

Theoretical study of the regioselectivity in the intramolecular Diels–Alder Reaction of the Molecule Triene Amide.

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Abstract

The regioselectivity in the intramolecular Diels Alder reaction (IMDA) of the molecule triene-amide for the synthesis in the hexahydroindole product, is done the object of our present work, two product regioisomers are feasible, the analysis of PES (potential energy surface) shows that the fused isomer is the main product and that bridged isomer is the minority product, this preference is also confirmed by the maximum hardness global (MHP), in this study we used the density functional theory (DFT) at the hybrid B3LYP and basis set level 6-31G (d, p), the geometries are optimized for reagents, thus the transition states and for products, the calculation of the bond order (BO) using natural population analysis (NBO) explains that all the transition states are asynchronous, and the analysis by IRC (intrinsic reaction coordinate) of the majority compound shows that the reaction IMDA is concerted. The effect of the solvent toluene is taken into account by using the polarizable continuum model (PCM).

Keywords: Regioselectivity, Intramolecular, Regioisomers, Fused, Bridged, DFT, IRC.

Introduction

The Diels Alder (DA) reaction is a powerful tool, he used frequently in the synthesis of six members with excellent regio and stereoselective [1, 2]. And also one of the flexible

tool in the synthetic organic with the access to again polycyclic [3-10]. Diels alder reactions have attracted the interest of experimental and theoretical chemists [11-14]. There are many variants of the Diels–Alder reaction, by varying the nature of the (D) diene and (Dp) dienophile, many different types of six carboxylic acid structures can be composed, the intramolecular Diels–Alder reaction (IMDA) 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) in the fragments D and Dp of same reagent to produce a new bonds bearing in the same molecule to produce a polycyclic compound.

In our present work we will try to study the regioselectivity observed experimentally [17] the intramolecular Diels Alder IMDA reaction of triene amide, this reaction gives two different orientations, lead to the product corresponding to the fused mode as majority regioisomer. And the bridged product is the minority (fig. 1). In this study we will apply the chemical models generally applied in the intermolecular reactions (DA) to properly predict the chemical reactivity of the molecule of triene amide and know the majority produced by theoretical methods.

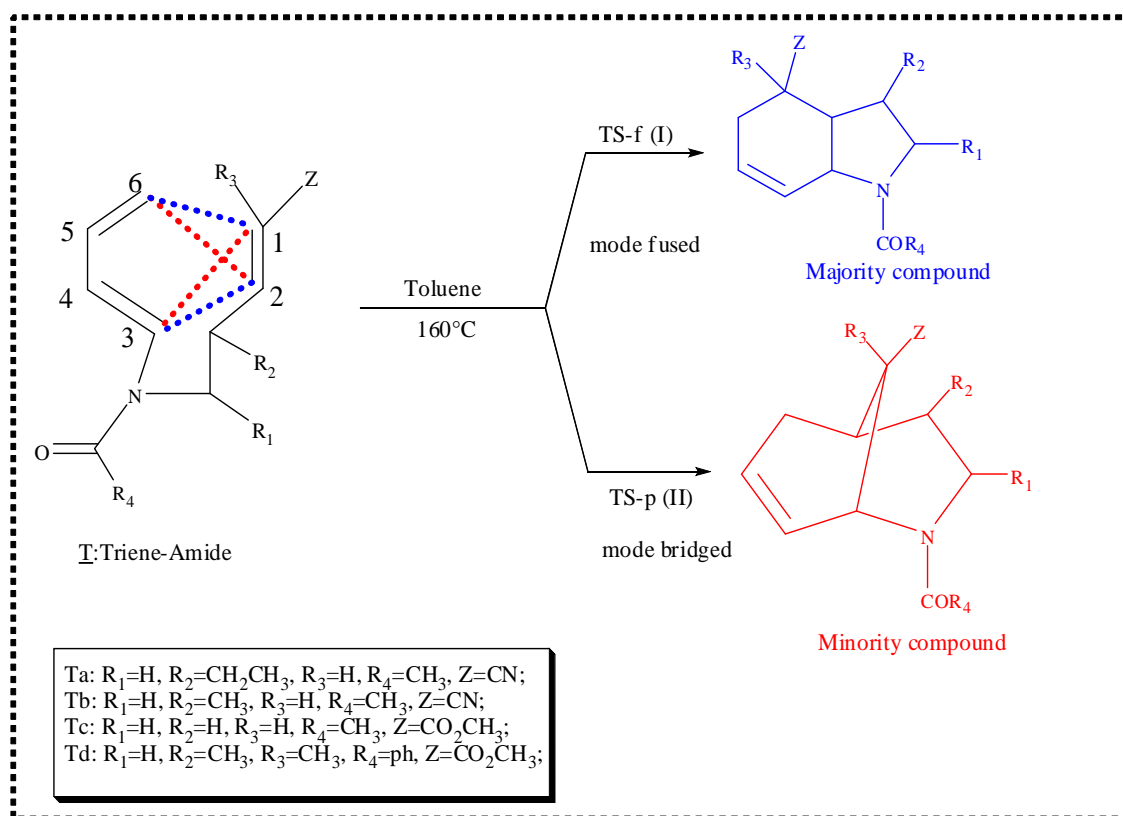


Figure 1: Cycloaddition intramolecular diels-alder Reaction of the Triene-Amide molecule.

2. Equation model and methods

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

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 surface potential of the system, Parr and Pearson [18] have proposed to use the method of finite differences, we obtain:

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

Such that 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 orbital molecular frontier ϵ_{HOMO} and ϵ_{LUMO} as follows [19-20]:

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

It has been shown that the structure is more stable when the gap of energy HOMO-LUMO is largest [21-25], it is the case of the maximum hardness principle (MHP), which was introduced by Pearson [26-30], and the State that "be a rule define the nature of molecules, hard molecules which arrange themselves also as possible". This principle is in accordance with the (hard and soft acid and bases' principle (HSAB), this principle is applied in a series of reactions, the number of examination from reactions, during which the hardness of a few atoms or radicals of a molecule always increases [31]. In addition, the test of the MHP and their advantage is well written in several literatures [32-34].

In this study, the geometry of reactants and products, have been optimized by the method of the functional of exchange and correlation B3LYP [35] with the standard 6-31 G * [36] by the analytical method of Berny [37]. Transition States have been localized at the level of basic B3LYP / 6-31G * and is subsequently followed by analysis IRC (intrinsic reaction coordinate) the two directions products and reagents, the stationary points are determined by the calculation of frequency as a transition state is characterized by a single imaginary frequency [38].

The calculation of bond order (BO) requires the calculation of the NBO (natural bond order) using the package [39], using the wiberg index [40]. The effect of the solvent was assessed by computing single point (SP). Calculations of stationary points of the reaction in solvent have included using the integral equation formalism in the group

polarizable continuum model (IEF - PCM) of the group of Tomasi [41–43]. Since the solvent is toluene, we used a dielectric constant $\epsilon = 2.374$. The calculation is done using the GAUSSIAN program 09 [44].

3. Results and discussion

In order to highlight the mode cyclization preferential (fused vs. bridged) and therefore the major product of the triene amide IMDA reaction, we have localized the transition state and calculated activation barriers for the two possible reaction pathways (scheme1).

3.1. Location of transition states:

The states of transitions TS-f and TS-p, corresponding to the two regioisomers fused and bridged respectively, were localized of calculation at the level B3LYP/6 - 31 G (d, p). The two transition states have been confirmed by the presence of one and only own negative value in the matrix of the force constants, there is only one imaginary frequency into Hessian matrix and she corresponding to the mode of vibration equivalent to the formation of two new bonds. The states of transition TS-f (fused) and TS-p (bridged) for the compound Ta, Tb, Tc and Td are represented in figure 1. The interatomic distances between the carbons interacting and bond orders (between brackets) are noted on the structures of the transition states and imaginary frequencies are given in cm^{-1} (figure 1).

➤ Internal interatomic distances for the transition states of the fused isomer are lower than those of external interatomic distances and are given with bond orders (between brackets) respectively for the compounds: Ta from 2.10Å [0.42] # 2.39Å [0.30], Tb from 2.10Å [0.42] # 2.41Å [0.30], Tc from 2.13Å [0.40] # 2.36Å [0.31] and Td from 2.08Å [0.45] # 2.44Å [0.29], These results show that CC (carbon-carbon) bonds of internal interatomic distances is formed first during the formation of the hexahydroindole compound. Other hand, the bond formed by the interior carbon of the dienophile and exterior carbon of the diene are shorter for the interatomic distances of the transition states of the bridged isomer so are formed first such for Ta's 1.99Å [0.58] # 2.78Å [0.22], Tb from 1.98Å [0.58] # 2.80Å [0.22], Tc from 2.10Å [0.51] # 2.61Å [0.26] et Td from 2.00Å [0.57] # 2.95Å [0.19] (figure 1).

➤ According the results of the bonding orders, we inscribe the following observation: for TS-f and TS-p, the bond orders are quite different. Therefore, the two processes are asynchronous (formation of a bond is advanced compared to the second). However, the process through the TS-p is slightly more asynchronous than through the TS-f (figure1).

The hydrogens are omitted. Formed bonds distances are given in Å, bond orders (OL) are written between brackets and the imaginary frequencies are given in cm^{-1} .

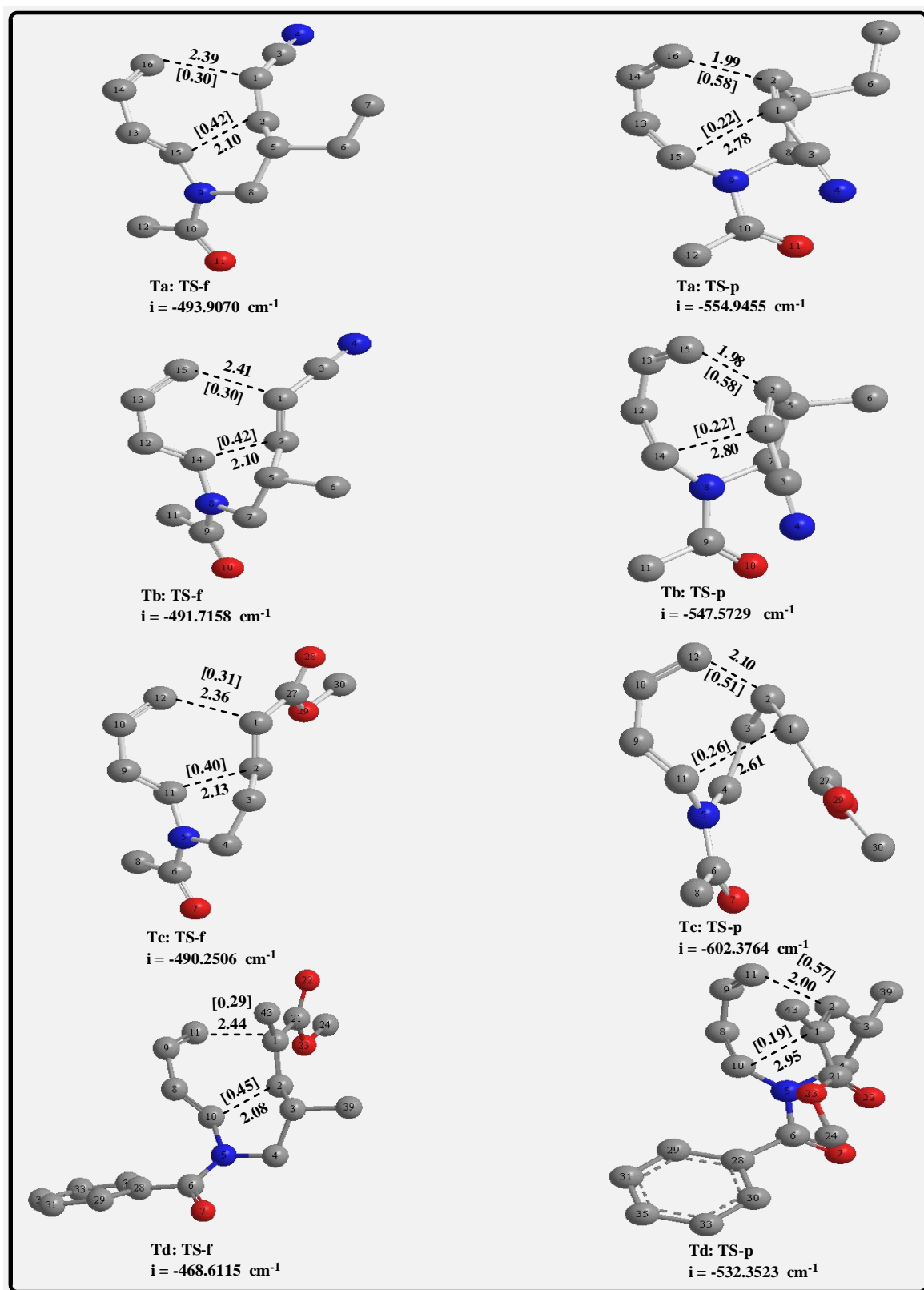


Figure 1. Optimized geometries of transition states from structures fused and bridged,

calculated in the level B3LYP/6-31G (d, p).

3.2. Determination of the reaction path (IRC):

The location of a transition state is followed by an IRC (Intrinsic Reaction Coordinate) calculation [45] to determine the reaction pathway of the reaction and connect the TS to the two minima (reactive and product). The IRC corresponding to the fused process favoured experimentally for both direction Reverse (to the product) and Forward (towards the reagent) of compound Ta, Tb, Tc and Td are presented in figures 1.1 and 1.2, calculating IRC was performed to the method B3LYB to the level basis set 6-31G (d, p) for the transition states structures for fused compounds (majority) and diagrammed subsequently by the software of visualisation gauss view (5.0.8) [46].

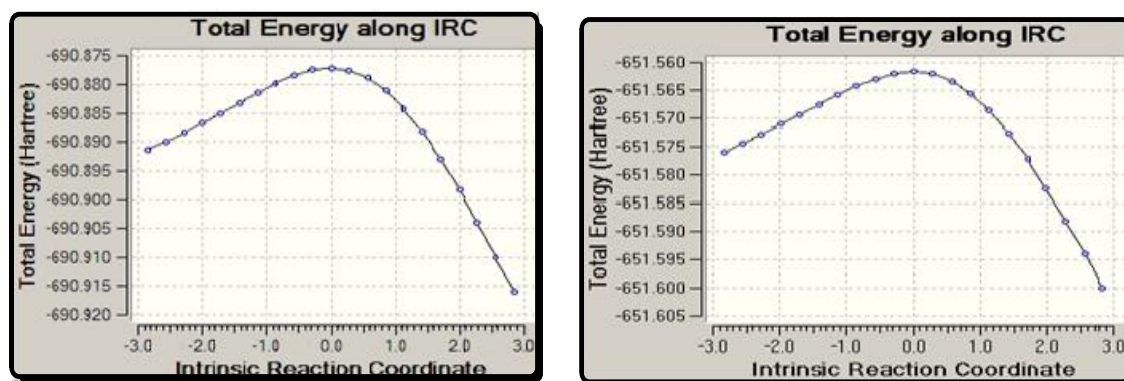


Fig 1.1: Calculation IRC global in IMDA reaction of compound Ta (left) and Tb (right) in absence of solvent toluene.

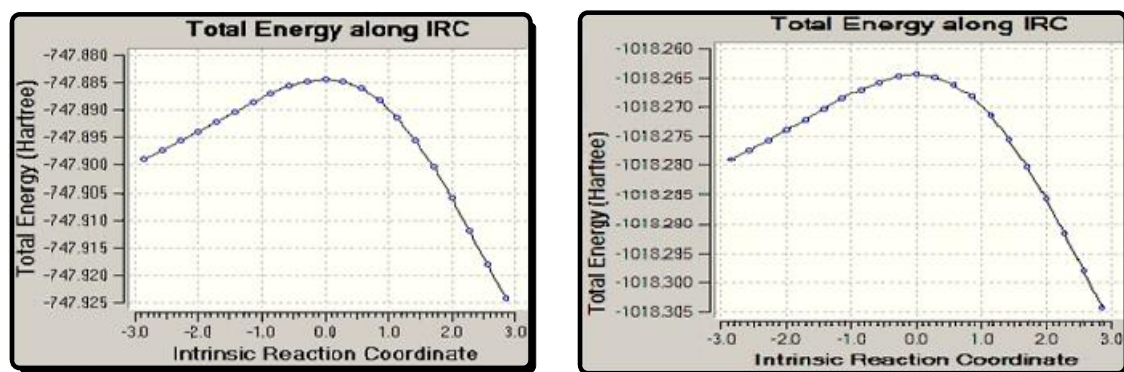


Fig 1.2: Calculation IRC global in IMDA reaction of compound Tc (left) and Td (right) compound in absence of solvent toluene,

According with figures 1.1 and 1.2 which represent the graphs of global IRC calculation (to product and reactive) of the Ta, Tb, Tc and Td reagents. The complete optimization of the last structure obtained with an IRC (direction to the product) calculation and the

first structure (direction towards reagent) we at gives deal a structure practically identical to that of the final product and the starting product for all studied compounds Ta, Tb, Tc and Td, at the cycloaddition intramolecular Diels Alder reaction IMDA. These results confirm the absence of a reaction intermediate. Therefore, these reactions follow a concerted mechanism.

3.3. Calculation of activation energies and energy of the reaction:

Table 1. Groups, the relative energy of reagents E_r , the activation energy E_a of the transition states, the enthalpy of formation ΔH_f , the Gibbs free energy ΔG and energy ΔE of the reaction in the temperature of 433.15 K and 1 atm in the presence of the solvent toluene, calculated to the method B3LYP/6-31G **.

<i>Compounds</i>	<i>E_r (u.a)</i>	<i>E_a (*)</i>	<i>ΔH_f (*)</i>	<i>ΔG (*)</i>	<i>ΔE (*)</i>
Ta	-690.928552				
TS (Ta-f)		27.822			
TS (Ta-p)		64.616			
Pd (Ta-f)			-21.008	-13.378	-18.801
Pd (Ta-p)			-15.353	-6.119	-12.790
Tb	-651.612484				
TS (Tb-f)		27.388			
TS (Tb- p)		63.771			
Pd (Tb-f)			-21.144	-13.385	-18.889
Pd (Tb-p)			-15.799	-6.631	-13.218
Tc	-747.932989				
TS (Tc-f)		26.803			
TS (Tc- p)		64.218			
Pd (Tc-f)			-21.302	-13.919	-19.113
Pd (Tc-p)			-17.304	-7.724	-14.802
Td	-1018.300986				
TS (Td-f)		25.019			
TS (Td- p)		66.690			
Pd (Td-f)			-21.794	-14.042	-20.614
Pd (Td-p)			-16.758	-7.614	-14.309

* : (kcal/mol)

Flowing the results given in table 1, we remark that:

➤ E_a (TS-fused) < E_a (TS-bridged); which shows that the product fused is more favoured kinetically of product bridged.

As a result, the fused cyclization is easier to achieve compared to the bridged cyclization.

➤ ΔE (Pd-f) < ΔE (Pd-p) et ΔH_f (Pd-f) < ΔH_f (Pd-p) et ΔG (Pd-f) < ΔG (Pd-p) which shows that the fused product is more thermodynamically favoured than bridged product. Therefore, the fused product is more stable compared to the bridged product.

The potential energy surface (PES) corresponding to the two modes of the fused and bridged cyclizations in the intramolecular Diels-Alder reaction of triene amide is shown in figure 2.

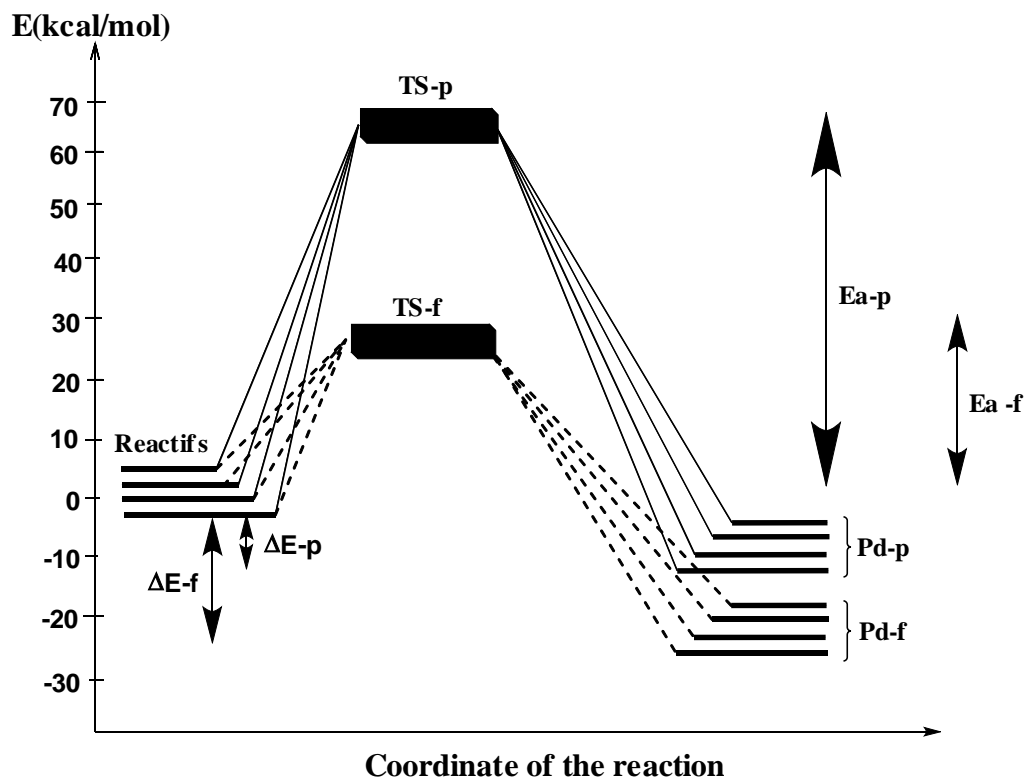


Figure 2. Energy profile in kcal/mol for the IMDA reaction for triene-amide molecule from two isomers fused and bridged compound.

3.4. Use of the maximum hardness principle:

The values of the global hardness η -f and η -p corresponding to two transition states TS-f and TS-p are given in table 2.

Table 2: represents the energy of orbital HOMO, the energy of orbital LUMO, hardnesses global η -f and η -p of the compound fused and bridged respectively.

Compounds	<i>TS-f</i>			<i>TS-p</i>		
	HOMO	LUMO	η -f	HOMO	LUMO	η -p
Ta	-0.230	-0.067	0.162	-0.195	-0.089	0.106
Tb	-0.231	-0.070	0.162	-0.195	-0.090	0.105
Tc	-0.225	-0.056	0.169	-0.194	-0.073	0.122
Td	-0.220	-0.058	0.162	-0.180	-0.080	0.099

The MHP rule established that "maximum hardness corresponds to the maximum stability. The results show that global hardnesses TS-f is higher than those of the TS-p; which implies that the transition states TS-f are harder than the transition states TS-p and therefore the fused regioisomer is more stable than bridged regioisomer.

Conclusion

The regioselectivity fused and bridged of the reaction in cycloaddition IMDA of triene amide of systems Ta, Tb, Tc and Td have been elucidated with two theoretical approaches (maximum hardness and activation barriers), with the method B3LYP/6-31G(d, p) in the presence of toluene and temperature of 433.15K at 1 atm, the two approaches justify and rationalize properly fused preference experimentally observed. And that all reactions are concerted and asynchronous.

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