

## A Useful Classification of Organic Reactions Based on the Flux of the Electron Density

Luis R. Domingo, Mar Ríos-Gutiérrez ✉

Department of Organic Chemistry, University of Valencia, Dr. Moliner 50, 46100 Burjassot, Valencia, Spain

✉ Correspondence to: m.mar.rios@uv.es

**Abstract:** A useful classification of polar organic reactions in Forward Electron Density Flux (FEDF) and Reverse Electron Density Flux (REDF), based on the unambiguously analysis of the direction of the flux of the global electron density transfer (GEDT) at the transition state structures (TSs), has been recently proposed (RSC Adv. 2020, 10, 15394) within the Molecular Electron Density Theory. Further, non-polar reactions have been classified as Null Electron Density Flux (NEDF) (Eur. J. Org. Chem. 2020, 5938). This classification allows characterizing the nucleophilic/electrophilic species participating in polar reactions. Analysis of the electronic chemical potential  $\mu$ , and the electrophilicity  $\omega$  and nucleophilicity  $N$  indices, defined within Conceptual DFT, at the ground state (GS) of the reagents also permits to establish this classification of polar reactions.

**Keywords:** polar reactions, global electron density transfer, electron density flux, molecular electron density theory

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### Introduction

One of the most useful classifications of the organic reactions is in non-polar and polar reactions. While non-polar reactions are experienced mainly by hydrocarbons, many of the polar reactions are characteristic of organic molecules containing C–X, C=X and C≡X functional groups, where X is a heteroatom. Unsaturated hydrocarbon compounds also

experience polar reactions when they are adequately substituted by electron-withdrawing (EW) or electron-releasing (ER) groups. While non-polar reactions usually present high activation energies, the energetic barrier of polar reactions is low; *i.e.* the more polar the reaction, the faster.

The concept of polar reactions in organic chemistry was used at the beginning of the past century. Unlike inorganic chemistry, which is associated mainly with the chemistry of ionic and metallic compounds, organic chemistry is associated with the molecular chemistry of species covalently bound. This important structural difference also causes a different reactivity; while the ionic chemistry is mainly thermodynamically controlled, molecular chemistry is kinetically controlled as it demands changes in the ground state (GS) electronic structure. In other words, in organic chemistry activation energies control reactions.

The polar character of the reactions depends on the electrophilicity and the nucleophilicity of the reagents. These concepts were introduced by K. Ingold [1], who replaced the terms 'anionoid' and 'cationoid' proposed earlier by A. J. Lapworth in 1925 [2]. Ingold proposed the nucleophilic (nucleus-seeking) and electrophilic (electron-seeking) species as a generalization of the concepts of bases and acids, defined by Lewis as species the neutralization of which involves the donation or acceptance of an electron-pair. However, while nucleophilicity and electrophilicity emphasized the kinetic aspect of reactivity, the Lewis basicity and acidity emphasized the thermodynamic aspect of the Lewis adduct formation.

Based on these kinetic properties, an unambiguous classification of organic reactions in Forward Electron Density Flux (FEDF) [3], Reverse Electron Density Flux (REDF) [3], and Null Electron Density Flux (NEDF) [4], has been recently proposed within the Molecular Electron Density Theory (MEDT) [5]. This classification allows characterizing the nucleophilic/electrophilic species participating in polar reactions. With the purpose of gathering this classification in a single reference, in this mini-review, the scientific background that led to establish it is summarized, providing some examples of its application. Despite only cycloaddition reactions are gathered herein because the traditional classifications were established for them, the proposed classification applies to any type of organic reaction.

## **Discussion**

### Molecular orbitals and chemical reactivity

Based on the molecular orbital (MO) theory [6], developed in 1930 as an approximation to the resolution of the Schrödinger's equation (see Equation 1) [7], in 1964 K. Fukui proposed the Frontier Molecular Orbital (FMO) theory [8] to study how molecules

react with each other. FMO theory, which establishes that “*the most favorable interaction along a chemical reaction will take place by overlapping and mixing the HOMO and LUMO with the lowest energy separation in such a manner that the rate of reaction is inversely related to the energy gap*”, is still widely used today to study the reactivity in organic chemistry [9].

$$H\Psi = E\Psi$$

*Schrödinger equation*

Equation 1

Both, atomic orbitals (AOs) and MOs are only mathematical artefacts created to approach the Schrödinger's equation resolution. On the other hand, it is important to remember that Schrödinger expressed that the wavefunction  $\Psi$  has no physical significance; but rather the square of the wavefunction  $\Psi$  can be related with the probability to locate electrons. Unfortunately, similar to the wavefunction  $\Psi$ , the square of a MO was associated with the probability to find electron pairs in a molecule. It is also interesting to comment on that while Hückel used simple hydrogenoid-like AOs to study unsaturated hydrocarbons in 1931 [10–13], today quantum chemistry (QC) uses complex mathematical representations named basis sets.

### Sustmann and Houk classifications of cycloaddition reactions

In 1972, R. Sustmann applied, for the first time, the FMO theory to the study of the mechanism of [3+2] cycloaddition (32CA) reactions [14]. Depending on the relative disposition of the HOMO and LUMO of the three-atom-component (TAC) and the ethylene in the MO energy diagram, Sustmann classified 32CA reactions into three types (see Fig. 1) [15]: (i) in *type-I* (generally referred to as “*normal electron demand*”), the dominant FMO interaction is that of HOMO<sub>TAC</sub> with LUMO<sub>ethylene</sub>; (ii) in *type-II*, FMO energies of the TAC and the ethylene derivative are similar, so that both have to be considered; and finally, (iii) *type-III* cycloadditions (generally referred to as “*inverse electron demand*”) are dominated by interactions between LUMO<sub>TAC</sub> and HOMO<sub>ethylene</sub>. However, Sustmann concluded that, “*though a plethora of data could be explained in a unifying model, molecules are more than HOMOs and LUMOs and, thus, one should not try to overdraw this model based on an oversimplified one-electron treatment of the Hückel type*”. [15]

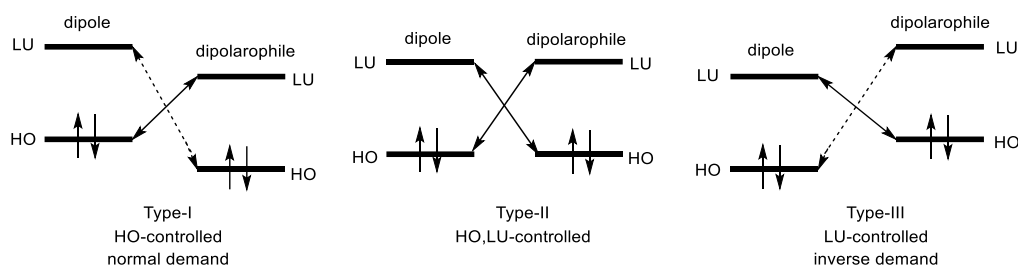


Fig. 1. Sustainmann's classification of 32CA reactions and Houk's terminology.

Later, in 1973, K. N. Houk calculated a set of FMO energies and coefficients for ten parent and some substituted nitrilium betaines, diazonium betaines, azomethinium betaines and carbonyl betaines, and for a series of substituted alkenes, with the aim of rationalizing and predicting relative rates and regioselectivities of 32CA reactions [16]. He renamed the three Sustainmann's types as HO-controlled (*type-I*), HO,LU-controlled (*type-II*) and LU-controlled (*type-III*) reactions (see Fig. 1) and, based on these generalized FMOs, provided a qualitative explanation for the differential reactivity and regioselectivity phenomena [17].

### Density Functional Theory (DFT) and the Conceptual DFT (CDFT)

Based on the theorems by P. Hohenberg and W. Kohn, a new QC theory to study the electronic structure of the matter, known as Density Functional Theory (DFT) [18], in which the GS energy of a non-degenerated N electron system is only a functional of the electron density  $\rho(\mathbf{r})$ , was developed in 1964 (see Equation 2). Similar to the QC theory based on Schrödinger's equation (see Equation 1) [7], the resolution of the functional of the electron density  $\rho(\mathbf{r})$  for a complex system is neither computationally feasible. As an approximation, W. Kohn and L. J. Sham proposed in 1965 the Hartree-Fock equations to obtain the matrix of the electron density, which is further used in the resolution of Hohenberg-Kohn's equation [19]. However, it is important to emphasize that within the DFT framework, the Kohn-Sham orbitals do not define any wavefunction although they are only used to calculate the one-electron density distribution function [19]. Nonetheless, it is important to highlight that MOs are not physical observables but only mathematical constructs that cannot be determined by experiment [20]. In contrast, the electron density distribution in a molecule or crystal can be observed by electron diffraction and X-ray crystallography [21, 22]; and it can also, and often more readily, be obtained from *ab initio* or DFT calculations.

$$E[\rho(\mathbf{r})] = \int \rho(\mathbf{r})v(\mathbf{r}) d\mathbf{r} + F[\rho(\mathbf{r})] \quad \text{Equation 2}$$

*Hohenberg-Kohn equation*

One of the most relevant traits of the density functional language is its suitability for defining and elucidating important chemical concepts of molecular structure and reactivity.

Parallel to the development of QC models to approach the Hohenberg-Kohn equation [18], R. G. Parr developed the so-called Conceptual DFT (CDFT) in the late 1970s and early 1980s [23].

CDFT tries to extract from the electron density  $\rho(\mathbf{r})$  relevant concepts and principles that make it possible to understand and predict the chemical behavior of a molecule. Parr and co-workers, and later a large community of theoretical chemists, have been able to give precise definitions for chemical concepts which had already been known and used for many years in various branches of chemistry. Concepts such as the electronic chemical potential  $\mu$  [24], which is the opposite of the electronegativity  $\chi$ , and the chemical hardness  $\eta$  [24], are the most noticeable examples, thus providing their calculations with a quantitative use.

In 1999, R. G. Parr introduced the electrophilicity  $\omega$  index [25], and further in 2008 L. R. Domingo introduced the empirical relative nucleophilicity  $N$  index [26]. These reactivity indices provide a quantitative rationalization of chemical concepts developed at the beginning of the past century such as the nucleophilic and electrophilic reactivity in organic chemistry [1]. The analysis of the electronic chemical potential  $\mu$ , the electrophilicity  $\omega$  index and the nucleophilicity  $N$  index have become powerful tools to study many of the most relevant organic reactions [27, 28].

### The Molecular Electron Density Theory (MEDT)

The development of QC tools at the end of the past century, able to perform a topological analysis of the molecular electron density  $\rho(\mathbf{r})$  obtained by *ab initio* Hartee-Fock [29] or DFT calculations, such as the Quantum Theory of Atoms in Molecules [30, 31] (QTAIM) and the Electron Localization Functions [32] (ELF), have allowed proving the inconsistency of the MOs to interpret chemical structure, and consequently, chemical reactivity. Many QTAIM and ELF studies carried out in the present century of relevant organic reactions, such as Diels-Alder (DA) and 32CA reactions, which were interpreted during the end of the past century as pericyclic reactions by means of the FMO theory [33], have shown that at most of the transition state structures (TSs) of these reactions, formation of the new C–C or C–X single bonds has not yet begun [34, 35]. QTAIM topological analysis of the electron density  $\rho(\mathbf{r})$  at the TS associated with the DA reaction between butadiene **1** and ethylene **2**, which is considered as the prototype of pericyclic reactions, indicates that the critical points (CPs) corresponding to the C–C interacting regions have no covalent nature as they have a  $\nabla^2\rho(\mathbf{r}) > 0$  (see Fig. 2).

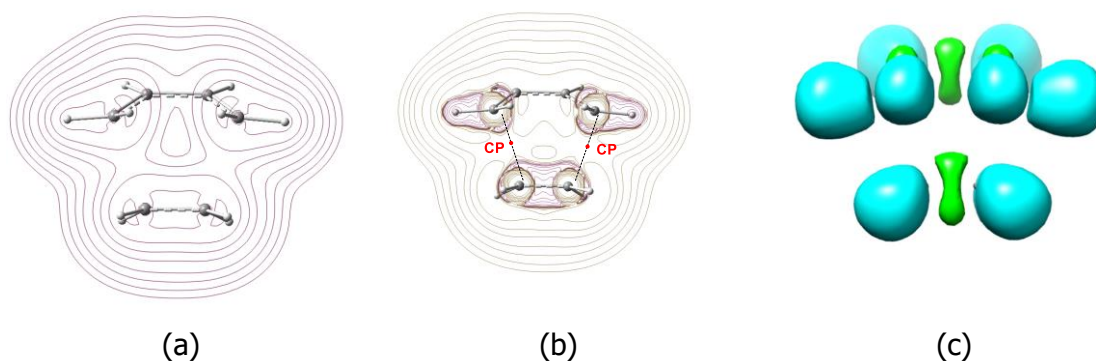


Fig. 2. (a) map of the electron density  $\rho(\mathbf{r})$ , (b) map of the Laplacian of the electron density  $\nabla^2\rho(\mathbf{r})$ , (c) ELF valence basins of the TS associated to the N-DA reaction between butadiene **1** and ethylene **2**.

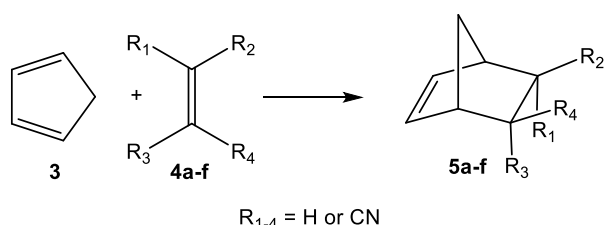
In other words, the activation energies associated with the TSs are mainly due to the electron density changes demanded to reach the electronic structure of products, and electron density repulsions between the two interacting reagents positioned at distances below the van der Waals radius, and not due to MO interactions.

After an exhaustive study of chemical organic reactivity, in 2016 L. R. Domingo proposed the MEDT [5], which states that *changes in electron density and not MO interactions are responsible for molecular reactivity in organic chemistry*, and which opposes to FMO concepts. Within MEDT, QC calculations are performed in order to study the changes in electron density along a chemical reaction, and the energies associated with these changes are calculated and interpreted. MEDT involves a complete coverage of QC principles to interpret the molecular reactivity from electron density changes. Within MEDT, the CDFT [23] is used as a powerful tool to predict chemical reactivity [27, 28].

Interestingly, many recent MEDT studies have shown that while the EW or ER substitution on unsaturated systems participating in DA and 32CA reactions practically does not modify the GS electronic structure of the non-substituted parent, the CDFT analysis at the GS of the reagents is able to predict their chemical reactivity in polar processes. Thus, while analysis of the electrophilicity  $\omega$  and nucleophilicity  $N$  indices permits analysing the participation of the reagents in polar reactions, analysis of the Parr functions [36] allows establishing the regio- and chemoselectivity in polar processes. Note that the definition of Parr functions intrinsically implies a transfer of electron density and, consequently, selectivity in non-polar reactions is controlled by other factors such as electronic stability or steric hindrance.

Global Electron Density Transfer (GEDT) as a measure of the polar character of the reactions

After studying numerous experimental DA reactions during the period 1995-2009, the very good correlation found between the activation energy and the global electron density transfer [34] (GEDT) could be established. In 2003, the DA reactions between cyclopentadiene (Cp) **3** and the cyanoethylene series **4a-f**, experimentally studied by J. Sauer in 1964 [37] and described in most organic textbooks as an example of the effects of the EW substitution in DA reactions [38], were theoretically studied (see Sch. 1) [39].



Sch. 1. DA reactions between Cp **3** and the cyanoethylene series **4a-f**.

Two appealing conclusions were obtained from this DFT study: i) the asynchronicity in the C–C bond formation is dependent on the asymmetric substitution of the ethylene; ii) a very good correlation between the GEDT found at the TSs and the logarithm of the experimental rate constant was established for the first time, indicating that the GEDT could be one of the key factors in the activation energy (see Fig. 3) [40].

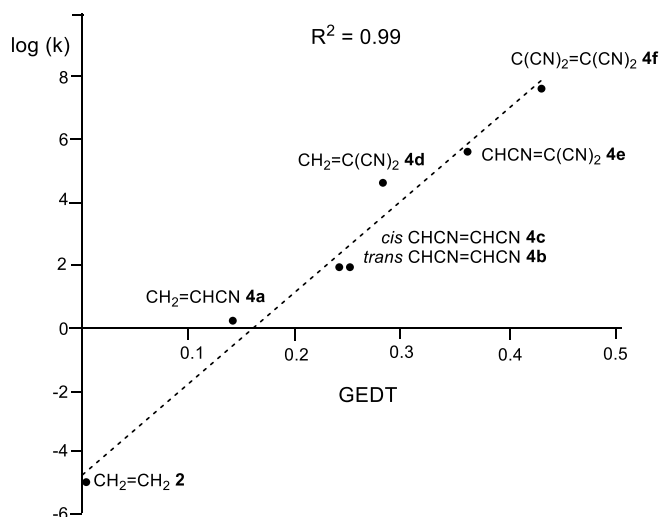


Fig. 3. Plot of the logarithm of the experimental rate constant  $k$  vs GEDT, in average number of electrons,  $e$ , for the DA reactions of Cp **9** with ethylene **2** and the cyanoethylene series **4a-f**;  $R^2 = 0.99$ .

What is the origin of the GEDT in polar organic reactions? An appealing concept defined within CDFT is the electronic chemical potential  $\mu$ , which correlates with the absolute

electronegativity  $\chi$  through the simple equation  $\chi = -\mu$  [24]. The electronic chemical potential  $\mu$ , defined as  $\mu = (\partial E/\partial N)_v$ , is associated with the feasibility of a molecule to exchange electron density with the environment at the GS. R. T. Sanderson proposed the *electronegativity equalisation* principle [41, 42] in chemistry, according to which electronegativity tends to equalise. The correctness of Sanderson's principle comes from the fact that the electronic chemical potential  $\mu$  is a property of an equilibrium state. Consequently, when two molecules A and B, with  $\mu_A > \mu_B$ , approach each other, there is a flux of electron density from A, the less electronegative species, towards B, the more electronegative one, to equilibrate the electronic chemical potential  $\mu_{AB}$  in the new interaction. The larger the electronic chemical potential difference is,  $\Delta\mu_{A-B}$ , the larger the GEDT.

Afterward, in 2009, the very good correlation found between the computed activation energies and the GEDT values at the TSs involved in the DA reactions of Cp **3** with twelve substituted ethylene derivatives of increased electrophilicity  $\omega$  index allowed introducing the concept of polar DA (P-DA) reactions, followed by experimental DA reactions (see Fig. 4) [43]. The DA reactions were classified as non-polar DA (N-DA), which do not take place easily experimentally, P-DA reactions, and ionic DA (I-DA) reactions, which are the extreme of P-DA reactions in which one reagent is an ionic species [43].

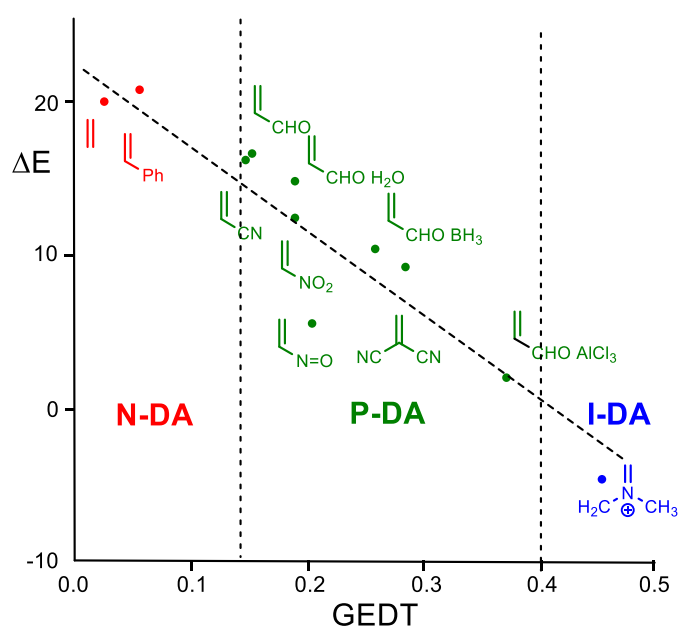
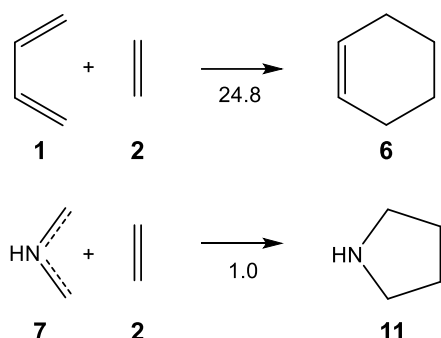


Fig. 4. Plot of the activation barriers ( $\Delta E$ ) vs GEDT,  $R^2 = 0.89$ , for the DA reactions of Cp **3** with the substituted ethylene series.

Interestingly, 32CA reactions experience a different reactivity than DA reactions. Thus, unlike the N-DA reaction between butadiene **1** and ethylene **2**, which presents a very



high activation energy,  $24.8 \text{ kcal}\cdot\text{mol}^{-1}$  [34], due to the marginal electrophilic character of ethylene **2**, the non-polar 32CA reaction between the simplest azomethine ylide (AY) **7** and ethylene **2** presents an unappreciable activation energy,  $1.0 \text{ kcal}\cdot\text{mol}^{-1}$  (see Sch. 2) [44].



Sch. 2. Non-polar DA and 32CA reactions of butadiene **1** and the simplest AY **7** with ethylene **2**. Activation energies are given in  $\text{kcal}\cdot\text{mol}^{-1}$ .

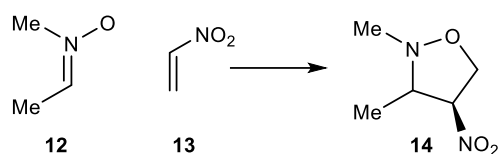
Recent MEDT studies of 32CA reactions allowed establishing a very good correlation between the electronic structure of simplest TACs and their reactivity towards ethylene **2** [45]. Accordingly, depending on the electronic structure of TACs, i.e. *pseudodiradical*, *pseudo(mono)radical*, carbenoid or zwitterionic, 32CA reactions have been classified into *pdr*-, *pmr*-, *cb*- and *zw*-type reactions, respectively (see Fig. 5) [45], in such a manner that while *pdr*-type 32CA reactions take place very easily [46], *zw*-type 32CA reactions demand suitable nucleophilic/electrophilic activations [47]. The structure of TACs, which determines this classification, is characterized from the topological analysis of the ELF; thus, the ELF topological analysis of *pseudodiradical* TACs shows the presence of two *pseudoradical* centers, *pseudo(mono)radical* TACs have only one *pseudoradical* center, carbenoid TACs present a carbenoid center, and zwitterionic TACs present neither *pseudoradical* nor carbenoid centers.

Azomethine ylide 7	Azomethine imine 8	Nitron 9	Nitrile ylide 10
<b>Structure</b>			
<i>pseudodiradical</i>	<i>pseudoradical</i>	zwitterionic	carbenoid
<b>Reactivity</b>			
<i>pdr</i> -type	<i>pmr</i> -type	<i>zw</i> -type	<i>cb</i> -type
1.0 kcal/mol	7.7 kcal/mol	13.4 kcal/mol	7.8 kcal/mol

Fig. 5. Electronic structure of simplest TACs and proposed reactivity types in 32CA reactions. MPWB1K/6-311G(d) gas phase activation energies of the non-polar 32CA reactions between the four

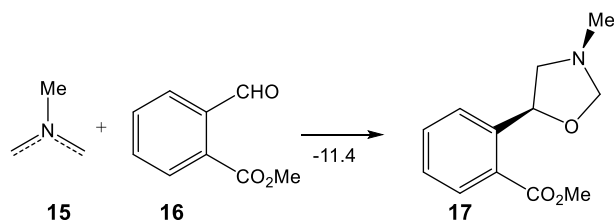
simplest TACs **7** – **10** and ethylene **2**, relative to the corresponding molecular complexes, are given in kcal·mol<sup>-1</sup>.

In 2018, the 32CA reactions of *C,N*-dimethyl nitron **12** with a series of ethylene derivatives of increased electrophilic character were studied within MEDT (see Sch. 3) [47]. Nitrones are zwitterionic TACs participating in *zw-type* 32CA reactions. *C,N*-dimethyl nitron **12** has a high nucleophilicity *N* index, *N* = 3.57 eV, being classified as a strong nucleophile. The activation energies of these *zw-type* 32CA reactions were noticeably reduced by using strong electrophilic ethylenes. Thus, when nitron **12** reacted with nitroethylene **13**, the gas phase activation energy strongly decreased by 15 kcal·mol<sup>-1</sup> with respect to that involving ethylene **2** [47]. Just as in DA reactions, a good correlation between the GEDT at the TSs and the decrease of the activation energy was found [47].



Sch. 3. Polar *zw-type* 32CA reactions of nucleophilic *C,N*-dimethyl nitron **12** with electrophilic nitroethylene **13**.

The four types of 32CA reactions shown in Fig. 5 are also favored by the polar character of the reaction. As many of the TACs have a high nucleophilic character, they react easily with electrophilic ethylenes. Thus, the experimental 32CA reaction between supernucleophilic AY **15** and the strong electrophilic methyl 2-formyl-benzoate **16** was recently studied within MEDT (see Sch. 4). The TS, which showed a GEDT = 0.17 e, was found 11.4 kcal·mol<sup>-1</sup> below the separated reagents [48].

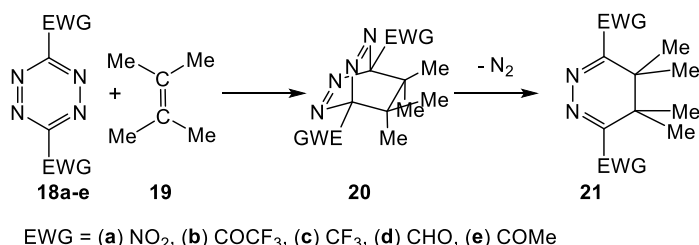


Sch. 4. 32CA reaction between AY **15** and methyl 2-formyl-benzoate **16**.

On the other hand, 1,2,4,5-Tetrazines are useful reagents participating in aza-Diels-Alder (ADA) reactions with a wide range of ethylene and acetylene derivatives, providing rapid access to a range of highly substituted pyridazines [49]. These ADA reactions have been classified as “inverse electron demand” DA reactions within the FMO theory.

Recently, the ADA reactions of a series of tetrazines **18a-e** of increased electrophilic character with nucleophilic tetramethylethylene (TME) **19** were studied within MEDT (see

Sch. 5) [3]. These reactions are domino processes comprising an ADA reaction between tetrazines **18a-e** and TME **19**, followed by an extrusion of molecular nitrogen at the corresponding cycloadducts **20a-e**, yielding dihydropyridazines **21a-e** (see Sch. 5). Analysis of the conceptual CDFT indices showed the increase of the electrophilicity and the decrease of the nucleophilicity of tetrazines **18a-e** with the increase of the EW character of the substituent (see Table 1). As expected, a very good correlation between the GEDT at the TSs and the activation enthalpies for the corresponding ADA reactions was found (see Fig. 6) [3].



Sch. 5. Domino reactions of tetrazines **18** with TME **19**.

Table 1. B3LYP/6-31G(d) electronic chemical potential  $\mu$ , chemical hardness  $\eta$ , global electrophilicity  $\omega$ , and global nucleophilicity  $N$ , in eV, for tetrazines **18a-e** and TME **19**.

	R	$\mu$	$\eta$	$\omega$	$N$
<b>18a</b>	NO <sub>2</sub>	-6.59	3.63	5.99	0.72
<b>18b</b>	COCF <sub>3</sub>	-6.09	3.26	5.69	1.40
<b>18c</b>	CF <sub>3</sub>	-5.85	3.66	4.68	1.44
<b>18d</b>	CHO	-5.71	3.44	4.74	1.70
<b>18e</b>	COMe	-5.26	3.53	3.91	2.10
<b>19</b>		-2.46	6.94	0.43	3.20

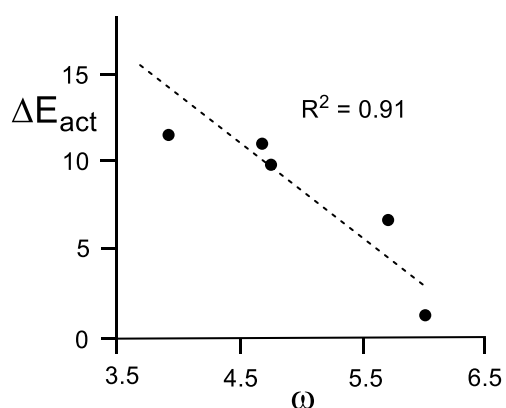


Fig. 6. Plot of the activation enthalpies,  $\Delta E_{\text{act}}$  in kcal·mol<sup>-1</sup>, of the ADA reactions between disubstituted tetrazines **18a-e** and TME **19** vs the electrophilicity  $\omega$  index, in eV, of tetrazines.

A useful classification of the organic reactions based on the flux of the electron density

As has been aforementioned, Sustmann's classification [14] of cycloaddition reactions is widely used in organic chemistry, but it has no chemical meaning since MOs do not physically exist. However, a classification of polar reactions based on the electron density flux is very useful for organic chemists as it allows identifying the nucleophilic and electrophilic species participating in a chemical reaction. In 2020, L. R. Domingo et al. classified polar reactions into *forward electron density flux* (FEDF) and *reverse electron density flux* (REDF) reactions, depending on the direction of electron density flux between the diene or the TAC and the ethylene derivative (see Fig. 7) [3]. This classification is general and can be applied to any type of polar reaction other than cycloadditions. In FEDF reactions, the electron density fluxes from a nucleophilic diene or TAC to an electrophilic ethylene, while in REDF reactions, the flux takes place from a nucleophilic ethylene to an electrophilic diene or TAC. In other words, the GEDT always originates from the nucleophilic reagent and depending on the relative size of its conjugated system, the reaction will be FEDF (when the larger component is the nucleophile), or REDF (when the smaller component is the nucleophile). Note that this classification is completely arbitrary when choosing the diene or the TAC as the electron donor in an FEDF reaction; this selection was done because non-substituted dienes participating in P-DA reactions, and most of the TACs participating in 32CA reactions, have a strong nucleophilic character. When generalizing this classification, one should only take into account the relative size and electronic nature of the reacting systems (see Fig. 7).

Subsequently, the 32CA reactions of cyclic AYs with acetylene, which showed to have a non-polar character displaying a GEDT lower than 0.05 e, were classified as reactions of *null electron density flux* (NEDF) [4].

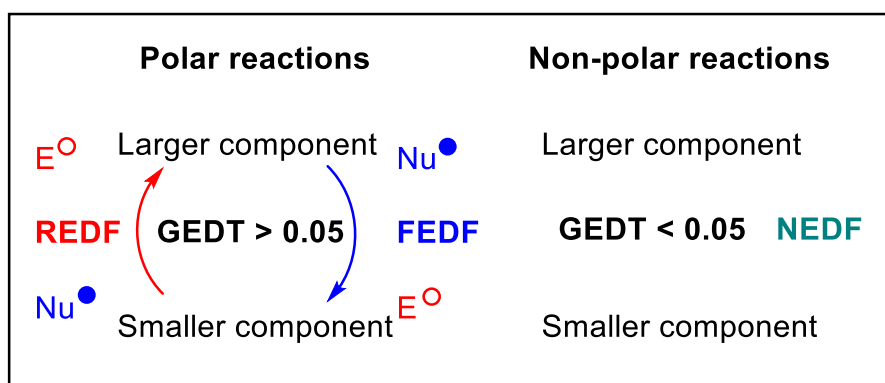


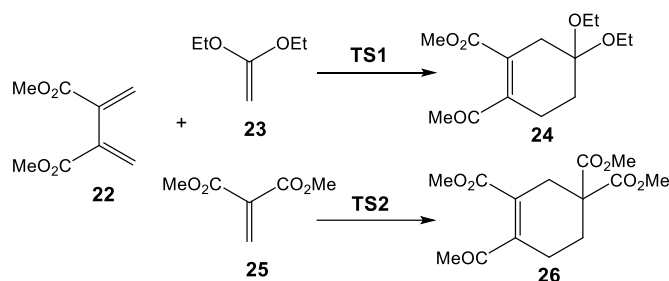
Fig. 7. Classification of the organic reactions based on the direction of the electron density flux at the TSs.

This useful classification of organic reactions based on the analysis of the electron density flux at the TS of the reaction is unambiguous. Thus, the ADA reactions of the series of tetrazines **18a-e** given in Sch. 5 were classified as REDF, a behaviour that allows characterizing tetrazines **18a-e** as electrophilic species.

### Application of the classification in Organic Reactions

#### P-DA reactions between electrophilic reagents

In 2004, C. Spino et al. [50] experimentally studied the DA reactions of the electrophilic diene **22** with nucleophilic ethylene **23** and electrophilic ethylene **25** (see Sch. 6). As expected, the DA reaction with nucleophilic ethylene **23** was fast, but the reaction with electrophilic ethylene **25** was just a bit slower. These authors suggested that “*in the case of normal Diels-Alder cycloadditions, the FMO theory could predict the relative reactivities between dienophiles, while in the case of inverse-electron demand Diels-Alder reactions, it could not*” [50].



Sch. 6. P-DA reactions of electrophilic diene **22** with the nucleophilic ethylene **23** and the electrophilic ethylene **25**.

A subsequent theoretical study of these DA reactions allowed explaining the high reactivity of electrophilic diene **22** with electrophilic ethylene **25** [51]. On the one hand, the P-DA reaction between electrophilic diene **22** and nucleophilic ethylene **23** has an activation energy of  $15.3 \text{ kcal}\cdot\text{mol}^{-1}$  (see Fig. 8); i.e. approximately  $9 \text{ kcal}\cdot\text{mol}^{-1}$  lesser than that associated with the unfavorable N-DA reaction between butadiene and ethylene [34]. Analysis of the GEDT at **TS1**,  $-0.41 \text{ e}$ , showed the high polar character of this DA reaction, which is classified as REDF. Analysis of the electronic chemical potentials  $\mu$  of the reagents clearly indicates that the electron density fluxes from the nucleophilic ethylene **23**,  $\mu = -1.97 \text{ eV}$ , towards electrophilic diene **22**,  $\mu = -4.27 \text{ eV}$  (see Table 2).

Table 2. B3LYP/6-31G(d) electronic chemical potential  $\mu$ , chemical hardness  $\eta$ , global electrophilicity  $\omega$ , and global nucleophilicity  $N$ , in eV, of diene **22** and ethylenes **23** and **25**.

$\mu$	$\eta$	$\omega$	$N$
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<b>25</b>	-4.58	5.81	1.81	1.64
<b>22</b>	-4.27	5.68	1.60	2.01
<b>22'</b>	-3.92	5.52	1.39	2.45
<b>23</b>	-1.97	7.28	0.27	3.52

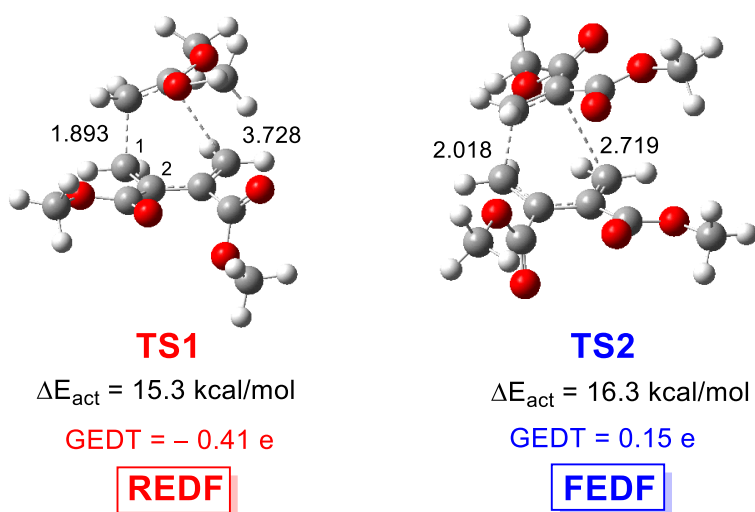


Fig. 8. TSs involved in the P-DA reactions of electrophilic diene **22** with nucleophilic ethylene **23** and electrophilic ethylene **25**.

On the other hand, the electrophilic 1,1-disubstituted ethylene **25**,  $\omega = 1.81 \text{ eV}$ , is more electrophilic than 2,3-disubstituted diene **22**,  $\omega = 1.60 \text{ eV}$ , which is less nucleophilic,  $N = 2.01 \text{ eV}$ , than butadiene **1**,  $N = 2.89 \text{ eV}$ , a nucleophilic species participating in P-DA reactions of FEDF. The electrophilic behavior of diene **22** is a consequence of the presence of the two EW  $\text{CO}_2\text{Me}$  groups in the diene system, which efficiently delocalizes the electron density transferred in polar processes of REDF. To enable this phenomenon efficiently, the  $\text{CO}_2\text{Me}$  group positioned in the C2 carbon should be coplanar to the butadiene framework (see Fig. 8). Thus, when the two EW  $\text{CO}_2\text{Me}$  groups are in a perpendicular conformation with respect to the planar butadiene system, the electrophilicity  $\omega$  index of diene **22'** decreases to  $1.39 \text{ eV}$ , and the nucleophilicity  $N$  index increases to  $2.45 \text{ eV}$  (see **22'** in Table 2). Consequently, the DA reaction between diene **22'** and electrophilic ethylene **25** has a polar character, in which ethylene **25** acts as a strong electrophile and diene **22'** acts as a moderate nucleophile. Thus, while the P-DA reaction of diene **22** with nucleophilic ethylene **23** is classified as an REDF reaction, that of diene **22'**,  $\mu = -3.92 \text{ eV}$ , with strong electrophilic ethylene **25**,  $\mu = -4.58 \text{ eV}$ , is classified as FEDF, indicating that diene **22** acts a nucleophilic species in a P-DA reaction.

#### High order of cycloaddition (HOC) reactions

Very recently, the HOC reactions of heptafulvene **26**, tropone **27**, and the imine and ylidenehydrazine derivatives **28** and **29**, respectively, with ethylene **2**, electrophilic dicyanoethylene (DCE) **30**, and nucleophilic cyclic ketene acetal (CKA) **31** have been studied within MEDT (see Fig. 9) [52].

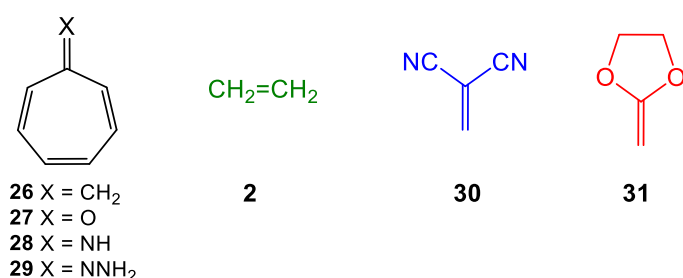


Fig. 9. Heptafulvene **26**, tropone **27**, imine derivatives **28** and ylidenehydrazine derivatives **29**, whose reactions with ethylene **2**, DCE **30** and CKA **31** were studied within MEDT.

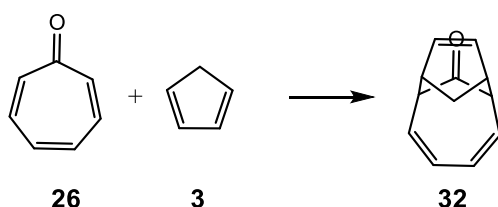
The CDFT reactivity indices allow classifying heptafulvene **26** and the two nitrogen derivatives **28** and **29** as strong nucleophiles, and tropone **27** and the ylidenehydrazine **29** as strong electrophiles participating in polar reactions (see Table 3). Thus, while heptafulvene **26** and the two nitrogen derivatives **28** and **29** react with the strongly electrophilic DCE **30** in a FEDF reaction, tropone **27** and ylidenehydrazine **29** react with the strongly nucleophilic ethylene **2** in a REDF reaction. These heptafulvene derivatives do not have any tendency to react with ethylene **2**, the corresponding non-polar HOC reactions being classified as NEDF. These classifications, anticipated by the analysis of the CDFT reactivity indices, were further supported by analysis of the GEDT at the corresponding TSs [52].

Table 3. B3LYP/6-31G(d) electronic chemical potential  $\mu$ , chemical hardness  $\eta$ , electrophilicity  $\omega$ , and nucleophilicity  $N$ , in eV, of the reagents involved in the HOC reactions of heptafulvene **26**, tropone **27**, and the imine and ylidenehydrazine derivatives **28** and **29**.

	$\mu$	$\eta$	$\omega$	$N$
DCE <b>30</b>	-5.64	5.65	2.82	0.65
tropone <b>27</b>	-4.28	4.20	2.18	2.75
imine <b>28</b>	-3.84	3.81	1.94	3.37
ylidenehydrazine <b>29</b>	-3.31	3.30	1.66	4.17
heptafulvene <b>26</b>	-3.31	3.41	1.61	4.10
Cp <b>3</b>	-3.01	5.48	0.83	3.37
ethylene <b>2</b>	-3.37	7.77	0.73	1.87
CKA <b>31</b>	-1.94	7.30	0.26	3.53

Afterward, the HOC reaction of tropone **27** with Cp **3** yielding the [6+4] cycloadduct **32** was studied within MEDT (see Sch. 7) [53]. The strong electrophilic character of tropone

**26** together with the strong nucleophilic character Cp **3** pointed out the polar character of this HOC reaction, which presents a GEDT of  $-0.19$  e. This HOC reaction was therefore classified as REDF, a behavior anticipated by analysis of the electronic chemical potential  $\mu$  of tropone **26**,  $\mu = -4.28$  eV, and Cp **3**,  $\mu = -3.01$  eV (see Table 3). Note that in these HOC reactions, the highly unsaturated heptafulvenes are taken as the reference for the direction of the electron density flux.



Sch. 7. HOC reaction of tropone **27** with Cp **3** yielding the [6+4] cycloadduct **32**.

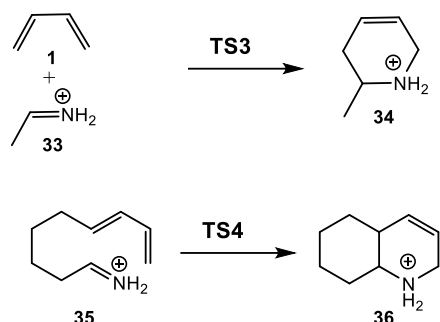
#### Intramolecular I-DA reactions

Finally, an interesting case of organic reactions is the intramolecular polar reactions, in which the changes of electron density take place in a single molecule. Recently, the intermolecular [54] and intramolecular [55] ionic DA (I-DA) reactions of iminium cations **33** and **35** were studied within MEDT (see Sch. 8). I-DA are the extreme case of P-DA reactions [43]. Due to the superelectrophilic character of cationic species and the supernucleophilic character of anionic species, the TS associated with corresponding I-DA reactions, which are characterized by high GEDT values, present low activation energies [56]. Thus, **TS3** associated with the intermolecular DA reaction of iminium cation **33** with butadiene **1**, which presented a high GEDT =  $0.45$  e, has an activation energy of  $8.6$  kcal·mol<sup>-1</sup>, being the I-DA reaction classified as FEDF (see Fig. 10). As expected, the flux of the electron density at **TS3** goes from butadiene **1** to iminium cation **33**, in complete agreement with the very low electronic chemical potential  $\mu$  of the latter,  $\mu = -11.83$  eV, classified as a superelectrophile,  $\omega = -8.97$  eV (see Table 4).

The intramolecular I-DA reaction of **35** presented an activation energy of  $13.6$  kcal·mol<sup>-1</sup>. A comparative analysis of the TSs participating in these inter- and intramolecular I-DA reactions shows a great similitude between them (see Fig. 10). The GEDT at **TS4**,  $0.43$  e, which fluxes from the diene framework to the iminium one, allowed classifying the intramolecular I-DA reaction also as FEDF. Note that intramolecular reactions cannot be classified within the Sustmann's classification. In addition, the HOMO and LUMO energy gap at **35** is  $0.1385$  a.u.; i.e.  $86.9$  kcal·mol<sup>-1</sup>, a very high energy difference when it is compared with the activation energy of this intramolecular I-DA reaction,  $13.6$  kcal·mol<sup>-1</sup>.



Consequently, the HOMO-LUMO gap used in the Sustmann's classification has no physical significance.



Sch. 8. Inter- and intramolecular I-DA reactions of iminium cations **33** and **35**.

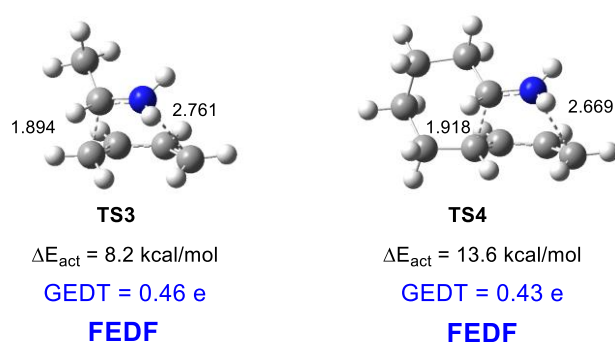


Fig. 10. TSs involved in the inter- and intramolecular I-DA reactions of iminium cations **33** and **35**.

Table 4. B3LYP/6-31G(d) electronic chemical potential,  $\mu$ , chemical hardness,  $\eta$ , electrophilicity,  $\omega$ , and nucleophilicity,  $N$ , in eV, of butadiene **1** and iminium cations **33** and **35**.

	$\mu$	$\eta$	$\omega$	$N$
<b>35</b>	-8.23	3.76	9.01	-0.99
ethaniminium <b>33</b>	-11.82	8.27	8.46	-6.83
butadiene <b>1</b>	-3.42	5.62	1.04	2.89

## Material and methods

DFT calculations of the mentioned reactions were performed by using the B3LYP,[57, 58] the MPWB1K [59], and the  $\omega$ B97X-D [60] functionals, together with the standard 6-31G(d) or 6-311G(d,p) [29] basis sets. The GEDT [34, 30] values at the TSs were computed using the equation  $GEDT(f) = \sum q_f$ , where  $q$  are the natural charges [61, 62] of the atoms belonging to one of the two frameworks (f) at the TS geometries. CDFT reactivity indices [27, 28] were calculated using the equations in reference [27]. All calculations were carried out with the Gaussian16 suite of programs [63]. Molecular geometries and maps of the electron density  $\rho$  and of the Laplacian of the electron density  $\nabla^2\rho$  were visualized with the

Gaussview program [64], while ELF localization domains were represented using Chimera [65].

## Conclusions

Many MEDT studies of organic reactions carried out in this century have proved that the GEDT taking place at the TS of an organic reaction has a decisive role in the activation energies; the higher the GEDT at the TS, the faster the polar reaction. Due to the relevance of the GEDT in chemical organic reactivity, a useful classification of polar organic reactions in FEDF and REDF, based on the unambiguous analysis of the direction of the flux of the electron density at the TSs was recently proposed [3]. This classification permits a straightforward characterization of the nucleophilic and electrophilic species participating in polar reactions; along a polar reaction, the electron density always fluxes from the nucleophilic species to the electrophilic one. On the other hand, non-polar reactions are classified as NEDF [4].

Unlike the Sustmann's [15] and Houk's [16] classifications carried out within the outdated FMO theory, based on the gap of the HOMO and LUMO energies, this useful and unambiguous classification allows characterizing the nucleophilic/electrophilic species participating in any polar reactions. Thus, despite the original classification was only applied to cycloaddition reactions, the proposed classification based on the GEDT flux within MEDT is general and applies to all organic reactions. For experimental organic chemists, the analysis of the CDFT indices, such as the electronic chemical potential  $\mu$ , the electrophilicity  $\omega$  and the nucleophilicity  $N$ , at the GS of the reagents permits to establish easily this classification of polar reactions without the need of further calculations.

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