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# Conceptual DFT study based on the characterization of the local electrophilicity and nucleophilicity for intramolecular Diels Alder reaction of the *trans* isomers of 4-[(4E)-4,6-heptadien-1-yl]-2-cyclohepten-1-one

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*Abstract:* One of the most powerful methods for the rapid synthesis and formation of complex polycyclic molecules with biological interest involves the use of Diels-Alder (DA) reaction especially its intramolecular variant. The *trans* isomers of 4-substituted cycloheptenones were experimentally found to be excellent ethylenes, readily undergoing DA reactions. In this study we were interested to elucidate and predict the reactivity of the intramolecular Diels-Alder (IMDA) reactions of the trans-A and trans-B isomers of 4-substituted cycloheptenone by means of the indexes of reactivity derived from DFT, at B3LYP/6-31G+(d,p) level of theory, using Gaussian09 program. In order to identify the reactional sites and to predict site selectivity of these compounds towards electrophilic and nuclophilic attack, the electrophilic $P_k^+$ and nucleophilic $P_k^-$ Parr functions, the local electrophilicity $\omega_k$ and local nucleophilicity $N_k$ were used in order to characterize the most electrophilic and nucleophilic sites. For the purpose to make clear classification of the electrophilicity and nucleophilicity of the interacting diene and ethylene moieties within the same molecule the local reactivity difference index $R_k$ was used as a power full descriptor to study this IMDA cycloaddition. The fragments electrophilicity and nucleophilicity indices were calculated, according to the fragmentation model. The dual philicity index γ and the degree of transferability were determined. Our calculations showed, as expected, that the electronic transfer will take place from diene to ethylene moiety. The predictions thus made are in good agreement with other theoretical studies that analyse the electronic transfer through global electronic density transfer (GEDT).

*Keywords:* cycloalkenone; cycloaddition; fragmentation; IMDA; diene; ethylene.

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## INTRODUCTION

For a long time chemists have sought to establish relationships uniting the structure and chemical reactivity of molecules. On the experimental level, the means of analyzing molecular structures have become both numerous and more efficient. From a theoretical point of view, quantum chemistry methods represent increasingly useful and reliable tools in the study of the structure and reactivity of chemical compounds. The study of reactivity is based on two main aspects. The first one consists of the calculation of thermodynamic parameters and the second one is the prediction of the reaction mechanism which is done from a theoretical point of view: Either by locating the transition state structure (TS), calculating the activation energies or highlighting the optimal reaction path. Either by the use of reactivity indices and descriptors in order to determine the preferential sites of interaction between reagents.

The work presented in this article is part of this latter approach, i.e. the prediction of reaction sites using reactivity indices and descriptors. Indeed, predicting the reactivity and selectivity of a chemical process is crucial. Our interest was particularly focused on the theoretical study of the reactivity of two isomers of 4-[(4E)-4, 6-Heptadien-1-yl]-2-cyclohepten-1-one. These compounds were experimentally found to be excellent ethylenes, readily undergoing Diels-Alder (DA) reaction to form the corresponding *trans*-fused intramolecular Diels-Alder (IMDA) reactions cycloadduct in very high yields. The Diels-Alder (DA) reaction is undoubtedly one of the most powerful and widely used approaches synthetic organique chemistry.[1] This reaction, which proceeds via a one-step mechanism, consist on a cycloaddition between a conjugated diene and a susbstituted ethylene, resulting in the formation of unsaturated six-membered rings. It is regioselective, stereoselective, atom economic and highly efficient, making it a valuable tool for synthesizing cyclic structures, particularly in the construction of complex molecules and natural products.[2] Depending on the nature of the diene and ethylene, many different types of six carboxylic structures can be composed,[3] this makes it important in the pharmaceutical and biological field in particular even in modern industry.[4] For instance, the synthesis of products with biological activities such as: vibsamin E which deals with the inhibition of plant growth,[5] cytotoxicity, and growth promotion activity of neuritis,[6] and mogolide A which is used to selectively modify biochemical structures.[7]

Due to its usefulness and efficiency in carbon-carbon bond formation, Diels-alder reactions have sparked the interest of experimental and theoretical chemists and continues to be an important subject for both computational[8] and experimental studies.[9]

The intramolecular Diels-Alder (IMDA) reaction is a variant of the Diels-Alder reaction in which the diene and the ethylene are linked in a same molecule,[10] but it does not modify its reactivity, which can only be modify by the strain

associated to the intramolecular process. Due to its flexibility and its notable stereoselectivity in the construction of fused cycles in only one synthetic step, IMDA reaction has been utilized to construct many pharmacological and biological and also as a pathway in the total synthesis of natural products.[11]

Diels-alder reaction of cycloalkenones is considered to be a simple method of backbone construction which has made it possible to obtain fused or bridged tricyclic products.[12] Stereoisomerism is controlled by the *endo*/*exo* approach and depends on the length of the chain that separates the diene from the ethylene as well as the *cis*/*trans* configuration of the latter. In a general way, the product in *endo* mode is majority or exclusive in the case of 2-cycloalkenones.[13] These results have been explained by steric genes, electronic effects.[14]

Dorr and Rawal described a powerful method using UV radiation to generate, in good yield, tricyclic compounds from relatively simple precursors. These are the first examples of IMDA reactions of 2-cycloalkenones.[15] This reaction occurs in two steps, the first being a photochemical isomerization of *cis*-cycloheptenone to *trans*-cycloheptenone. The IMDA thermal reaction at room temperature then takes place on the *trans* isomers. It is very interesting to recall and confirm that *trans*-enones are excellent ethylenes.[16] It was concluded that isomerization of the ethylene of *cis* 2-cycloheptenone yields two diastereoisomers trans-A and trans-B.

Interpreting and predicting the preferred direction of a reaction and product formation is one of the most important issues related to the problem of molecule reactivity.[17] The main purpose of this theoretical study is to predict the reactivity of cycloheptenone diastoisomers trans-A and trans-B and the selectivity of the intramolecular Diels-Alder reaction by means of the conceptual density functional theory (CDFT).[18] In the first time, the global electrophilicity and nucleophilic indices, the electrophilic and nucleophilic Parr functions, and the single reactivity difference indices have been successfully used to the study of the IMDA title reaction. Indeed, on 2009 Domingo et al proposed the polar Diels-Alder (P-DA) mechanism,[19] which is followed by many and various of the experimental Diels-Alder reactions, in which the nucleophilic and electrophilic interactions taking place at the TSs are responsible for the feasibility of the reaction. In this sense, the use of the electrophilicity and nucleophilicity indices, and the Parr functions have become powerful tools to study DA reactions.

In 2012 Chattaraj *et al*. introduced a single reactivity difference index Rx allowing to characterized the electrophilic/nucleophilic center of a molecule, permitting the study of polar intramolecular processes.[20] In 2013, the electrophilic and nucleophilic Parr functions were proposed to study the local reactivity in polar reactions within the CDFT.[21] In 2016, Domingo proposed a new theory of reactivity in organic chemistry baptized Molecular Electron Density Theory (MEDT), which rejects all theories, models and interpretations based on Molecular

Orbital Analyses, in which the changes in electron density along a chemical reaction are responsible for the chemical reactivity of organic molecules.[22]

The partitioning of global electronic properties into fragments groups within a same molecule serves as a powerful technique when discussing the nucleophilicity and electrophilicity of Diene and ethylene fragments in IMDA processes.[23-24] To this end, an appropriate fragmentation model, in which trans-A and trans-B isomers were arbitrarily partitioned into Diene fragment (D), ethylene fragment (Dp) and the corresponding chain of union (Ch) as illustrated in Fig. 1, were used, in the second time, to calculate the fragment electrophilicity and nucleophilitity indices and in order to characterize the nucleophilicity and electrophilicity of the interacting fragments.

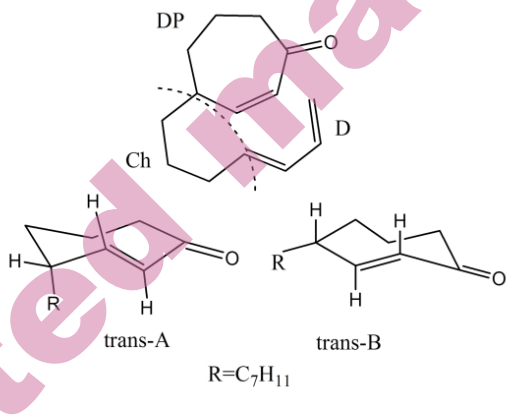


Fig 1. Fragmentation scheme for IMDA and the *trans* isomers of 2-cycloheptenone.

The structure of this paper is as follows: After this brief introduction, section 2 deals the computational details. Section 3 contains the main results and general discussion concerning the prediction of the global and local electrophilicity and nucleophilicity reactivity the title compounds. Also, we discuss results concerning the fragment electrophilicity and nucleophilicity indices for IMDA reaction of trans-A and trans-B isomers of 4-substituted cycloheptenone. Finally, we end this article by recalling the main conclusions.

## CALCULATION DETAILS

The Gaussian 09 package has been used to perform all calculations presented in this work.[25] To obtain fully optimized geometries for the *trans* isomers of 2-cycloheptenone derivatives, we undertook calculations at B3LYP/6-31G+(d,p) level of theory. All optimized structures were identified as minima on the potential energy surface, with no imaginary frequencies appeared in their frequency calculations results, at the same level of theory. To predict the site selectivity of the molecules under study towards electrophilic and nucleophilic attack and to elucidate their nucleophilicity and electrophilicity, various reactivity and

selectivity descriptors and the appropriate local quantities have been calculated. The global and local reactivity descriptors used in the present work are described below.[26]

The global hardness $\eta$ (Eq. 1), based the energies of the frontier molecular orbital $E_{HOMO}$ and $E_{LUMO,}$ are defined as follows:[27]

$$\eta = E_{LUMO} - E_{HOMO} \quad (1)$$

The chemical potential $\mu$ (Eq. 2) can be expressed, using the energies of the frontier molecular orbital, as:[28]

$$\mu = (E_{HOMO} + E_{LUMO})/2 \quad (2)$$

The global electrophilic index[29] $\omega$ was calculated using the following expression (Eq. 3)

$$\omega = \mu^2/2\eta \quad (3)$$

By the Kohn-Sham method, the empirical (relative) nucleophilic index $N$ is defined as follows (Eq. 4).[30]

$$N = E_{HOMO(NU)} - E_{HOMO(TCE)} \quad (4)$$

Where $E_{HOMO(NU)}$ corresponds to the *HOMO* energy of the Nucleophile and $E_{HOMO(TCE)}$ is the HOMO energy of the Tetracyanoethylene *(TCE)* taken as reference.

The Parr function P(r) are expressed by the following equations:[21]

$$p^-(r) = \rho_s^{rc}(r) \text{ for electrophilic attacks} \quad (5)$$

$$p^+(r) = \rho_s^{ra}(r) \text{ for nucleophilic attacks} \quad (6)$$

where $\rho_s^{rc}(r)$ is the Mulliken atomic spin density (ASD) at the r atom of the radical cation of a considered molecule $\rho_s^{ra}(r)$ is the ASD at the r atom of the radical anion. Each ASD condensed at the different atoms of the radical cation and radical anion of molecule provides the local nucleophilic $P_k^-$ and local electrophilic $P_k^+$ Parr functions of the natural system.

Accordingly, the local electrophilicity $\omega_k$ (Eq. 7) and the local nucleophilicity $N_k$ (Eq. 8) indices are defined as follows:

$$\omega_k = \omega \, . \, P^+_k \quad (7)$$

$$N_k = N \, . \, P^-_k \quad (8)$$

The local reactivity difference index $R_k$ is given by the following three conditions to identity the centers with electrophilic ($R_k$ = +n.nn) or nucleophilic ($R_k$ = −n.nn) behavior as well as the ambiphilic ($R_k$ = ±n.nn) behavior in addition to eliminate the centers with marginal reactivity:[31]

$$\text{if } (1<\omega_k/N_k<2) \text{ Or } (1<N_k/\omega_k<2)$$

$$\text{then } R_k=(\omega_k+N_k)/2 \text{ ambiphilic } (R_k= \text{n.nm}) \quad (9)$$

$$\text{else } R_k=(\omega_k-N_k) \quad (10)$$

$$\text{where } R_k>0 \text{ electrophilic } (R_k= + \text{ n.nm})$$

$$\text{and } R_k<0 \text{ nucleophilic } (R_k= - \text{ n.nm})$$

$$\text{If } |R_k| <0.1 \text{ thene } R_k=0.$$

The local hardness (k) on an atom (k) was expressed by Meneses and al, in terms of the Fukui indices for both nucleophilic and electrophilic attacks, as well as the energies of HOMO and LUMO[32]. This approach allowed for the determination of group hardness associated with each fragment (Eq. 10), namely $\Omega$ = D, Dp, and Ch, within the compound 2-cycloheptenone,

which can be arbitrarily divided into diene (D), ethylene (Dp), and the union chain (Ch) fragments, as illustrated in Fig. 1:

$$\eta_\Omega = \sum \eta_k \text{ or } \eta_k = E_{LUMO}.f_k^+ - E_{HOMO}.f_k^- \quad (10)$$

Using Koopmans' theorem, we can write the electronic chemical potential of the D and Dp fragments in the forms (Eq. 11): [32]

$$\mu_\Omega = \sum(E_{HOMO}/2f_k^-) + \sum(E_{LUMO}/2f_k^+) \quad (11)$$

The local electrophilic index of each fragment (Eq. 12) [32]:

$$\omega_D = \omega.\sum_{k\in D} f_k^+ \text{ and } \omega_{Dp} = \omega.\sum_{k\in Dp} f_k^+ \quad (12)$$

We can determine the local nucleophilic index of each fragment is (Eq. 13):[32]

$$N_D = N.\sum_{k\in D} f_k^- \text{ and } N_{Dp} = N.\sum_{k\in Dp} f_k^- \quad (13)$$

The dual philicity indexes γ (Eq. 14).[32]

$$\gamma_1 = \omega_{Dp} + N_D \text{ and } \gamma_2 = \omega_D + N_{Dp} \quad (14)$$

## RESULTS AND DISCUSSION

The main optimized geometric parameters of the trans-A and trans-B isomers of 4-[(4e)-4,6-heptadien-1-yl]-2-cyclohepten-1-one are given in Table I following the labeling of the atoms reported in Fig 2. B3LYP/6-31+G (d,p) method predicts that the trans-A isomer is more stable than the trans-B isomer. The energy gap between them is of the order of 24.22 kJ/mol.

Table I. The energy and the geometry parameters of 4-substituted 2-cycloheptenone isomers.

| | trans-A | trans-B |
|---|---|---|
| E u.a | -620.70148 | -620.69225 |
| $C_{14}$-$C_{33}$ | 7.75 Å | 5.91 Å |
| $C_{16}$-$C_{27}$ | 5.00 Å | 3.37 Å |
| $C_{12}$-$C_{14}$-$C_{16}$-$C_3$ | -113.51° | 115.27° |
| $C_{27}$-$C_{28}$-$C_{30}$-$C_{33}$ | -29.53° | -31.01° |
| $C_3$-$C_{17}$-$C_{20}$-$C_{23}$ | -179.72° | -70.07° |
| $H_{35}$-$C_{16}$-$C_3$-$H_7$ | -177.81° | -17.97° |
| $H_{35}$-$C_{16}$-$C_3$-$C_{17}$ | 55.27° | -141.52° |

*Global Reactivity*

The global reactivity indices of 4-substituted 2-cycloheptenone isomers, which include the electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω), global nucleophilicity (N), global softness S, were calculated at B3LYP/6-31+G(d,p) level of theory and are reported in Table II.

These results show that trans-B isomer is more nucleophilic than trans-A isomer. The global nucleophilicity calculated indices predict that the nucleophilic power decreases from trans-B (*N*= 3.12 eV) to trans-A (*N*= 3 eV). Moreover, trans-B isomer can be classified as a strong nucleophile, according to the nucleophilicity scale.[33] The nucleophilic character of these compounds is in agreement with the

calculated electronic chemical potentials. Indeed, trans-B is characterized by the highest chemical potential (μ= -3.78 eV) followed by trans-A (μ= -4.09 eV). Concerning the electophilic power, it decreases from trans-A (ω=1.81) to trans-B (ω=1.43). According to the elctrophilicity scale[33], trans-A isomer (ω >1.50 eV) is a strong electrophile, that is able to participate easily in polar Diels Alder reactions.[19]

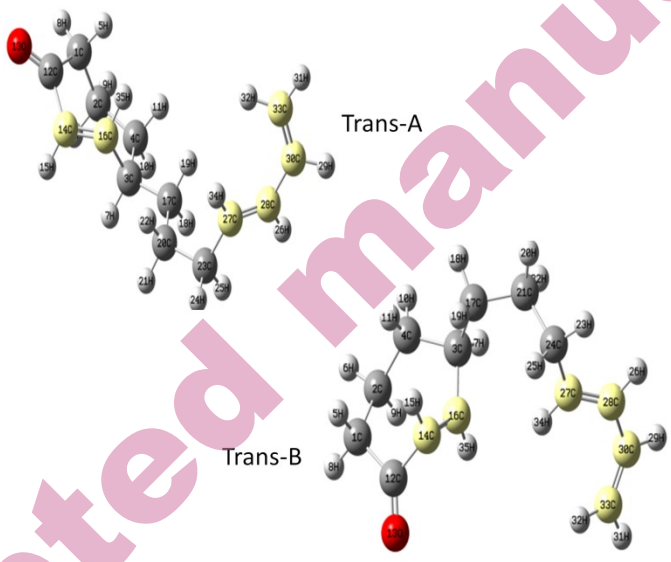


Fig 2. Optimized geometries of 4-substituted 2-cycloheptenone isomers calculated at B3LYP/6-31+G(d,p) method.

Table II. Global electronic properties and reactivity indices of trans-A and trans-B isomers of 4-substituted 2-cycloheptenone calculated at B3LYP/6-31+G(d,p) level of theory

| isomer | $E_{HOMO}$ | $E_{LUMO}$ | η eV | μ eV | ω eV | $N$ eV | $S$ eV |
|---|---|---|---|---|---|---|---|
| trans-A | -0.23 | -0.06 | 4.62 | -4.09 | 1.81 | 3.00 | 0.10 |
| trans-B | -0.23 | -0.04 | 4.99 | -3.78 | 1.43 | 3.12 | 0.10 |

*Local reactivity:*

In order is to predict the preferred electrophilic and nucleophilic sites within molecules under study, it will be necessary to focus attention to the calculated local electrophilicity and nucleophilicity reactivity indices. The corresponding values for both nucleophilic and electrophilic functions are recapitulated in Table III.

The local value of Parr function provides insight into the reactivity and selectivity of the specific site in the molecule. In most polar cycloaddition

reactions, the regioisomeric channel most likely to form involves the interaction between the most nucleophilic center of the nucleophile and the most electrophilic center of electrophile. Therefore, analysis of the local electrophilicity $\omega_k$ and local nucleophilicity $N_k$ derived from Parr functions $P_k^+$ and $P_k^-$ can explain the experimentally observed regioselectivity.

In both trans-A and trans-B isomers, the electrophilic $P_k^+$ Parr function shows the $C_{16}$ carbon to be the most electrophilic center, whereas the nucleophilic $P_k^-$ Parr function displays $C_{33}$ atom as nucleophilic center. The local electrophilicity $\omega_k$ predicts that $C_{16}$ is the main electrophilic center with 1.56 eV and 0.82 eV, in trans-A isomer and trans-B isomer, respectively. However, the local nucleophilicity $N_k$ suggests that $C_{33}$ is the main nucleophilic center of trans-A and trans-B isomers with 0.87 eV and 1.09 eV, respectively. Accordingly, The IMDA reaction path of the *trans* isomers of 4-[(4E)-4,6-heptadien-1-yl]-2-cyclohepten-1-one that is more privileged in terms of regioisomerism will be characterized by the first formation of the $C_{16}$-$C_{33}$ single bound.

In order to simultaneously predict the electrophilicity and nucleophilicity sites of a given molecular system, $R_k$ index has been calculated. The negative values of $R_k$ correspond to nucleophilic centers. Whereas the positive values of $R_k$, correspond to electrophilic centers. The predicted values of $R_k$ show, as expected, that $C_{16}$ site with the high positive value acts as the most electrophilic center, while the most nucleophilic center is attributed to $C_{33}$ site. One important point to note is that the strong local electrophilicity value is assigned to the β conjugated carbon $C_{16}$ atom which is activated because of the withdrawing mesomeric effect of the adjacent carbonyl group, enhancing then its electrophilic character. Accordingly, the cycloaddition IMDA reaction of the *trans* isomers of 4-[(4E)-4,6-heptadien-1-yl]-2-cyclohepten-1-one may be regiospecific.

Table III. electrophilic ( $P_k^+$ )and nucleophilic ($P_k^-$ ) Parr functions , local electrophilicity ($\omega_k$), local nucleophilicity $N_k$ ,and local reactivity difference of trans-A and trans-B isomers

| | | Site | $P_k^+$ | $P_k^-$ | $\omega_k$ | $N_k$ | $R_k$ |
|---|---|---|---|---|---|---|---|
| trans-A | Dp | $C_{14}$ | 0.02 | 0.26 | 0.03 | 0.79 | -0.75 |
| | | $C_{16}$ | 0.86 | 0.04 | 1.56 | 0.13 | +1.42 |
| | D | $C_{27}$ | -0.01 | 0.19 | -0.01 | 0.58 | -0.59 |
| | | $C_{33}$ | 0.00 | 0.29 | 0.00 | 0.87 | -0.86 |
| trans-B | Dp | $C_{14}$ | 0.22 | 0.30 | 0.32 | 0.96 | -0.63 |
| | | $C_{16}$ | 0.57 | -0.01 | 0.82 | -0.03 | +0.85 |
| | D | $C_{27}$ | 0.08 | 0.17 | 0.12 | 0.55 | -0.43 |
| | | $C_{33}$ | 0.13 | 0.35 | 0.19 | 1.09 | -0.90 |

As shown in Fig.3 illustrating the 3D representation of Mulliken atomic spin density (ASD) of the radical anions and radical cations, the electrophilic $P_k^+$ Parr functions of both trans-A and trans-B isomers which are mainly located at ethylene

fragment, particularly at the reactives sites $C_{16}$ and $C_{14}$**.** The highest $P_k^+$value is assigned to $C_{16}$ atom. Alternatively, the nucleophilic $P_k^-$ Parr functions are principally centered at diene fragment, precisely, at the reactive sites $C_{33}$ and $C_{27}$. ASD analysis allows to characterize the most nucleophilic and most electrophilic centers, and to establish the chemoselectivity and regioselectivity in polar reactions.

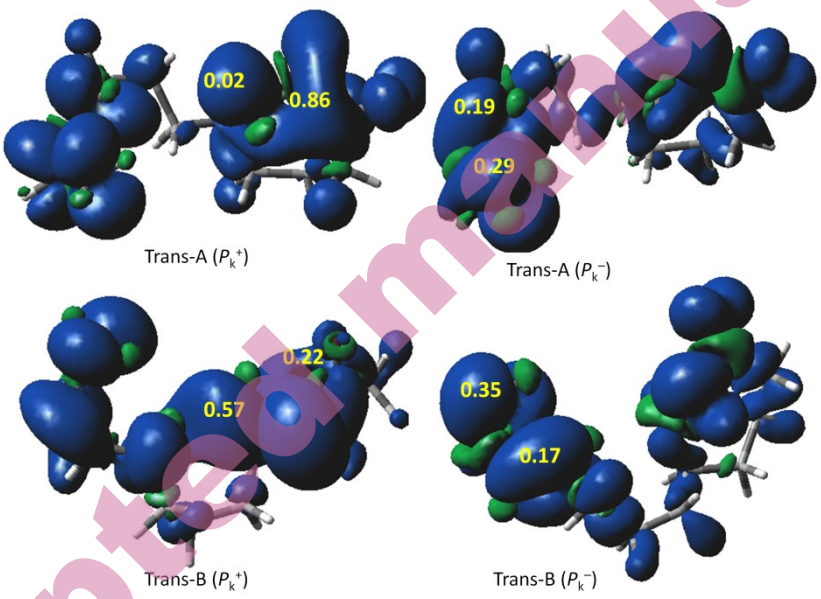


Fig.3: 3D representation of ASD of the radical anion and the radical cation of trans-A and trans-B isomers of 4-[(4e)-4,6-heptadien-1-yl]-2-cyclohepten-1-one.

*Fragment electrophilicity and nucleophilicity indices.*

In this part, we were interested on the characterization of group nucleophilicity and electrophilicity for intramolecular Diels Alder reactions of the compounds under study. To this end, fragment electrophilicity and nucleophilicity indices consisting of the global electrophilicity (ω) and nucleophilicity (*N*) within IMDA reagents associated with the fragmentation scheme given in Scheme 1 and the degree of transferability $T_W$, $T_N$ of the diene (D), ethylene (Dp) and the chain (Ch) that connects them were calculated at B3LYP/6-31+G(d,p) and are represented in Table V.

The electrophilic index of the ethylene Dp fragment for trans-A and trans-B isomers is higher than that of the diene D fragment. The nucleophilic index of diene fragments for both trans-A and trans-B isomers is much higher than that of ethylene fragments, the nucleophilicity values of D fragment are much higher

compared to electrophilic ones ($N_D/\omega_D > 1$). The contribution of the union chain to both nucleophilic and electrophilic is marginal compared to the D and Dp fragments. The degree of transferability of the fragment's electrophilicity is higher at ethylene fragment than at diene fragment ($T\omega_{Dp} > T\omega_D$). Thus, trans-A and trans-B isomers present the electrophilicity pattern accumulated at the ethylene Dp fragment. On the other hand, the degree of transferability of the fragment's nucleophilicity show that $T_{ND}$ is higher and $T_{NDp}$, in both trans-A and trans-B isomers. This suggests that the nucleophilicity pattern involved in IMDA reaction is concentrated at the diene fragment. The compounds under study are expected to undergo IMDA processes of D to Dp electron flow (DDpF), with fragment D acting as the nucleophile and fragment Dp acting as an electrophile (i.e. the normal electron demand process). Our predictions are in good agreement with those reported by Jorge Soto-Delgado and his collaborators.[32]

Table V. Fragment Electrophilicity and Nucleophilicity indexes for IMDA reaction of trans-A and trans-B isomers of 4-substituted cycloheptenone. .

| | trans-A | trans-B |
|---|---|---|
| $\omega_D$ eV | 0.42 | 0.37 |
| $N_D$ eV | 1.09 | 1.36 |
| $\omega_{Dp}$ eV | 0.74 | 0.56 |
| $N_{Dp}$ eV | 0.78 | 0.61 |
| $\omega_{ch}$ eV | -0.02 | -0.02 |
| $N_{ch}$ eV | -0.07 | -0.11 |
| % ($T\omega_D = \omega_D / \omega$) | 23.4 | 26.4 |
| %($T\omega_{Dp} = \omega_{Dp} / \omega$) | 41.2 | 39.3 |
| %($T_{ND} = N_D / N$) | 36.4 | 43.5 |
| %($T_{NDp} = N_{Dp} / N$) | 26.2 | 19.6 |

The calculated dual philicity indexes γ reported in Table VI, can be utilized to describe the direction of the electron flux in IMDA process. Specifically, if the charge transfer CT occurs from the Diene to the ethylene fragments or inversely, from the ethylene to the Diene to fragments. It may be noted that ($\gamma_1 > \gamma_2$) in both trans-A and trans-B isomers. Consequently, in this IMDA reaction, the charge transfer took place rather from the diene fragment to the ethylene fragment. This finding is in agreement with other computational studies that characterize the charge transfer by examining the global electron density transfer GEDT.[34]

Table VI. The dual philicity indexes $\gamma_1$ and $\gamma_2$ predicted values

| | $\gamma_1$ | $\gamma_2$ | $\Delta\gamma_{12}$ |
|---|---|---|---|
| trans-A | 1.83 | 1.21 | 0.62 |
| trans-B | 1.92 | 0.99 | 0.93 |

The fragment's electrophilicity difference $\Delta\omega_\Omega$ indices provide insight into the polar character of the IMDA reaction. The calculated values are displayed in Table VII. For trans-A and trans-B isomers, these values, that are not significative, are 0.27 and 0.28 eV, respectively.

Table VII. Electrophilic index of $\omega_D$, $\omega_{Dp}$ and the invariance of electrophile ($\Delta\omega_\Omega$) of D and Dp fragments.

| | D | | | Dp | | | |
|---|---|---|---|---|---|---|---|
| | η (eV) | μ (eV) | ω (eV) | η (eV) | μ (eV) | ω (eV) | $\Delta\omega_\Omega = \lvert w_D - W_{Dp} \rvert$ |
| trans-A | 1.91 | -1.37 | 0.49 | 0.97 | -1.20 | 0.77 | 0.27 |
| trans-B | 2.31 | -1.62 | 0.57 | 0.55 | -0.97 | 0.86 | 0.28 |

## CONCLUSION

In summary, in order to predict which atoms within molecules under investigation are most likely to suffer electrophilic and nucleophilic attacks, various global and local reactivity and selectivity descriptors have been shown to be very powerful to predict the most electrophilic and nucleophilic sites. These descriptors prove to be well adapted to study the reactivity of title molecules. It seems useful to recall the main results that we obtained in this theoretical study and which can be summarized as follows:

- The global nucleophilicity indices predict that the trans-B isomer can be classified as a strong nucleophile, according to the nucleophilicity scale. It is is more nucleophilic than the trans-A isomer. The trans-A isomer (ω>1.50 eV) is a strong electrophile, that is able to participate easily in polar Diels Alder reactions.

In order to predict the preferred electrophilic and nucleophilic sites within molecules under study, it will be necessary to focus attention to the calculated local electrophilicity and nucleophilicity reactivity indices. In both trans-A and trans-B isomers, the electrophilic $P_k^+$ Parr function shows the β conjugated $C_{16}$ carbon to be the most electrophilic center, whereas the nucleophilic $P_k^-$ Parr function displays $C_{33}$ atom as nucleophilic center.

The local electrophilicity $\omega_k$ and local nucleophilicity $N_k$ gave the same trends of reactivity by favoring $C_{16}$ and $C_{33}$ as the most electrophilic and most nucleophilic sites, respectively. Accordingly, The IMDA reaction path of the *trans* isomers of 4-[(4E)-4,6-heptadien-1-yl]-2-cyclohepten-1-one that is more privileged in terms of regioisomerism will be characterized by the first formation of the $C_{16}$-$C_{33}$ single bound.

With an aim to simultaneously predict the electrophilicity and nucleophilicity sites of the molecules under investigation, The local reactivity difference index $R_k$ is shown to be very efficient in predicting nucleophilic and electrophilic centers at particular site through their sign. This index is also able to identify the stronger

electrophilic and nucleophilic sites that are assigned, as expected, to $C_{16}$ and $C_{33}$, respectively.

According to the fragmentation technique, describing the electrophilic and nucleophilic group, the diene fragment behaves like a good nucleophile (electron donor) while the ethylene fragment behaves like an electrophile (electron acceptor) in this IMDA reaction. The dual descriptors γ1 and γ2 clearly show that the charge transfer occured rather from the diene fragment to the ethylene fragment.

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## И З В О Д

### КОНЦЕПТУАЛНА ТЕОРИЈА ФУНКЦИОНАЛА ГУСТИНЕ ЗАСНОВАНА НА КАРАКТЕРИЗАЦИЈИ ЛОКАЛНЕ ЕЛЕКТРОФИЛНОСТИ И НУКЛЕОФИЛНОСТИ ЗА ПРОУЧАВАЊЕ ИНТРАМОЛЕКУЛСКЕ ДИЛС-АЛДЕРОВЕ РЕАКЦИЈЕ ТРАНС-ИЗОМЕРА 4-[(4E)-4,6-ХЕПТАДИЕН-1-ИЛ]-2-ЦИКЛОХЕПТЕН-1-ОНА

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Једна од најзначајнијих метода за ефикасну синтезу и формирање сложених полицикличних молекула од биолошког значаја обухвата употребу Дилс-Алдерове (ДА) реакције, нарочито њене интрамолекулске варијанте. Експериментално је утврђено да су транс изомери 4-супституисаних циклохептенона изванредни диенофили, који без проблема учествују у ДА реакцијама. У овом раду смо желели да разјаснимо и предвидимо реактивност интрамолекулских Дилс-Алдер (ИМДА) реакција транс-А и транс-Б изомера 4-супституисаних циклохептенона помоћу индекса реактивности изведених из теорије функционала густине (ДФТ), на B3LYP/6-31G+(d,p) нивоу теорије, користећи Gaussian09 програм. Како бисмо идентификовали реакционе центре и предвидели селективност ових једињења према електрофилном и нуклеофилном нападу, коришћене су електрофилне Парове функције ($P_k^+$) и нуклеофилне Парове функције ($P_k^-$), као и локална електрофилност ($\omega_k$) и локална нуклеофилност ($N_k$). Ради јасније класификације електрофилности и нуклеофилности интерагујућих сегмената унутар молекула, локални индекс разлике реактивности ($R_k$) коришћен је као дескриптор за проучавање ове ИМДА циколадиције. Индекси електрофилности и нуклеофилности фрагмената израчунати су према моделу фрагментације. Дуални индекс филности (γ) и степен трансферабилности су такође одређени. Наши прорачуни су показали, како је и очекивано, да ће се електронски трансфер дешавати са диена ка диенофилном сегменту. Ова предвиђања су у складу са другим теоријским студијама које анализирају електронски трансфер путем глобалног преноса електронске густине.

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