

## An approached method for predict the nature of the reaction mechanism by assessment of the binding chain $(CH_2)_n$ ( $n=1, 2$ and $3$ ) role to the intramolecular cycloaddition Diels-Alder reaction of triene amide

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### Abstract

In this study, we propose a new approach that their purposes to facilitate the theoretical examinations of the intramolecular Diels-Alder (IMDA) reactions of triene amide and other IMDA reactions. In this end, the nature of reaction mechanism (NRM) will be determined by evaluating the contribution of binding chain on the HOMO and LUMO energies of triene amide. During our study, we have used the density functional theory (DFT) combined with B3LYP hybrid and 6-31G(d,p) basis set level. The results found shows that the binding chain has a negligible contribution on the HOMO and LUMO energies of triene amide molecule. Therefore, the diene and dienophile are treated as they were in isolated fragments. Thus the calculation of the NRM reveals that these reactions are at normal electronic demand (NED) in accordance with the results found by charge transfer between fragments in the transition state.

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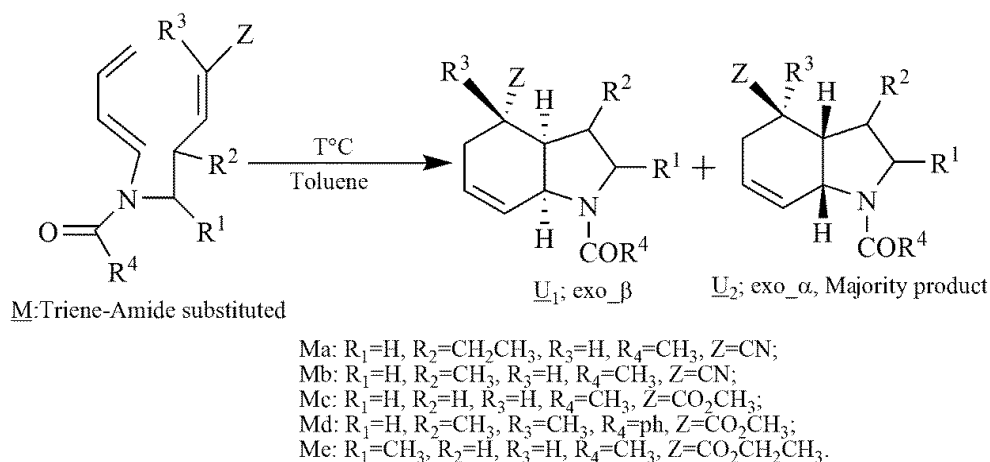
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**Keywords:** IMDA, NED, Binding chain, NRM, Intramolecular, Transition state.

## 1. Introduction

Diels Alder (DA) reaction is one of the most useful methods for the construction of six cycles. And attracted a considerable interest of the experimental [1-8] and theoretical scientists [9-14]. 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 the natural products [16,17]. The distribution of global electronic properties in fragments or in functional groups within a single molecule is a powerful tool to discuss the reactivity of 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. In 2014 [18], we have shown by the computation of charge transfer (CT) in the transition state of intramolecular triene amide reaction (Scheme 1) that these reactions have a normal electronic demand (NED). Thus, the diene behaves as an electron donating and the dienophile behaves an electron withdrawing. However, this method is expensive on time the computation as well the appropriate transition state is very difficult to be determined in the intramolecular reactions and especially for the complex molecules. In view to overcoming this difficulty, we thought of another solution. In our present work we will attempt to know the nature of the reaction mechanism (NRM) for the intramolecular Diels-Alder of triene-amide reaction [19,21] (Scheme 1) by applying a simple method in which involves dividing the triene-amide molecule at the separated fragments (diene and dienophile) by estimating subsequently the effect of binding chains ( $\text{CH}_2$ )<sub>n</sub> (with n= 1, 2 and 3) on the HOMO and LUMO energies (Scheme 1). Therefore, The obtained results will be used for evaluation of the frontier molecular orbital (FMO) in which provide a qualitative information about the feasibility of the DA reaction [22,23] and moreover to predict the NRM of the triene amide reaction.



**Scheme 1:** Intramolecular cycloaddition Diels-Alder reaction of triene-amide.

## 2. Materials and methods

The geometry optimizations were performed at the B3LYP exchange-correlation energy functional [24,25] with the most popular basis sets 6-31G(d,p). All the calculations were performed with the GAUSSIAN G09 program package [26] and visualization of the output files are performed using the Gauss-View 5.0.8 software. To identify the nature of the reaction mechanism (NRM) for the IMDA reaction of the triene-amide, we will be needed to determine the absolute value of the difference energy of HOMO and LUMO [27]:

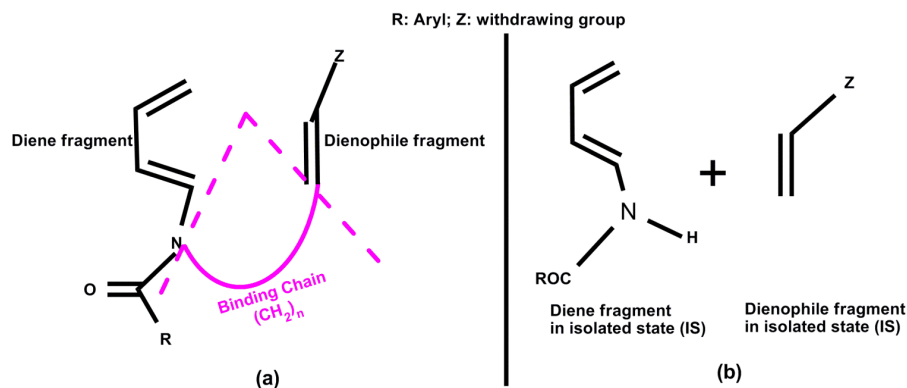
$$E1|\epsilon_{\text{HOMO(Diene)}} - \epsilon_{\text{LUMO(Dienophile)}}| \quad (1)$$

$$E2|\epsilon_{\text{HOMO(Dienophile)}} - \epsilon_{\text{LUMO(Diene)}}| \quad (2)$$

Such as the reaction is:

- Normal electronic demand (NED) if  $E1 < E2$
- Inverse electronic demand (IED) if  $E2 < E1$ .

We suppose that the triene amide molecule contains three portions, in which two fragments are diene and dienophile as well a binder (binding chain) (Figure 1)



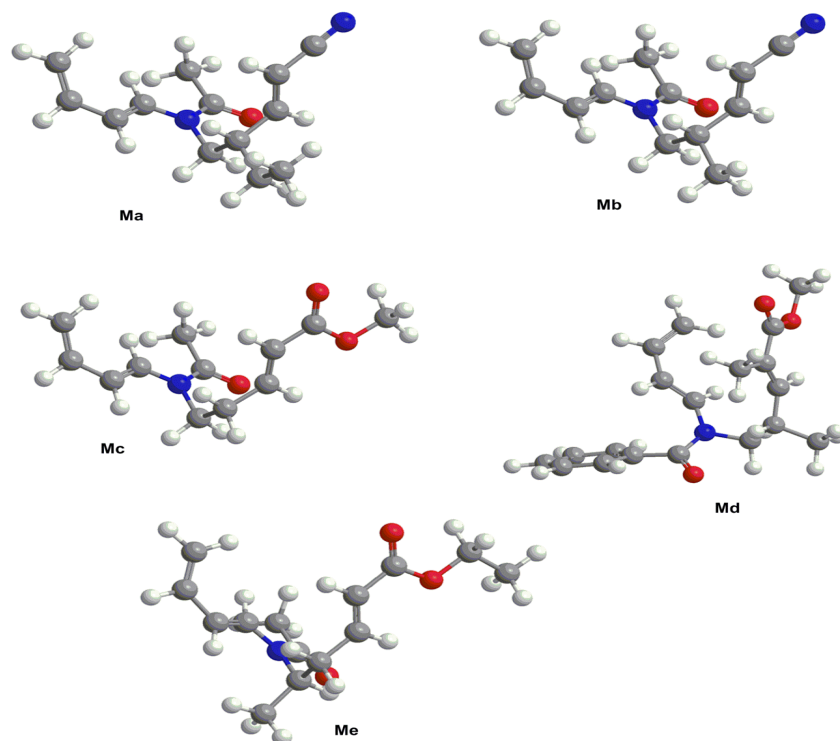
**Figure 1.** (a) diene and dienophile in the attached fragment, (b) diene and dienophile in the isolated fragment.

### 3. Results and Discussions

The graphical representation of different compounds Ma, Mb, Mc, Md and Me are shown schematically in Figure 2, the energies of the frontier molecular orbital of HOMO and LUMO are represented in Table 1. In order to make out the contribution of the binding chain on the HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) energies of triene-amide molecule, we will be tried to study the diene and dienophile fragments as are in the isolated fragments whereas the binding chain (CH<sub>2</sub>)<sub>n</sub> (n=1, 2 and 3) will be added in succession to these fragments. So the diene, dienophile and binding chain are donated in blue, red and black color respectively. The results are given in Tables 2 and 3.

**Table 1.** HOMO and LUMO energies of Ma, Mb, Mc, Md and Me compounds.

Compounds	HOMO(a.u.)	LUMO(a.u.)
Ma	-0.21396	-0.04396
Mb	-0.21437	-0.04384
Mc	-0.20884	-0.03716
Md	-0.20534	-0.04570
Me	-0.20921	-0.03820



**Figure 2.** Optimized geometries of Ma, Mb, Mc, Md, and Me compounds.

**Table 2.** HOMO and LUMO energies of Dienes fragments.

Compounds	Structure	HOMO (au)	LUMO (au)
(A)	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$	-0.23002	-0.02566
(B)	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{N}(\text{H})\text{COCH}_3$	-0.20920	-0.03078
(Ba)	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{N}(\text{H})\text{COC}_2\text{H}_5$	-0.20803	-0.03250
(Bb)	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{N}(\text{H})\text{COC}_3\text{H}_7$	-0.20772	-0.03227
(Bc)	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)\text{COCH}_3$	-0.20497	-0.02878
(Bd)	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{N}(\text{CH}_2\text{CH}_3)\text{COCH}_3$	-0.20406	-0.02863
(Be)	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{N}(\text{C}_3\text{H}_7)\text{COCH}_3$	-0.20315	-0.02811
(C)	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{N}(\text{H})\text{CO}-\text{benzene}$	-0.20867	-0.04868
(Ca)	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)\text{CO}-\text{benzene}$	-0.20995	-0.04425

**Table 3.** HOMO and LUMO energies of Dienophiles fragments.

Compounds	Structures	HOMO (au)	LUMO (au)
(1)	$\text{CH}_2=\text{CH}_2$	-0.26540	0.01622
(2)	$\text{CH}_2=\text{CH}-\text{CH}_3$	-0.24848	0.02666
(3)	$\text{N}\equiv\text{C}-\text{CH}=\text{CH}_2$	-0.28956	-0.05699
(3a)	$\text{N}\equiv\text{C}-\text{CH}=\text{CH}-\text{CH}_3$	-0.27264	-0.04504
(3b)	$\text{N}\equiv\text{C}-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_3$	-0.27165	-0.04477
(3c)	$\text{N}\equiv\text{C}-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_3$	-0.27089	-0.04473
(4)	$\text{CH}_3-\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}_2$	-0.27199	-0.04575
(4a)	$\text{CH}_3-\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{CH}_3$	-0.26588	-0.03662
(4b)	$\text{CH}_3-\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_3$	-0.26525	-0.03707
(4c)	$\text{CH}_3-\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{C}_3\text{H}_7$	-0.26477	-0.03666
(4d)	$\text{CH}_3-\text{O}-\text{C}(=\text{O})-\text{C}(\text{CH}_3)=\text{CH}_2$	-0.26766	-0.03850
(4f)	$\text{CH}_3-\text{O}-\text{C}(=\text{O})-\text{C}(\text{CH}_3)=\text{CH}-\text{CH}_3$	-0.25179	-0.03229
(4g)	$\text{CH}_3-\text{O}-\text{C}(=\text{O})-\text{C}(\text{CH}_3)=\text{CH}-\text{CH}_2-\text{CH}_3$	-0.25149	-0.02956
(4k)	$\text{CH}_3-\text{O}-\text{C}(=\text{O})-\text{C}(\text{CH}_3)=\text{CH}-\text{CH}(\text{CH}_3)_2$	-0.25109	-0.02987
(5)	$\text{CH}_3-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}_2$	-0.26943	-0.04586
(5a)	$\text{CH}_3-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{CH}_3$	-0.26304	-0.03432
(5b)	$\text{CH}_3-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{C}_2\text{H}_5$	-0.26266	-0.03563
(5c)	$\text{CH}_3-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{C}_3\text{H}_7$	-0.26183	-0.03489

**Table 4.** HOMO and LUMO Energy of Dienes and Dienophiles fragments with the binding chain (CH<sub>2</sub>)<sub>n</sub>, n= 4, 5 and 6.

BC number	Fragments	HOMO(au)	LUMO(au)
n=6	CH <sub>2</sub> CHCHCHNCO <sub>2</sub> CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub>	-0.203158	-0.028732
	CH <sub>2</sub> CHCHCHNCO <sub>2</sub> Ø(CH <sub>2</sub> ) <sub>6</sub>	-0.207188	-0.042816
	NCCHCH(CH <sub>2</sub> ) <sub>6</sub>	-0.269047	-0.040738
	H <sub>3</sub> CCO <sub>2</sub> CHCH(CH <sub>2</sub> ) <sub>6</sub>	-0.263994	-0.036132
n=5	CH <sub>2</sub> CHCHCHNCO <sub>2</sub> CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>	-0.203306	-0.028643
	CH <sub>2</sub> CHCHCHNCO <sub>2</sub> Ø(CH <sub>2</sub> ) <sub>5</sub>	-0.207365	-0.042865
	NCCHCH(CH <sub>2</sub> ) <sub>5</sub>	-0.269195	-0.040880
	H <sub>3</sub> CCO <sub>2</sub> CHCH(CH <sub>2</sub> ) <sub>5</sub>	-0.264155	-0.036219
n=4	CH <sub>2</sub> CHCHCHNCO <sub>2</sub> CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub>	-0.203416	-0.028590
	CH <sub>2</sub> CHCHCHNCO <sub>2</sub> Ø(CH <sub>2</sub> ) <sub>4</sub>	-0.207701	-0.042827
	NCCHCHCN(CH <sub>2</sub> ) <sub>4</sub>	-0.269371	-0.041069
	H <sub>3</sub> CCO <sub>2</sub> CHCH(CH <sub>2</sub> ) <sub>4</sub>	-0.264356	-0.036319

Ø: benzene substituent

In Table 4, we are found the same findings noted previously (tables 2 and 3) in which the HOMO and LUMO energies values of these fragments did not much have affected by the binding chain in such the values of these energies are slightly changed with the elevation of binding chain number. Consequently following these results, the binding chain has a very small contribution to the HOMO and LUMO energies of the triene amide molecule. These conclusions lead us to make a comparison between the obtained energies of HOMO and LUMO of both cases: of the isolated fragments and of the attached fragments constituted one molecule (Tri-portions) of triene amide of Ma, Mb, Mb, Mc and Me compound, the results are given in Table 5.

**Table 5.** Distribution of HOMO(au) and LUMO(au) energy of Dienes and Dienophiles fragments and of triene-amide molecule.

Entry	Fragments	Molecule		fragment (D)		fragment (Dp)	
		HOMO	LUMO	HOMO	LUMO	HOMO	LUMO
<b>Ma</b>	(3c + Bc)	-0.21396	-0.04396	-0.20497	-0.02878	-0.27089	-0.04473
<b>Mb</b>	(3b + Bc)	-0.21437	-0.04384	-0.20497	-0.02878	-0.27165	-0.04477
<b>Mc</b>	(4a + Bc)	-0.20884	-0.03716	-0.20497	-0.02878	-0.26588	-0.03662
<b>Md</b>	(4k + Ca)	-0.20534	-0.04570	-0.20995	-0.04425	-0.25109	-0.02987
<b>Me</b>	(5a + Bd)	-0.20921	-0.03820	-0.20406	-0.02863	-0.26304	-0.03432

In Table 5, we are noted for Ma, Mb, Mc and Me compounds in which the substituent CH<sub>3</sub> at position R<sub>4</sub> that the diene and dienophile in the attached fragment have equal energies to those fragment in the isolated fragments as: HOMO<sub>(diene in the isolated fragment)</sub> energy ≈ HOMO<sub>(diene in the attached fragment)</sub> energy and LUMO<sub>(dienophile in the isolated fragment)</sub> energy ≈ LUMO<sub>(dienophile in the attached fragment)</sub> energy. Otherwise, the compounds Md in which at the position R<sub>4</sub> the substituent benzene in such the diene fragment has a predominates nucleophilicity character in the triene-amide molecule in which render negligible the role of dienophile fragment, then in this case we have been constated that HOMO<sub>(diene in the</sub>

isolated fragment) energy  $\approx$  HOMO<sub>(diene in the attached fragment)</sub> energy and LUMO<sub>(diene in the isolated fragment)</sub> energy  $\approx$  LUMO<sub>(diene in the attached fragment)</sub> energy. The difference found between Md and Ma, Mb, Mc, Me compounds is due mainly to  $\pi$  electrons delocalization of the benzene substituent in position R<sub>4</sub>. Therefore, the benzene has remarkable effects on the HOMO and LUMO energies of these fragments independently as long as of the fragments in the attached molecule. However, the binding chain attachment of these fragments does not change many great things to these frontier molecular orbital energies. In this condition we consider that for compound Md: HOMO<sub>(diene in the attached fragment)</sub>  $\approx$  HOMO<sub>(diene in the isolated fragment)</sub> and LUMO<sub>(dienophile in the isolated fragment)</sub>  $\approx$  LUMO<sub>(dienophile in the attached fragment)</sub>. According to these significant results, we can conclude that the binding chain plays a perturbing role between the diene and dienophile fragments in which entrain a different chemical potential between fragments  $\mu_{\text{Diene}} \neq \mu_{\text{Dienophile}}$  [28-32]. Thus, the intramolecular becomes an intermolecular reaction between diene and dienophile fragments. Consequently, prediction the nature of reaction mechanism (NRM) to the intramolecular reaction has become simple, practical and operational in such requires only the application of equation 1 and 2 given in above of different fragment belonging of Ma, Mb, Md, Mc and Me compounds. The results are given in Table 6.

**Table 6.** Demand electronic normal  $\Delta N$  and inverse  $\Delta I$  values.

Entry	$\Delta N(E_{\text{HOMO(D)}} - E_{\text{LUMO(Dp)}})$	$\Delta I(E_{\text{HOMO(Dp)}} - E_{\text{LUMO(D)}})$
Ma (3c + Bc)	0.16024	0.24211
Mb (3b + Bc)	0.16020	0.24287
Mc (4a + Bc)	0.16835	0.23710
Md (4k + Ca)	0.17964	0.20764
Me (5a + Bd)	0.16974	0.23441

In Table 6 we are noted that these reactions have a normal electronic demand (NED), such as we have been remarked that the values found for the normal electronic demand systems are always less than those for the inverse electronic demand (IED) systems. Whereas, the dienes are electrons donating as well as the dienophiles are electrons withdrawing in accordance with the results found previously by the charge transfer (CT) calculation in the transition states [18].

#### 4. Conclusion

In this work, we have been tried to carry out a study in which their aims to have a method approached in order to facilitate the investigation of the intramolecular Diels-Alder reactions. For this purpose, the prediction of nature the reaction mechanism was realized by assessing the binding chain  $(\text{CH}_2)_n$  role with  $n=1, 2$  and  $3$  between diene and dienophile fragments. Such we were able to conclude on the one hand, that these binding chains have a weak effect on the HOMO and LUMO energies of the triene-amide molecule. On the other hand, the HOMO and LUMO energies of the main fragments of the diene and dienophile in the isolated state (IS) are approximately equal to those fragment in the attached fragment (AM) as HOMO<sub>(DIS)</sub>  $\approx$  HOMO<sub>(DAM)</sub> and LUMO<sub>(DpIS)</sub>  $\approx$  LUMO<sub>(DpAM)</sub>. In addition this approach has helped to minimize the computation time and also the failure rate in the localization of the transition states used in the previous method for determining the nature of reaction mechanism in IMDA reaction. Consequently, this study allowed us to deduce that these reactions have a normal electronic demand in accordance with the results found by the charge transfer in the transition states.

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