recovered from the semi local contributions condensed to atoms,[4]

$$\omega_k = \omega f_k^+ \tag{2}$$

where f_k^+ is the electrophilic Fukui function (*i.e.*, the Fukui function for nucleophilic attack[5]) at the atomic center k. The

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† Electronic supplementary information (ESI) available: Geometries in Cartesian coordinates and total energies for the ground state molecules (S1). Geometries Cartesian coordinates, total energies and imaginary frequencies for transition state structures (S2). Complete reference 9. See DOI: 10.1039/c004628k

electrophilicity of fragments may be easily obtained by using the extensive property described in eqn (2) There results:

$$\omega(Fragment) = \omega_F = \omega \sum_{k \in F} f_k^+ \tag{3}$$

In the previous work devoted to the intermolecular DA processes we arbitrary assigned three categories of electrophiles for a series 32 compounds: strong electrophiles, moderate electrophiles and marginal electrophiles (nucleophiles). In this work we propose a different scheme by introducing a global nucleophilicity index defined by:[6]

$$N = \varepsilon_{HOMO}(Nu) - \varepsilon_{HOMO}(TCE) \tag{4}$$

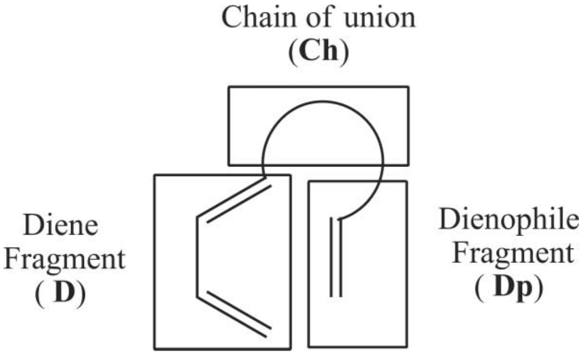
where $\varepsilon_{HOMO}(Nu)$ is the global nucleophilicity of the electron donor Nu, represented by the one electron energy of the HOMO state, and $\varepsilon_{HOMO}(TCE)$ is the global nucleophilicity of tetracyanoethylene, used as reference[7] The (relative) nucleophilicity index N may be conveniently regionalized by using the nucleophilic Fukui function, f_k^- as follows:[7]

$$N_k = N f_k^- \tag{5}$$

Using a similar procedure leading to the definition of group electrophilicity in eqn (3), the fragment nucleophilicity may be readily obtained as:

$$N(Fragment) = N_F = N \sum_{k \in F} f_k^- \tag{6}$$

In this way, electrophilicity and nucleophilicity are conveniently defined as different electronic properties thereby raising the arbitrariness of the previous model.[2] Note however that there is an additional difficulty with the IMDA processes, because this time we have two different reactivity patterns within a single molecule. This problem may be raised using an appropriate partitioning technique which is described in Scheme 1.



Scheme 1 Fragmentation scheme for IMDA.

Therein we define three regions corresponding to the diene moiety (D), the dienophile moiety (Dp) and the chain (Ch) that connects the D and Dp regions. We then evaluated the global electrophilicity and the global nucleophilicity for the series of molecules displayed in Scheme 2 and projected them onto the three regions defined in Scheme 1.

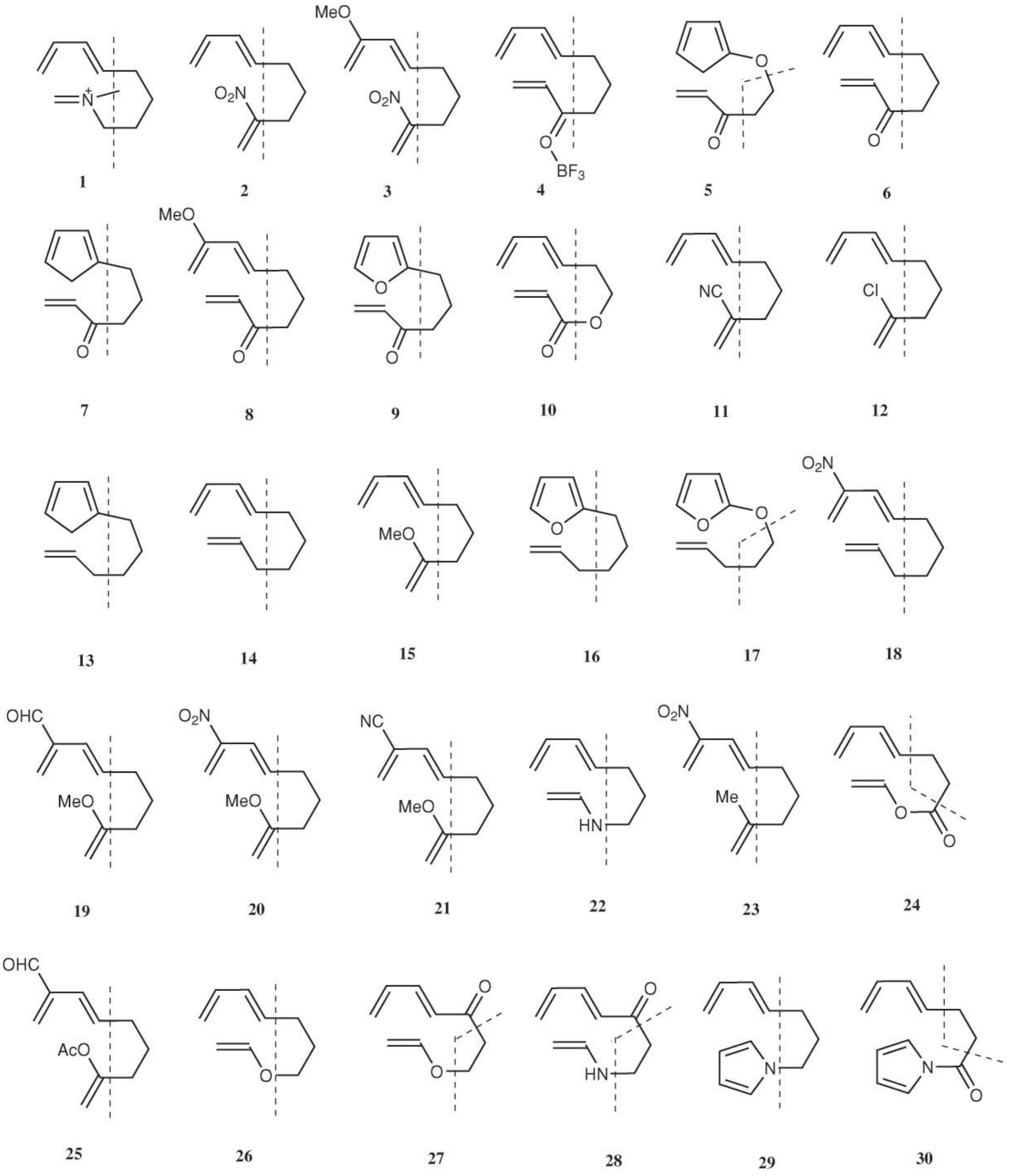
All structures were optimized using B3LYP/6-31G(d) level of theory.[8] All calculations were carried out using the Gaussian 03 suite of programs.[9] The stationary points were characterized by frequency calculations in order to verify that the TS structures had one and only one imaginary frequency. The electronic structures of the stationary point were analyzed by the natural bond orbital (NBO) method[10] to describe the charge transfer (CT) patterns at the TS. This method has been described as reliable to interpret charge transfer based on population analysis using the B3LYP functional.[11] The global electrophilicity was evaluated using eqn (1) and the global nucleophilicity using eqn (4). Regional Fukui functions for electrophilic (f_k^+) and nucleophilic (f_k^-) attacks were obtained from single point calculations at the optimized structures of the ground state of molecules by a method described elsewhere[7b]

Result and discussion

The analysis of the degree of transferability of electrophilicity and nucleophilicity from the intermolecular to the intramolecular regimes is made with reference to the corresponding property of the isolated fragments, ω and N in Table 1. The results describing the group electrophilicity and nucleophilicity according to the partitioning technique defined in Scheme 1 are displayed in Table 1.

It may be seen that in general, the chain of union (Ch) makes marginal contributions to both nucleophilicity and electrophilicity respect to the D and Dp fragments. The second and main result is that the partitioning scheme used reveals the high complexity introduced by the fact of having electrophilic and nucleophilic functionalities within the same molecule: it is impossible to cleanly separate both reactivity patterns for the series of compounds **1–30** in Scheme 2. However, some preliminary conclusions may be drawn by looking at compounds **1–11** in Table 1. For instance, we may conclude that, with respect to the reference electrophilicity ω values; the group electrophilicity of the corresponding IMDA reagent is cleanly accumulated at the Dp moiety. Note that compounds **2**, **3** and **11** show a high degree of transferability (ω_{Dp}/ω) due to the strong electron-withdrawing effect promoted by the $-NO_2$ and –CN substituents at the Dp moiety of these molecules. Note also that for compounds **1**, **4–9**, the degree of transferability slightly diminishes due to the substitution pattern at the Dp moiety. For instance, compounds **4**, **5** and **6** bearing carbonyl substitutions display a lower electron-withdrawing effect on the Dp moiety even in the case where a Lewis acid catalyst is coordinated in compound **4**. Compound **10** significantly diminishes its transferability due to the presence of a low activating ester group bound to the Dp fragment. Compounds **12–17** bear groups that have been classified as moderate electrophiles in the previous intermolecular scale of electrophilicity.[2] Note that the transferability is almost complete towards fragment D. This effect may be traced to the fact that the Dp moiety bears an ethylenic functionality which has been classified as a marginal electrophile,[2] as well as the methoxy-ethylene fragment.

Compounds **18–26** bear fragments that have been classified as strong or moderate electrophiles in reference 2. Note that the electrophilic pattern is now inverted: the electrophilicity is transferred towards the D fragment as a consequence of the inverted substitution pattern, namely electron-withdrawing groups on the D moiety and electron-releasing groups on fragment Dp. These molecules are predicted to undergo Dp to D electron flow (DpDF) IMDA processes with fragment Dp acting as nucleophile and fragment D acting as electrophile. This case corresponds to an inverse electron demand process.



Scheme 2 Set of IMDA reagents selected for study.

Let us now consider the transferability of nucleophilicity between fragments in compounds **1–30**. It may be seen that the nucleophilicity of molecules **1–11** is almost concentrated at fragment D. These compounds are anticipated to undergo D to Dp electron flow (DDpF) IMDA processes with fragment D acting as nucleophile and fragment Dp acting as electrophile (*i.e.* normal electron demand process). For compounds **12–30** however there are two main results: first of all we can observe that there is a group of compounds (**12–18** and **24–26**) where both the electrophilic and nucleophilic patterns are concentrated in the same fragment. This result is interesting for it suggests that the frontier molecular orbital (FMO) prescription fails in IMDA processes: the HOMO and LUMO states are now centered in the same fragment within the molecule. These situations are illustrated in Fig. 1 for some representative cases. One important point worth emphasizing here is that the FMO states are determined by the molecular electronic structure of the whole molecule, whereas the extensive properties of nucleophilicity and electrophilicity allow the electron releasing and electron withdrawing abilities of fragments to be described as group properties within a single molecule.

This makes possible the replacement of the electron demand language (normal or inverse) by a more general language associated

Table 1 Global electrophilicity (ω) and nucleophilicity (N) numbers for isolated fragments, and the corresponding values within the IMDA reagents associated with the partitioning scheme shown in Scheme 1 and the degree of transferability. [a]Electronic properties are given in eV units

	ω	N	ω_{D}	ω_{Dp}	ω_{Ch}	N_{D}	N_{Dp}	N_{Ch}	Degree of transferability ω/%	Degree of transferability N/%
1	9.50	–0.48	0.45	8.89	0.02	–0.44	–0.02	–0.03	93.5 ($\omega Dp/\omega$)	97.7 (ND/N)
2	2.43	3.06	0.00	2.42	0.01	2.87	0.01	0.19	99.0 ($\omega Dp/\omega$)	93.7 (ND/N)
3	2.45	3.41	0.00	2.44	0.01	3.31	0.00	0.10	99.0 ($\omega Dp/\omega$)	97.0 (ND/N)
4	2.92	2.80	0.11	2.67	0.14	2.55	0.09	0.16	91.0 ($\omega Dp/\omega$)	92.0 (ND/N)
5	1.69	4.07	0.01	1.61	0.07	3.96	0.03	0.08	95.3 ($\omega Dp/\omega$)	97.3 (ND/N)
6	1.48	3.13	0.09	1.33	0.05	2.88	0.06	0.19	89.0 ($\omega Dp/\omega$)	92.0 (ND/N)
7	1.41	3.56	0.06	1.30	0.05	3.31	0.05	0.20	92.2 ($\omega Dp/\omega$)	93.0 (ND/N)
8	1.45	3.45	0.08	1.32	0.05	3.32	0.03	0.10	91.0 ($\omega Dp/\omega$)	96.2 (ND/N)
9	1.43	3.28	0.04	1.34	0.05	3.02	0.06	0.20	93.7 ($\omega Dp/\omega$)	92.1 (ND/N)
10	1.42	2.85	0.15	1.21	0.06	2.63	0.04	0.17	85.2 ($\omega Dp/\omega$)	92.3 (ND/N)
11	1.34	2.87	0.02	1.30	0.03	2.65	0.02	0.20	97.0 ($\omega Dp/\omega$)	92.3 (ND/N)
12	1.11	2.99	1.03	0.02	0.05	2.74	0.05	0.21	92.8 ($\omega D/\omega$)	91.6 (ND/N)
13	0.94	3.30	0.85	0.01	0.08	3.00	0.07	0.23	90.4 ($\omega D/\omega$)	90.9 (ND/N)
14	0.90	3.25	0.85	0.01	0.03	3.00	0.07	0.18	94.4 ($\omega D/\omega$)	92.3 (ND/N)
15	0.98	3.14	0.93	0.01	0.04	2.18	0.77	0.20	94.8 ($\omega D/\omega$)	69.4 (ND/N)
16	0.78	3.63	0.73	0.01	0.04	3.36	0.03	0.23	93.6 ($\omega D/\omega$)	92.6 (ND/N)
17	0.49	3.73	0.00	0.45	0.03	3.60	0.02	0.10	92.8 ($\omega Dp/\omega$)	96.5 (ND/N)
18	2.38	2.37	2.37	0.00	0.01	1.98	0.18	0.22	99.5 ($\omega D/\omega$)	83.5 (ND/N)
19	1.68	3.07	1.66	0.00	0.02	0.07	2.91	0.09	98.8 ($\omega D/\omega$)	94.7 (NDp/N)
20	2.30	2.79	2.29	0.00	0.01	0.13	2.60	0.05	99.5 ($\omega D/\omega$)	93.1 (NDp/N)
21	1.59	2.82	1.55	0.00	0.03	0.19	2.58	0.06	97.4 ($\omega D/\omega$)	91.4 (NDp/N)
22	0.86	4.02	0.81	0.01	0.04	0.08	3.68	0.26	94.1 ($\omega D/\omega$)	91.5 (NDp/N)
23	2.42	2.40	2.40	0.01	0.01	0.72	1.51	0.17	99.1 ($\omega D/\omega$)	62.9 (NDp/N)
24	0.98	3.00	0.94	0.00	0.04	2.84	0.00	0.16	95.9 ($\omega D/\omega$)	94.6 (ND/N)
25	1.97	2.67	1.94	0.01	0.02	2.44	0.03	0.20	98.4 ($\omega D/\omega$)	91.3 (ND/N)
26	0.82	3.34	0.79	0.00	0.03	2.51	0.64	0.19	96.3 ($\omega D/\omega$)	75.1 (ND/N)
27	2.18	3.46	2.14	0.00	0.04	0.01	3.30	0.16	98.2 ($\omega D/\omega$)	95,3 (NDp/N)
28	2.11	4.06	2.07	0.01	0.04	0.01	3.80	0.25	98,1 ($\omega D/\omega$)	93,5 (NDp/N)
29	0.96	3.66	0.91	0.00	0.04	0.00	3.64	0.02	94.7 ($\omega D/\omega$)	99.5 (NDp/N)
30	1.23	4.06	0.73	0.42	0.08	0.01	3.80	0.25	59.3 ($\omega D/\omega$)	92.9 (NDp/N)

[a] The chain of union only consider fragments of the type $(CH_2)_n$. See Scheme 2.

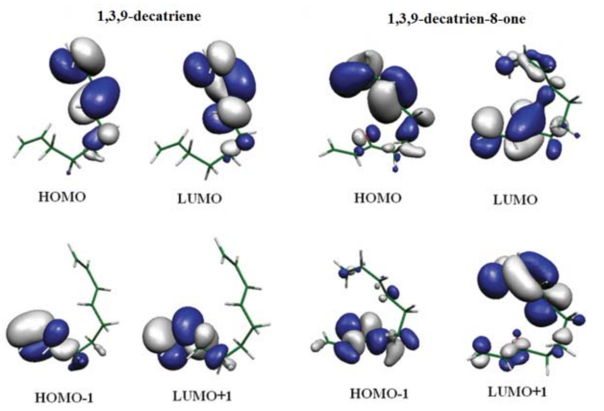
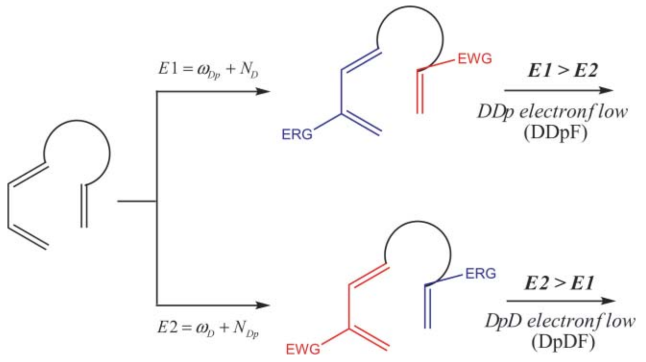


Fig. 1 Frontier molecular orbitals for 1,3,9-decatriene and 1,3,9-decatrien-8-one.

to electrophiles and nucleophiles. Note that this notation is more general for it embodies those cases where the HOMO and LUMO states are located in the same fragment for IMDA processes.

Although the previous analysis shed some useful light for the understanding of IMDA processes, the complexity arising from the fact of having nucleophilicity/electrophilicity patterns present in the same molecule makes the ordering of group reactivity a rather complex task. Some progress can be made however if we introduce an additional empirical scheme to rationalize group reactivity for IMDA processes. It is founded on the fact that the CT between groups within a molecule satisfies the electro-neutrality condition: $\Delta N = \Delta N_{D} + \Delta N_{Dp} + \Delta N_{Ch}$.

This condition leads to the definition of two new reactivity indexes, one for the DDpF and a second one for the DpDF IMDA processes. They are sketched in Scheme 3.



Scheme 3 Partition model for IED and NED IMDA processes.

The corresponding expressions are:

$$E1 = \omega_{Dp} + N_{D} \tag{7}$$

$$E2 = \omega_{D} + N_{Dp} \tag{8}$$

In this way, if $E1 > E2$ the process is expected to follow a DDpF channel and if $E1 < E2$, then the process will follow an DpDF IMDA process. Note that for cases where $E1 \approx E2$, the model

Table 2 Electrophilicity–nucleophilicity index $E1$, $E2$ and $\Delta E12$ in eV units and charge transfer at the TS in e units

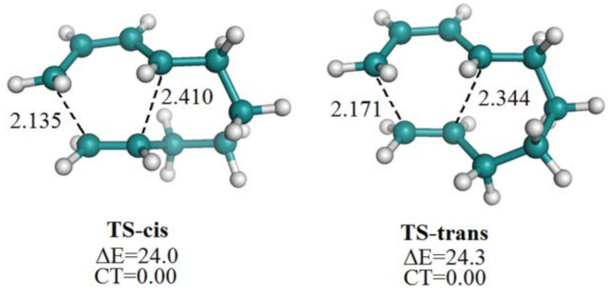
	$E1$	$E2$	$\Delta E12$	CT	Electron flux	Expected mechanism
1	8.46	0.43	8.03	0.57	DDpF	Polar
2	5.29	0.01	5.28	0.16	DDpF	Polar
3	5.75	0.00	5.75	0.23	DDpF	Polar
4	5.22	0.21	5.01	0.29	DDpF	Polar
5	5.02	0.04	4.98	0.19	DDpF	Polar
6	4.22	0.15	4.07	0.14	DDpF	Polar
7	4.61	0.11	4.50	0.16	DDpF	Polar
8	4.64	0.11	4.53	0.18	DDpF	Polar
9	4.36	0.10	4.26	0.19	DDpF	Polar
10	3.84	0.19	3.65	0.10	DDpF	Polar
11	3.94	0.04	3.90	0.13	DDpF	Polar
12	2.76	1.08	1.68	0.04	Negligible	Non-polar
13	3.01	0.92	2.09	0.05	Negligible	Non-polar
14	3.01	0.93	2.08	0.00	Negligible	Non-polar
15	2.19	1.70	0.49	0.00	Negligible	Non-polar
16	3.37	0.76	2.61	0.00	Negligible	Non-polar
17	3.51	0.02	3.49	0.07	Negligible	Non-polar
18	1.98	2.54	−0.56	0.16	DpDF	Polar
19	0.07	4.57	−4.50	0.27	DpDF	Polar
20	0.14	4.89	−4.75	0.26	DpDF	Polar
21	0.19	4.13	−3.94	0.21	DpDF	Polar
22	0.09	4.49	−4.40	0.11	DpDF	Polar
23	0.72	3.92	−3.20	0.15	DpDF	Polar
24	2.84	0.94	1.90	0.01	Negligible	Non-polar
25	2.45	1.97	0.48	0.08	Negligible	Non-polar
26	2.51	1.43	1.08	0.05	Negligible	Non-polar
27	5.44	0.01	−5.43	0.11	DpDF	Polar
28	5.87	0.02	−5.85	0.20	DpDF	Polar
29	4.55	0.00	−4.55	0.09	Negligible	Non-polar
30	4.53	0.43	−4.10	0.03	Negligible	Non-polar

predicts that the IMDA process will follow a non-polar channel with negligible CT at the TS. In order to test this hypothesis we compared the $E1$ and $E2$ indexes with the CT at the TS. For this purpose, we located the TS structures for the IMDA processes of the 30 compounds shown in Table 1. It is worth emphasizing here that IMDA reactions can present an *endo*-boat like or an *exo*-boat like selectivity. However, following a result reported by Houk *et al.*,[12] the *endo* boat like channel is favoured. These structures were selected for further analysis. The geometry and energies of the TS structures for the 30 reactions studied are given as supporting information to this work. Once the TS structures were located, we performed a NBO population analysis to assess CT at the TS. The results are summarized in Table 2.

From the calculated $E1$, $E2$ evaluated at the ground state and CT values evaluated at the TS, the following empirical reactivity rules may be outlined: (i) IMDA processes showing $E1 > E2$ may be classified as DDpF polar process; (ii) those processes where $E1 < E2$ may be classified as DpDF polar process and (iii) when $E1 \approx E2$, the process may be consistently classified as non-polar process. Note that for processes classified as (i) the difference $\Delta E12 = E1 - E2$ is big and positive and is consistently associated with a relatively high CT, in agreement with the rules derived for the corresponding intermolecular processes. For those cases classified as (ii), the difference $\Delta E12$ is big and negative with a relatively high CT at the TS of the reaction. Note also that the IMDA processes characterized by negligible $\Delta E12$ values are consistently classified as non-polar with a negligible CT at the TS.

Rules (i) and (ii) also match the empirical criterion derived for intermolecular processes. Note that despite the fact that compound **29** shows a high concentration of nucleophilicity at the Dp fragment, the corresponding process is predicted as non-polar. This result suggests that the polarity of the process depends mostly on a high electrophilicity value at any of both fragments, thereby suggesting that during an electrophile–nucleophile interaction the effect of electrophilicity outweigh the effect of nucleophilicity. In the case of compound **29** we have a high group nucleophilicity at the Dp moiety and a vanishing group electrophilicity value at the D end of the molecule. This requisite of high electrophilicity value before the process can be labeled as polar may be traced to the different role that electrophiles and nucleophiles play in their mutual interactions: while the nucleophile is expected to be a good electron releasing molecule or fragment, a property mainly determined by a high value of its electronic chemical potential, the electrophilic group or molecule must be soft enough to accept the transferred charge and then to rearrange it within the electrophilic structure, a molecule in the case of intermolecular process or a group in the case of an intramolecular process.

In order to illustrate the reliability and usefulness of the reactivity rules derived herein we may note the following features. The reaction of 1,3,9-decatriene, **14**, to yield decalins requires 340 °C at normal pressure with 95% yield and a product distribution 52 : 48 after 0.5 h.[13] Despite the lowering in activation entropy the activation free energy shows moderate lowering with respect to the intermolecular counterpart ethylene + butadiene reaction.[14] Note that this reaction presents two reactive channels, namely, those leading to the *cis*-decalinic and *trans*-decalinic cycloadducts. The selectivity and thermodynamic activation parameters have been elucidated by Houk *et al.*[15] These authors reported a difference in activation free energy of *ca.* 0.3 kcal mol^{-1} for the *cis* and *trans* channels. We re-evaluated this free energy profile at the B3LYP/6-31G(d) level of theory and found approximately the same difference. The TS structure is shown in Fig. 2. However the most relevant feature is that the population analysis suggests no CT at all, so that the process may be safely classified as non-polar, in agreement with the empirical rules derived herein.

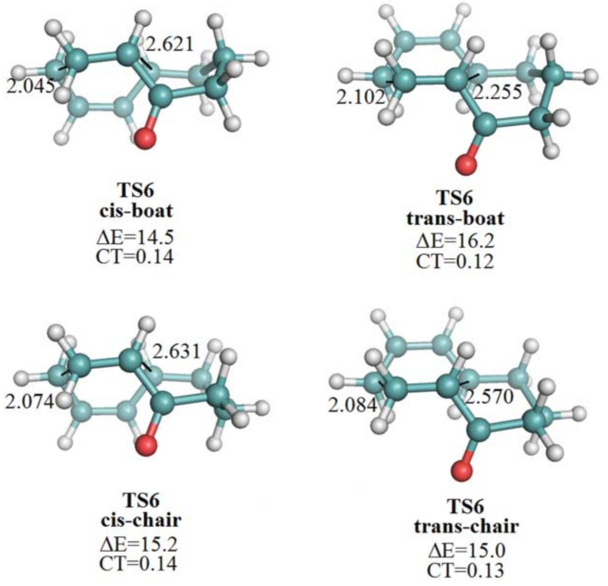


TS-cis
ΔE=24.0
CT=0.00

TS-trans
ΔE=24.3
CT=0.00

Fig. 2 Geometries of transition states for IMDA reaction of the 1,3,9-decatriene. Relative energy (ΔE) in kcal mol^{-1}, charge transfer CT in e units and bond distances in Å.

The intramolecular conversion of 1,3,9-decatrien-8-one, **6**, on the other hand goes under normal conditions of pressure and temperature.[16] It may be moderately accelerated in the presence of a Lewis acid.[17] This reaction proceeds through four stereo selective channels, depending on the chain conformation at the TS. They can have two chair-like and two boat like *cis*/*trans* selectivity. The corresponding TS structures are depicted in Fig. 3. Note that the favored channels display activation energies from 0.5 to 1.7 kcal mol^{-1} with respect to the *cis*-boat like approximation.



TS6
cis-boat
ΔE=14.5
CT=0.14

TS6
trans-boat
ΔE=16.2
CT=0.12

TS6
cis-chair
ΔE=15.2
CT=0.14

TS6
trans-chair
ΔE=15.0
CT=0.13

Fig. 3 Geometries of transition states for the four possible channels of the IMDA reaction for 1,3,9-decatrien-8-one. Relative energy (ΔE) in kcal mol^{-1}, charge transfer CT in *e*. and bond distances in Å.

Consistently, the evaluated CT at the TS stage is about 0.14*e*, a value which is consistently close to the CT pattern obtained for the corresponding intermolecular process, namely acrolein + butadiene cycloaddition (0.11*e*).[18] This result stresses the degree of transferability quoted in Table 1.

Finally, experimental plus theoretical studies show that the *cis*/*trans* conformations associated with the reaction products do not present significant variations in CT so that the lowering in selectivity may be cleanly associated with the strain induced by the chain of union.[19] In summary, the dual index introduced in this work consistently explain the reactivity and the reaction mechanism on electronic basis. Selectivity requires a thorough study of the effect induced by the chain of union.

Concluding remarks

We have shown that the empirical rules relating the electrophilicity/nucleophilicity differences with the polarity at the TS may be transferred to IMDA processes. Two main points have been addressed: first, the transferability of the empirical reactivity rules established for the intermolecular DA cycloadditions to the IMDA is not direct because the problem of having two different reactivity patterns, namely electrophilicity and nucleophilicity present in a single molecule. This problem hampers a clean classification of electrophilicity and nucleophilicity of the interacting fragments. Secondly, we have introduced dual philicity indices $E1$ and $E2$ that solve this problem by separating a series of 30 IMDA cycloadditions into two families, namely the DDpF and DpDF processes. The new indices enable the transfer of the empirical rules deduced for the intermolecular cycloadditions to the IMDA processes. The dual group philicity indexes introduced in this work consistently explain the reactivity and the reaction mechanism on electronic basis, while stereo selectivity requires a thorough study of the effect induced by the chain of union. Work along this line is in progress in our group.

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References

1 (*a*) M. Juhl and D. Tanner, *Chem. Soc. Rev.*, 2009, **38**, 2983; (*b*) K. Takao, R. Munakata and K. Tadano, *Chem. Rev.*, 2005, **105**, 4779; (*c*) W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford, 1990.
2 L. R. Domingo, M. J. Aurell, P. Pérez and R. Contreras, *Tetrahedron*, 2002, **58**, 4417.
3 P. G. Parr, L. von Szentpaly and S. Liu, *J. Am. Chem. Soc.*, 1999, **121**, 1922.
4 L. R. Domingo, M. J. Aurell, P. Pérez and R. Contreras, *J. Phys. Chem. A*, 2002, **106**, 6871.
5 (*a*) R. G. Parr and R. G. Pearson, *J. Am. Chem. Soc.*, 1983, **105**, 7512; (*b*) R. G. Parr, W. Yang, *Density Functional Theory from Atoms and Molecules*, Oxford University, New York, 1989.
6 L. R. Domingo, E. Chamoro and P. Pérez, *J. Org. Chem.*, 2008, **73**, 4615.
7 (*a*) R. Contreras, J. Andres, V. S. Safont, P. Campodonico and J. G. Santos, *J. Phys. Chem. A*, 2003, **107**, 5588; (*b*) R. Contreras, P. Fuentealba, M. Galván and P. Pérez, *Chem. Phys. Lett.*, 1999, **304**, 405.
8 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
9 M. J. Frisch, *et al. Gaussian 03, Revision C.02*, Gaussian: Wallingford, CT, 2004.
10 A. E. Reed, L. A. Curtiss and F. Weinhold, *Chem. Rev.*, 1988, **88**, 899.
11 C. Alemán, D. Curcó and J. Casanovas, *Phys. Rev. E*, 2005, **72**, 26704.
12 D. J. Tantillo, K. N. Houk and M. E. Jung, *J. Org. Chem.*, 2001, **66**, 1938.
13 Y.-T. Lin and K. N. Houk, *Tetrahedron Lett.*, 1985, **26**, 2269.
14 (*a*) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, 1928, **460**, 98; (*b*) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 781.
15 (*a*) F. K. Brown and K. N. Houk, *Tetrahedron Lett.*, 1985, **26**, 2297; (*b*) L. Raimondi, F. K. Brown, J. Gonzalez and K. N. Houk, *J. Am. Chem. Soc.*, 1992, **114**, 4796; (*c*) M. K. Diedrich, F.-G. Klärner, B. R. Beno, K. N. Houk, H. Senderowittz and W. C. Still, *J. Am. Chem. Soc.*, 1997, **119**, 10255.
16 J. L. Gras and M. Bertrand, *Tetrahedron Lett.*, 1979, **20**, 4549.
17 D. A. Smith, K. Sakan and K. N. Houk, *Tetrahedron Lett.*, 1986, **27**, 4877.
18 V. B. Blankenburg, H. Fiedler, M. Hampel, H. G. Hauthal, G. Just, K. Kahlert, J. Korn, K.-H. Müller, W. Pritzkow, Y. Reinhold, M. Röllig, E. Sauer, D. Schnurpfeil and G. Zimmermann, *J. Prakt. Chem.*, 1974, **316**, 804.
19 (*a*) T. N. Cayser, L. S-M Wong, P. Turner, M. N. Paddon-Row and M. S. Sherburn, *Chem.–Eur. J.*, 2002, **8**, 739; (*b*) T. N. Cayser, M. N. Paddon-Row, D. Moran, A. D. Payne, M. S. Sherburn and P. Turner, *J. Org. Chem.*, 2005, **70**, 5561; (*c*) M. N. Paddon-Row, A. I. Longshaw, A. C. Willis and M. S. Sherburn, *Chem.–Asian J.*, 2009, **4**, 126; (*d*) A. G. Fallis, *Acc. Chem. Res.*, 1999, **32**, 464.