

Quantitative study by the Electrophilic and Nucleophilic indexes of chemical reactivity for the intramolecular Diels-Alder reaction of the Triene-Amide Molecule. DFT investigation

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Received 14 May 2014, Revised 02 June 2014, Accepted 06 June 2014.

Abstract

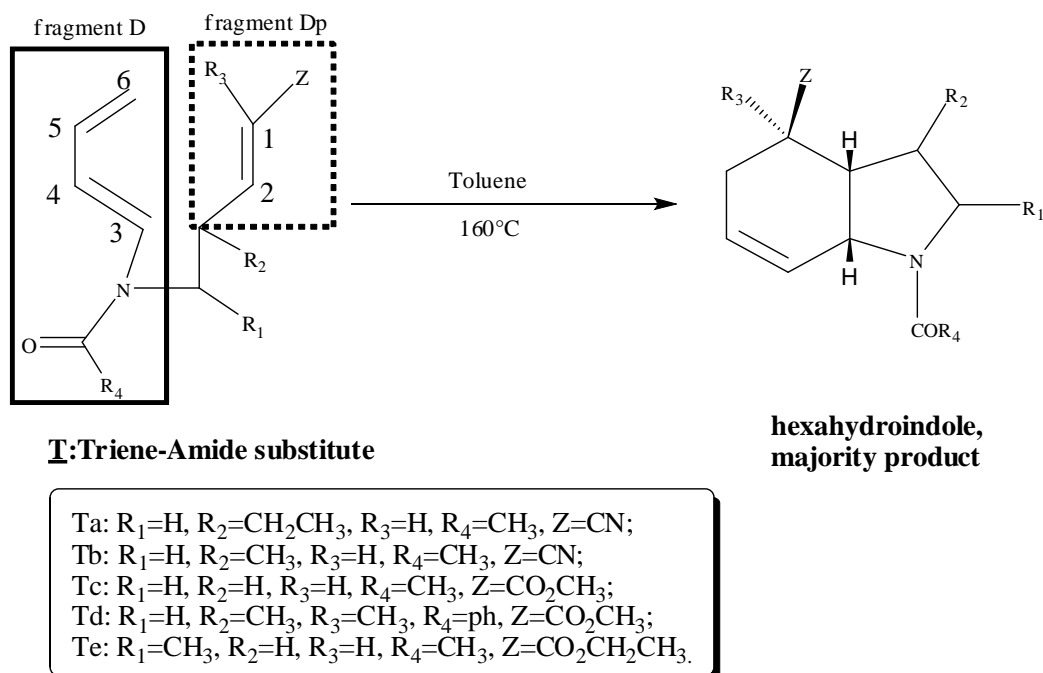
In this study, we proposed to examine the reactivity of the intramolecular cycloaddition Diels-Alder (IMDA) reaction of the molecule triene amide by chemical descriptors established globally in the intermolecular reactions (DA), such as of electrophilic index ω and the nucleophilic index N . In order to provide the power releasing or withdrawing of electrons of the diene (D) and dienophile (Dp) fragments in the intramolecular molecule, the polarity of the reaction can be evaluated by the application of these two factors, applied locally to the diene (D) and dienophile (Dp) fragments, other parameters have been introduced to enrich these results, such as transferability index γ and charge transfer (CT) in a transition state. During our study we used density functional theory (DFT) in the hybrid B3LYP and basis set level 6-31G (d, p), the geometries are optimized for the reactants, transition states as well for products, the calculation of the charge transfer is carried out using the natural population analysis (NPA), the results obtained show that the diene (D) fragment is donor of electrons in the IMDA reaction.

Keyword: regioselectivity, intramolecular, nucleophilic, electrophilic, IMDA, DFT.

1. Introduction

The Diels Alder (DA) reaction is one of the most useful methods for the construction of six cycles. And attracted a considerable interest for two experimental [1-8] and [9-14] theoretical scientists. There are many variants of the Diels–Alder reaction, by varying the nature of the diene (D) and dienophile (Dp) many different types of six carboxylic structures can be composed. The intramolecular Diels–Alder (IMDA) reaction is widely used for the construction of the cycles in a single synthetic process [15]. This reaction has been used in the construction of many biological and pharmacological systems and as a highway in the total synthesis of natural products [16]. The reaction occurs between two (carbon-carbon) of D and Dp fragments in the same reagent to produce new bonds bearing in the same molecule to produce a polycyclic compound. The distribution of global electronic properties in fragments or functional groups within a single molecule is a powerful tool to discuss the reactivity in the intramolecular reactions. However, the division of combinations or structures are usually arbitrary in nature and they may or may not have a chemical significance, Gazquez and al [17] they showed that the distribution of local properties, such as Fukui functions or the local softness, by the use of the functions based on density, provide support for the calculation of the chemical properties of fragments. This is the case of the partition prepared by Hirshfeld [18], which to lead the reliable values of the fukui function. This is consistent with the work of Ayers, Morrison and Roy [19], that shows that these functions can be used to determine the local properties of the fragments. Jorge Soto-Delgado and al [20] also used condensed Fukui function [21] for a large property to the instance of global electrophilicity ω which has been used successfully as the fragment or functional groups in a single molecule (IMDA) to predict the polarity and the electron flow between the divisions (fragments). A further indication of reactivity introduced by Domingo and al [22], the global nucleophilicity N applied similarly to the reaction DA to classify the nucleophilicity of some reagents.

in our present work we will try to study the chemical reactivity of the intramolecular Diels Alder of triene amide reaction [23] (scheme 1) as and to measurement of intermolecular fragments the normal electronic demand NED{diene (electro-releasing)- dienophile (electro-withdrawing)} or inverse electronic demand IED{diene (electro-withdrawing)-dienophile (electro-releasing) } by applying the elements used usually to the reaction intermolecular DA and transmute in the intramolecular Diels Alder (IMDA) reaction namely the global electrophilic index ω and the global nucleophilic index N .



Scheme 1: Intramolecular Diels–Alder reaction of triene amide for the synthesis of the hexahydroindole product.

2. Equation model and calculation details

There are a lot of parameters, which are used as descriptors of reactivity in chemical reactions.

a) Global Hardness η : one of these parameters is the hardness η , which is defined as:

$$\eta = \frac{1}{2} \left[\frac{\partial \mu}{\partial N} \right]_{v(r)} = \frac{1}{2} \left[\frac{\partial^2 E}{\partial N^2} \right]_{v(r)} \quad (1)$$

Where E , N , μ and $v(r)$ represent respectively, energy, number of electrons, chemical potential index and external potential of the system, Parr and Pearson [24] have proposed to use the method of finite differences, we obtain:

$$\eta = \frac{I - A}{2} \quad (2)$$

Such as I and A are respectively the ionization potential and electron affinity, on the other hand the global hardness η can be calculated from the energies of the frontier molecular orbital ϵ_{HOMO} and ϵ_{LUMO} as follows [25]:

$$\eta = (\epsilon_{LUMO} - \epsilon_{HOMO}) \quad (3)$$

Considering that the G molecule can be arbitrarily partitioned into two fragments A and B and the corresponding chain is the union $(CH_2)_n$ (**scheme 2**).

For an IMDA process, and that we need to calculate the group of electrophilicity of the fragments A and B within the molecule G . for this purpose, we count on previous work. In fact, Meneses and al [26], they expressed the hardness local η_k on an atom (k), by the terms of the indices of Fukui f_k^\pm for an electrophilic and nucleophilic attack and by the energies of the

frontier molecular orbital $\varepsilon_{\text{HOMO}}$ and $\varepsilon_{\text{LUMO}}$. This work can be used to define the group hardness associated with the fragment $\Omega = \text{A, B}$ by:

$$\eta_{\Omega} = \sum_{k \in \Omega} \eta_k \quad (4)$$

Such that:

$$\eta_k = I f_k^+ - A f \approx \varepsilon_L f_k^+ - \varepsilon_H f_k^- \quad (5)$$

The electronic chemical potential μ can be calculated from the energies of the frontier molecular orbital $\varepsilon_{\text{HOMO}}$ and $\varepsilon_{\text{LUMO}}$ as follows [27-28]:

$$\mu = (\varepsilon_{\text{HOMO}} + \varepsilon_{\text{LUMO}})/2 \quad (6)$$

The electronic chemical potential of the fragment Ω ($\Omega = \text{A or B}$), it is given by:

$$\mu_{\Omega} = - \sum_{k \in \Omega} \frac{I}{2} f_k^- - \sum_{k \in \Omega} \frac{A}{2} f_k^+ \quad (7)$$

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

By making the simplifications using Koopmans theorem, we can write the electronic chemical potential for fragments A and B by the forms:

$$\mu_A = \sum_{k \in A} \frac{\varepsilon_H}{2} f_k^- + \sum_{k \in A} \frac{\varepsilon_L}{2} f_k^+ \quad (8)$$

$$\mu_B = \sum_{k \in B} \frac{\varepsilon_H}{2} f_k^- + \sum_{k \in B} \frac{\varepsilon_L}{2} f_k^+ \quad (9)$$

b) Global electrophilic Index ω

The electrophilic index ω is introduced by Parr and al [29] the potential chemical μ is defined by the following relation:

$$\omega = \mu^2 / 2\eta \quad (10)$$

This index expresses the ability of an electrophile to acquire an additional electronic charge. It was noted that this electrophilic index has been used to classify a set of reagents involved in Diels-Alder reactions [31]. A good correlation between the difference of electrophiles for couples (diene/dienophile) and the feasibility of cycloaddition was found [31]. You can determine the electrophilic index of an atom to the site k of the molecule by applying the following equation:

$$\omega_k = \omega f_k^+ \quad (11)$$

$$\text{with } \sum \omega_K = \omega$$

Such as f_k^+ the index of Fukui electrophilic in attack nucleophilic in the atom k .

The electrophilicity of a fragment F is extracted easily from equation (12), can be written in the form:

$$\omega_F = \omega \sum_{k \in F} f_k^+ \quad (12)$$

c) Global nucleophilic Index N

We have used the (HOMO) energies obtained by the method of Kohn-Sham. The nucleophilicity index (N) empirical (relative) is defined as follows [22]:

$$N = \varepsilon_{HOMO(Nu)} - \varepsilon_{HOMO(TCE)} \quad (13)$$

It notes that the scale of the nucleophilicity is references compared with the tetracyanoethylene (TCE) molecule that is taken as a reference because it presents the lowest energy HOMO in a great series of molecules already studied in the context of the Diels-Alder cycloadditions polar.

You can determine the local nucleophilicity index of an atom to the site k of the molecule defined as the product of group nucleophilic index N and the nucleophilic index of Fukui f_k^- .

$$N_K = N f_k^- \quad (14)$$

with $N = \sum N_K$

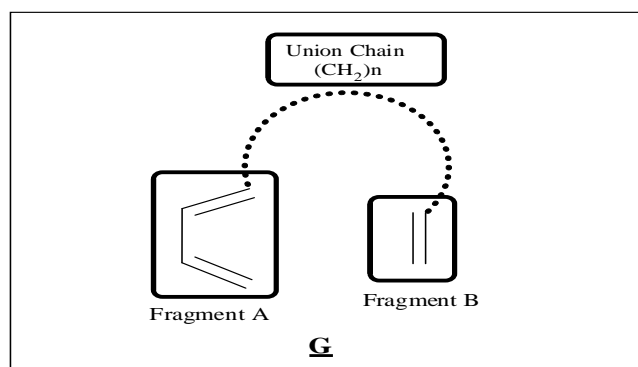
And then f_k^- the nucleophilic index of Fukui in attack electrophilic in the atom k.

The nucleophilicity of a fragment F is easily extracted from the equation (15), can be written in the form:

$$N_F = N \sum_{K \in F} f_k^- \quad (15)$$

However, there is an additional difficulty for the determination of the nucleophilicity and electrophilicity the reagents with the IMDA reactions, because both reactants lie within a single molecule.

This problem can be lifted by using a proper technique dividing the molecule into three parts as described in scheme 2.



Scheme 2: fragmentation for the IMDA reaction in the molecule G.

we proposed in our system, that there are two regions A and B can be considered non-homogeneous electron gas therefore $\mu_A \neq \mu_B$, this principle is used in some work the model of Tachibana and al [32, 33, 34] who considers that the two regions A and B change the heat, work and the electrons in the molecule, and the work of Jorge Soto-Delgado and al [20], in this we define three areas corresponding to the diene moiety (Fragment A), the dienophile moiety

(Fragment B) and the chain $(CH_2)_n$ that connects the region A and B. Specifically, the principle of inequality of the chemical potential [32], is defined as "the constancy of the chemical potential is perturbed when set an object between the pairs regions, when the transfer of particles is rather inhibited through the interface, to bring around at the finite difference regional of chemical potentials even after attains it global chemical equilibrium "[20]. In this case, relatively to the scheme 1, the body-perturbing is the methylene chain who plays bridge is the D and Dp fragments within the intramolecular molecule. It is worthy to be mentioned that this partition is similar to that shown in scheme 2, shows that the contribution of the intramolecular reactivity the methylene chain is negligible [35]. Thus, Tachibana [32] suggested in his model the chain of the union plays the role of agent perturbing. Noted that the unperturbed system naturally, becomes an intermolecular interaction between D and Dp fragments. We can assess evaluate the global electrophilicity and the global nucleophilicity and other chemical properties namely the potential chemical μ , and the hardness η for the series of molecules in scheme 1.

All structures are optimized by the theoretical method B3LYP and basis set level 6-31G (d, p). The calculations are performed with the Gaussian program 09 [36]. The electronic structures are analyzed at the stationary point by using the NBO (natural bond orbital) method [37]. To determine charge transfer ({CT}) corresponding to the transition state of different reactions IMDA, this method was designated as reliable to interpret the charge transfer and based on analysis of population using the B3LYP functional [38]. The global and local electrophilicity is calculated using the equation 11 and 12 and the global and local nucleophilicity is calculated by the equation 13 and 14, the indices of fukui nucleophilic f_k^+ and electrophilic f_k^- of an atomic site k are calculated using the following equations:

$$f_k^+ = [q_k(N+1) - q_k(N)] \quad \text{for nucleophilic attack} \quad (16)$$

$$f_k^- = [q_k(N) - q_k(N-1)] \quad \text{for electrophilic attack} \quad (17)$$

Such as $q_k(N)$, $q_k(N+1)$ and $q_k(N-1)$ are respectively the electron population of the atom k in the molecule cationic, anionic, and neutral.

3. Results and discussion

For different compounds, the energies of the frontier molecular orbitals HOMO and LUMO, the electronic chemical potential μ and global hardness η , the electrophilic index ω and nucleophilic index N , are represented in table 1.

<i>Reactifs</i>	<i>HOMO</i> (a.u.)	<i>LUMO</i> (a.u.)	μ (a.u.)	η (a.u.)	ω (eV)	<i>N</i> (eV)
Ta	-0.2140	-0.0440	-0.129	0.170	1.332	3.299
Tb	-0.2144	-0.0438	-0.129	0.171	1.324	3.288
Tc	-0.2088	-0.0372	-0.123	0.172	1.197	3.438

Td	-0.2053	-0.0457	-0.125	0.160	1.329	3.533
Te	-0.2092	-0.0382	-0.124	0.171	1.223	3.428

According to the results of table 1, observed as the reactants Ta and Tb in which the terminal function ($Z = \text{CN}$) have equal and the higher chemical potential among the other reagents at a value of $\mu = -0.129$ u.a., for the greatest value of the nucleophilicity N is registered to the reagent Td ($Z = \text{CO}_2\text{CH}_3$) with a value of 3.533 eV, This is an account for the phenyl function in position R_4 (scheme 1), however the lowest value of the potential chemical μ is noted to the reagent Tc with a value of $\mu = -0.123$ u.a.

3.1. Prediction of the Nucleophilic/Electrophilic character of fragments

To determine the electrophilic and nucleophilic characters to the D and Dp fragments from different reagents, we initiated a series of calculations to the cationic, anionic, and neutral molecule using the natural electron population NPA, to object to count the condensed Fukui function for different atoms of the reagents

Table. 2: represents the Fukui indices f_k^\pm , the electrophilicity index ω and the nucleophilicity index N of the diene D and dienophile Dp fragments of the compounds Ta, Tb, Tc, Td and Te, calculated by using the natural population analysis (NPA) by the method B3LYP/6-31 G (d, p).

Reactifs	Diene (D) Fragment				Dienophile (Dp) Fragment			
	$\sum_{k \in D} f_k^+$	$\omega_D (\text{eV})$	$\sum_{k \in D} f_k^-$	$N_D (\text{eV})$	$\sum_{k \in Dp} f_k^+$	$\omega_{Dp} (\text{eV})$	$\sum_{k \in Dp} f_k^-$	$N_{Dp} (\text{eV})$
Ta	0.545	0.725	0.904	2.983	0.455	0.606	0.096	0.316
Tb	0.556	0.736	0.866	2.848	0.444	0.588	0.090	0.297
Tc	0.554	0.662	0.896	3.079	0.446	0.534	0.097	0.332
Td	0.708	0.941	0.823	2.907	0.292	0.388	0.177	0.626
Te	0.530	0.648	0.932	3.195	0.470	0.575	0.077	0.264

The results in table 2 leads to deduce that:

- the electrophilic index of diene D fragments for different reagents are superior to those fragments dienophiles Dp, add that the diene fragment of the reagent Td have the largest value of electrophilicity ($\omega_D = 0.941 \text{ eV}$), the electrophilicity for the dienes fragments in reagents Tc and Te are very near and they have low values compared with other reagents of $\omega_D = 0.662$ and $\omega_D = 0.648$ respectively. The low values of electrophile ($\omega < 1$) show that the two fragments have a marginal electrophilic power (negligible).

- the nucleophilicity index of the dienes D fragments for different reagents are much higher than those of the Dp fragments, thus, the reagent Te take a high value in the order of ($N_D =$

3.195 eV). Nevertheless, the nucleophilicity values of D fragment are much higher relative to the electrophilicity such as $N_D/\omega_D > 1$, Therefore, the diene fragment behaves like a good nucleophile (electron donor) while the dienophile fragment behaves as electrophile (electron acceptor) in the reaction IMDA. The concentration of characters electrophile and nucleophile to the diene fragment can be considered a failure of the description of frontier molecular orbital (FMO) in the IMDA process. This is analogous to the work of Jorge Soto-Delgado and al [20], these results are confirmed by the represent graphics of frontier molecular orbital HOMO and LUMO of reagents (Figure 1).

According to graphical representations of the frontier molecular orbital HOMO and LUMO of different reagents listed in Figure 1, in compounds Ta, Tb and Td the molecular orbitals HOMO (electron-rich) and LUMO (poor in electrons) are totally concentrated at the diene fragment, this is agreement with the results found by applying the condensed Fukui function in site k atomic, by using the natural population analysis (NPA), in which the electrophilic and nucleophilic indexes to the diene fragments are many elevated compared with the results of electrophilic and nucleophilic indexes to dienophiles fragments (Table 2).

On the contrary, to the compounds Tc and Te we found the opposing results in the what found by the application of Fukui function, which the molecular orbitals HOMO (rich in electrons) are collected on the diene fragment and the molecular orbital LUMO (poor in electrons) are gathered in dienophiles fragments. On the one hand, the results of electrophile of the diene and dienophile fragments are comparable (Table 2), such as for compounds Tc and Te the electrophilic indexes $\{\omega_{D(Tc)} = 0.662 \text{ (eV)}, \omega_{D(Te)} = 0.648 \text{ (eV)}\}$ and $\{\omega_{Dp(Tc)} = 0.534 \text{ (eV)}, \omega_{Dp(Te)} = 0.575 \text{ (eV)}\}$ of diene and dienophile fragments respectively. On the other hand, the substituents at position R_2 (bridge chain) can perturb this distribution according to their releasing or withdrawing of electron powers such as: $\{Ta (R_2=CH_2CH_3), Tb (R_2= CH_3), Td (R_2=CH_3)\}$ and $\{Tc (R_2= H), Te (R_2= H)\}$.

According to these results, in the cycloaddition intramolecular Diels-Alder (IMDA) reaction, the application of condensed Fukui functions f_k^\mp , thus of electrophilic index ω and the nucleophile index N , commonly used in intermolecular (DA) reactions is not sufficient to be evaluated to classify the nucleophilicity and the electrophilicity of the fragments in the intramolecular molecule.

To confirm the Nucleophilic/Electrophilic character of the Diene and Dienophile fragments we use other factor namely electronic flow γ (Table 4) and the charge transfer CT to the transitions states (Table 3).

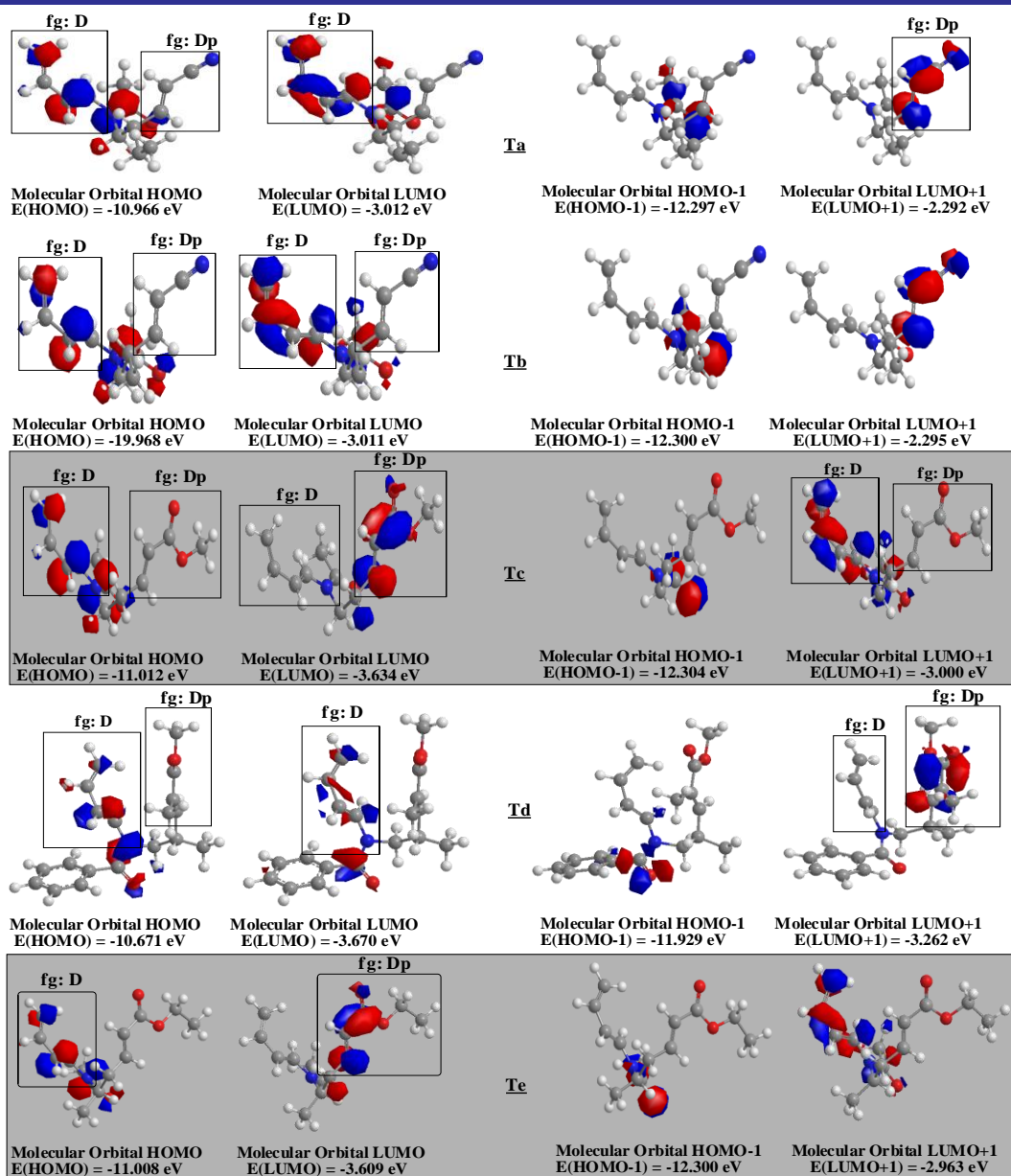


Figure 1: Graphical representation of the frontier molecular orbital HOMO, LUMO and HOMO-1 and LUMO+1 obtained by NPA analysis and visualized by the gauss view 5.0.8. Isocontour: 0.018.

3.2 Prediction of the polarity of the reaction IMDA

3.2.1. Calculation of transfer of charge CT at the transition states

Using the natural population analysis (NPA), we calculated the charge transfer for IMDA reaction for different reagents (Ta, Tb, Tc, Td and Te). The calculations show that the charge transfer to place of the diene D fragment to the dienophile Dp fragment. Therefore the diene fragment behaves like electro-releasing and the dienophile fragment behaves like electro-

withdrawing, the intramolecular cycloaddition Diels-Alder reaction the molecule of triene-amide is controlled by a normal electronic demand, the charge transfer in compounds Ta and Tb in which the terminal position related to the dienophile fragment is the CN function is higher compared to other compounds Tc (0.07e), Td (0.06 e) and Te (0.06 e). To the order of 0.11e and 0.10 e respectively. The CT values corresponding to the transition states (Figure 3) obtained are given in table 3.

Table 3: Charge transfer (CT) in e, between diene and dienophile fragments of the transition states in the reactants Ta, Tb, Tc, Te and Td.

<i>TS</i>	<i>Diene Fragment</i>	<i>Dienophile Fragment</i>
Ta	0.11e	-0.11e
Tb	0.10e	-0.10e
Tc	0.07e	-0.07e
Td	0.06e	-0.06e
Te	0.06e	-0.06e

3.2.2. Prediction of the direction of electron flow using the indexes duels:

The direction of electron flow ($D \rightarrow D_p$ or $D_p \rightarrow D$) in the IMDA reaction can be determined using indexes duels γ_1 and γ_2 [11] defined by:

$$\gamma_1 = \omega_{Dp} + N_D$$

$$\gamma_2 = \omega_D + N_{Dp}$$

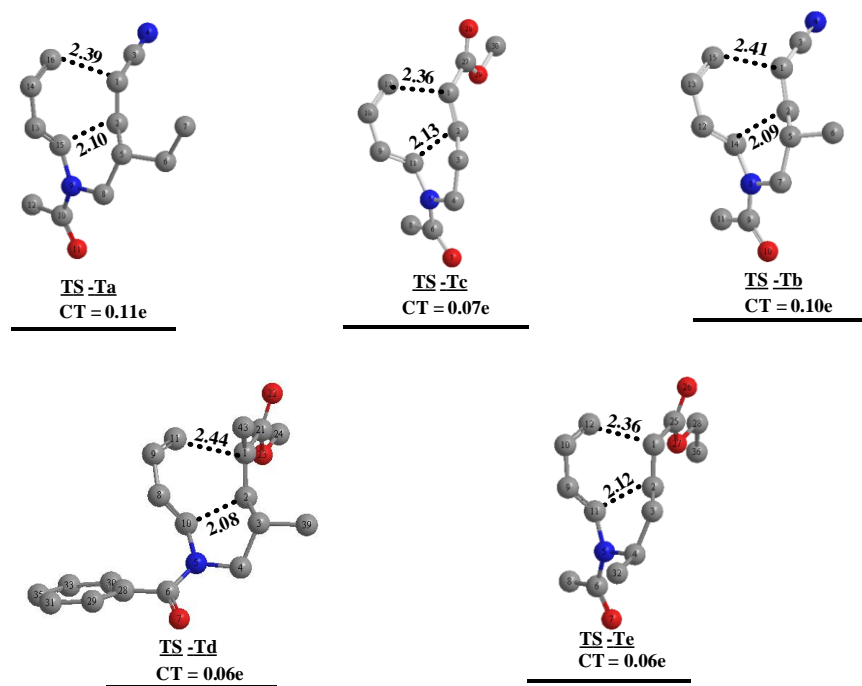
- If $\gamma_1 > \gamma_2$, the charge transfer will take place from diene fragment to the dienophile fragment.
- If $\gamma_1 < \gamma_2$, the charge transfer will take place from the dienophile fragment to the diene fragment.
- If $\gamma_1 = \gamma_2$, It is a chemical equilibrium between the two diene and dienophile fragments (CT= 0).

The values obtained for the IMDA reaction are reported in table 4:

<i>Reactifs</i>	γ_1 (eV)	γ_2 (eV)	$\Delta\gamma_{12}$ (eV)
Ta	3.59	1.04	2.55
Tb	3.43	1.03	2.40
Tc	3.61	0.99	2.62
Td	3.29	1.57	1.73
Te	3.77	0.91	2.86

According the results of table 4 we note that:

- $\gamma_1 > \gamma_2$, then the charge transfer has instead been from the diene fragment to the dienophile fragment, which confirms the results found by charge transfer.
- $\Delta\gamma_{12}$ is slightly significant; that shows that the IMDA is a weakly polar reaction.



Scheme 3: Geometry of the transition state of the IMDA reaction of triene-amide of the Compounds (Ta, Tb, Tc, Td and Td), charge-transfer {CT} is given in e , interatomic distances are given in Å.

3.2.3. Prediction of the polarity by using the electrophilic index of regional fragments ω_Ω :

The difference of electrophilic $\Delta\omega_\Omega$ fragments ω_Ω ($\Omega = A$ or B) is used in the intermolecular reactions to estimate the reactivity and the polarity of the reaction, is subsequently transmitted to the process IMDA [38]:

$$\Delta\omega_\Omega = |\omega_A - \omega_B|$$

The results obtained are summarized in table 5.

Table 5: Electrophilic index of ω_A , ω_B and the invariance of electrophile of A and B fragments ($\Delta\omega_\Omega$).

Compound	A			B			$\Delta\omega_\Omega = \omega_A - \omega_B $
	η (u.a)	μ (u.a)	ω (eV)	η (u.a)	μ (u.a)	ω (eV)	
Ta	0.169	-0.109	0.95	0.119	-0.064	0.46	0.49
Tb	0.161	-0.105	0.93	0.113	-0.062	0.47	0.46
Tc	0.167	-0.104	0.88	0.010	-0.021	0.60	0.28

Td	0.129	-0.101	1.07	0.023	-0.025	0.36	0.71
Te	0.175	-0.107	0.90	0.004	-0.018	1.10	0.20

➤ We note that the value $\Delta\omega_\Omega$ of the Td compound ($\Delta\omega_\Omega = 0.71$) is located between ($0.5 \leq \Delta\omega_\Omega \leq 1.50$), thus for Ta and Tb compounds is close to 0.5 then the IMDA process, for these systems follow a mechanism moderately polar and is characterized by a charge-transfer CT marginal in transition state [40], at the exception of compound Td, with a low charge-transfer CT in a transition state, for the other compounds Tc and Te their values of $\Delta\omega_\Omega$ is quite low of 0.28 and 0.20 ($\Delta\omega_\Omega \leq 0.5$) respectively, which confirms that these reactions are not polar and are characterized by a negligible charge transfer CT in transition state [40].

In order to know the percentage of transfer of the nucleophilicity and the electrophilicity between fragments, we calculated the degree of transferability of each fragment, the results are summarized in tables 6 and 7.

Table 6: Degree of transferability T_ω .

Compounds	ω_D (eV)	ω_{Dp} (eV)	ω (eV)	$\%(T_{\omega_D} = \omega_D/\omega)$	$\%(T_{\omega_{Dp}} = \omega_{Dp}/\omega)$
Ta	0.725	0.606	1.331	56	44
Tb	0.736	0.588	1.324	55	45
Tc	0.662	0.534	1.197	55	45
Td	0.941	0.388	1.330	70	30
Te	0.648	0.575	1.223	53	47

Table 7: Degree of transferability T_N .

Compounds	N_D (eV)	N_{Dp} (eV)	N (eV)	$\%(T_{N_D} = N_D/N)$	$\%(T_{N_{Dp}} = N_{Dp}/N)$
Ta	2.983	0.316	3.299	90	10
Tb	2.848	0.297	3.145	91	09
Tc	3.079	0.332	3.438	90	10
Td	2.907	0.626	3.530	82	18
Te	3.195	0.264	3.428	92	8

In taking into account the results of tables 6 and 7, the electrophilic and nucleophilic characters are concentrated in the diene D fragment to $\omega_D/\omega\%$ (54, 56, 55, 70 and 53) of electrophilicity characters and to $N_D/N\%$ (90, 91, 90, 82 and 92) of the nucleophilicity characters of the compounds Ta, Tb, Tc, Td and Te respectively. Therefore, the electronic transfer is done from the diene to the dienophile fragments.

Conclusion

In this study, during the intramolecular Diels Alder (IMDA) reaction, we applied the theoretical approaches namely electrophilic index ω and Nucleophilic index N used usually in the intermolecular process (DA), the analyses by groups electrophiles and nucleophiles from fragments show that these characters are concentrated in the fragment diene noted that the ratio N_D/ω_D is higher, thus the nucleophilicity is predominant. This is confirmed by the electron flow and the charge transfer to the transition states and subsequently the diene fragment plays the role of electron-releasing and the dienophile fragment plays the role electron-withdrawing of electron for all systems Ta, Tb, Tc, Td and Te. Thus, the charge transfer will take place from the diene to the dienophile NED (Normal Electronic Demand).

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