

# A DFT Study of the Regioselectivity in Intramolecular Diels-Alder Reactions with Formation of a Tricyclodecane Skeleton

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Received September 06, 2010; Revised October 27, 2010; Accepted November 02, 2010

**Abstract:** Three different intramolecular Diels-Alder (IMDA) reactions associated with the formation of *fused* and *bridged* tricyclodecane skeletons have been studied at the B3LYP/6-31G(d) computational level. While substitution on the diene and dienophile fragments modulates the polar character of the reaction, the strain effect produced by the methylene tether affects the activation energy, and its torsion controls the different regioisomeric channels of the IMDA process. Analysis of the reactivity indices recently proposed [J. Soto-Delgado *et al.*, *Org. Biomol. Chem.*, **2010**, 8, 3678] within the conceptual density functional theory allows for the characterization of the mechanism including the charge transfer within the reagents involved in these IMDA reactions as well as for the direction of the electronic flux in the intramolecular processes.

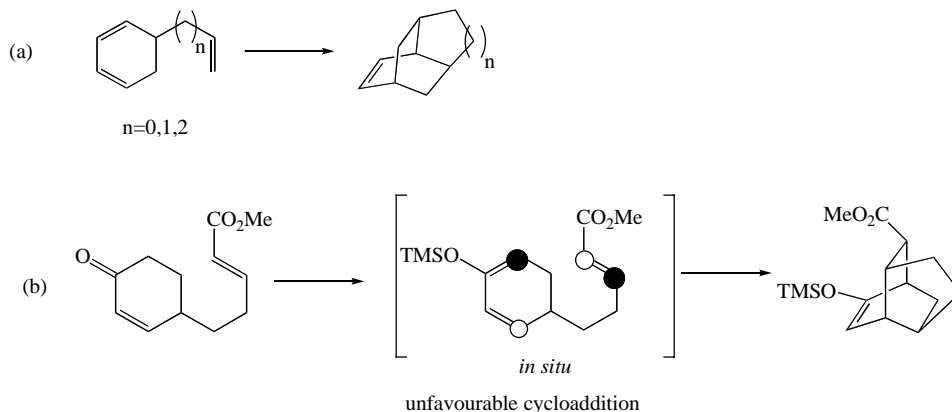
**Keywords:** Intramolecular cycloadditions, group electrophilicity, Intramolecular charge transfer.

## INTRODUCTION

The Diels-Alder (DA) reaction is one of the most useful synthetic reactions in organic chemistry. It belongs to a general class of cycloaddition reactions. By varying the

many biological and pharmacological systems and also as a route in the total synthesis of natural products [1].

Krantz and Lin studied reactions of 5-alkylen-1,3-cyclohexadienes and developed new routes for



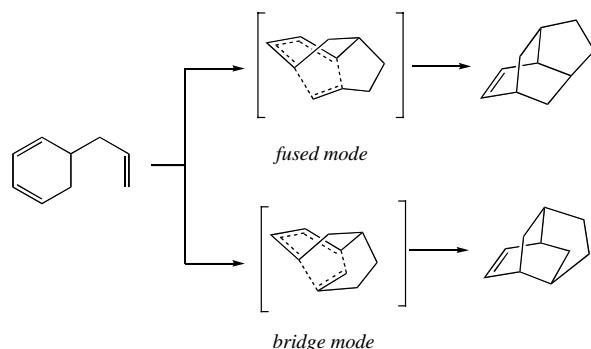
**Scheme 1.**

nature of the diene (D) and dienophile (Dp) many different types of six-membered carbocyclic structures can be built. The intramolecular Diels-Alder (IMDA) reaction is widely used for the construction of contiguous cycles in only one synthetic step. In this case the reaction generates two new carbon-carbon bonds to produce polycyclic compounds from reactants bearing the D and Dp frameworks in the same molecule. This reaction has been used in the construction of

functionalization of tricyclic derivatives having the bicyclo[2.2.2]octane skeleton (Scheme 1a) [2]. The substitution at either the D and/or the Dp fragments produces a change in reactivity, but the ratio of the observed regioisomers was different to that predicted by frontier molecular orbital theory (FMO) [3]. These unexpected results were traced to the activation at the reactive sites which is restricted by the methylene tether. This effect hampers a clean elucidation of the reaction mechanism [4] (see Scheme 1b). The present contribution is oriented to shed light on the regio- and stereo-chemical course of these intramolecular processes.

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While the rate of intermolecular DA reactions has been related to the polar character of the reaction [5], the flexibility of the tether to reach the transition state (TS) structure is the component that limits the reaction rate of IMDA processes. A molecular model analysis shows that, depending on the length of the tether and/or the substitution pattern, the approach between D and Dp fragments generate the bridge with or without a significant tension (see Scheme 2).



Scheme 2. Regiochemistry model to IMDA process.

## THE MODEL

In a previous article [6], Domingo et. al. proposed that the global electrophilicity index [7] introduced by Parr *et al.* could be used as a reliable quantity to classify the electrophilicity of a series of D and Dp involved in intermolecular DA reactions within a unique relative scale. Useful information about the polarity at the TS for a given reaction can be obtained from the difference in global electrophilicity  $\Delta\omega$  of the D/Dp interacting pair. Thus, small electrophilicity differences are related to non-polar mechanisms, while large electrophilicity differences are associated with polar mechanisms [6]. Recently, we have demonstrated that these rules can be transferred to IMDA process [8, 9] by introducing fragment's electrophilicity and nucleophilicity indices. These analyses indicated that electronic effects such as charge transfer (CT) along of the reaction coordinate are invariant in both inter and intramolecular processes [9]. Geometric effects on the other hand, such as the strain associated with the tether, can modulate the activation energies in intramolecular processes.

The global electrophilicity index [7],  $\omega$ , which measures the stabilization energy when the system acquires an additional  $\Delta N$  from the environment is given by the following simple expression:  $\omega = \mu^2/2\eta$ . It is expressed in terms of the electronic chemical potential,  $\mu$ , chemical hardness,  $\eta$ , at the ground state of the molecules. This index has been used to classify the dienes and dienophiles currently used in DA reactions within a unique scale of electrophilicity [6]. Both, the electronic chemical potential and chemical hardness may be further approached in terms of the one electron energies of the frontier molecular orbitals HOMO and LUMO,  $\varepsilon_H$  and  $\varepsilon_L$ , using the expressions  $\mu \approx (\varepsilon_H + \varepsilon_L)/2$  and  $\eta \approx (\varepsilon_L - \varepsilon_H)$ .

On the other hand, the nucleophilicity index for a given system was defined [10] as  $N = \varepsilon_{\text{HOMO}} - \varepsilon_{\text{HOMO(TCE)}}$  where  $\varepsilon_{\text{HOMO}}$  is the HOMO energy of the nucleophile and

$\varepsilon_{\text{HOMO(TCE)}}$  corresponds to the HOMO energy of the tetracyanoethylene (TCE) taken as reference.

In the present approach we start by introducing the fragment electrophilicity and nucleophilicity indices. They are given as follows:

$$\omega(\text{Fragment}) = \omega_F = \omega \sum_{k \in F} f_k^+ \quad (1)$$

and

$$N(\text{Fragment}) = N_F = N \sum_{k \in F} f_k^- \quad (2)$$

where F = D or Dp. Regional Fukui function for electrophilic ( $f_k^+$ ) and nucleophilic ( $f_k^-$ ) attacks can be obtained from single point calculations at the optimized structures of the ground state of molecules by a method described elsewhere [11].

The direction of the electronic flux within an IMDA reagent may be determined introducing the following dual indices:

$$E1 = \omega_{Dp} + N_D \quad (3)$$

$$E2 = \omega_D + N_{Dp} \quad (4)$$

Thus if  $E1 > E2$  the process is expected to display a D to Dp electronic flux; whereas if  $E1 < E2$  the process will be characterized by a Dp to D electronic flux. For cases  $E1 \approx E2$ , the model predicts that the IMDA process will follow a non-polar channel with negligible CT at the TS. The dual indices are used here to determine the electronic flux which is associated to the D and Dp moieties. However, this qualitative model is not sufficient to describe the charge transfer along the reaction coordinate. For this purpose we use a regional electrophilicity which is defined in Eq (5) below [9]:

$$\omega_\Omega = \frac{\mu_\Omega^2}{2\eta_\Omega} \quad (5)$$

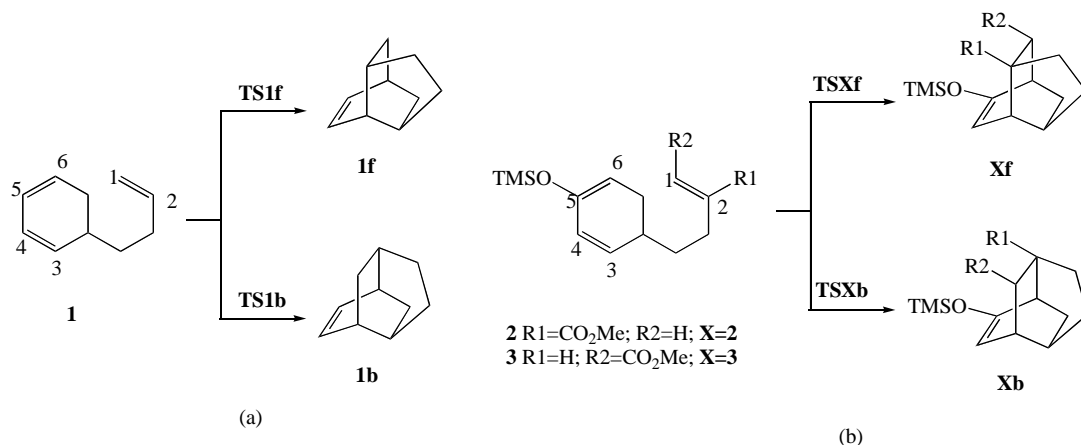
Where  $\Omega = A$  or  $B$ . This model of regional electrophilicity uses the inequality chemical potential principle [12]. The condensation process is however a little bit different because in the present case, the molecular orbital used are those centred at each molecular fragment [9].

All structures were optimized using B3LYP/6-31G(d) level of theory using the Gaussian 03 suite of programs [13]. The stationary points were characterized by frequency calculations in order to verify that the TS structures had one and only one imaginary frequency. The electronic structures of stationary points were analyzed using the natural bond orbital (NBO) method [14].

## RESULT AND DISCUSSION

### a) Analysis of Energies, Geometries and Electronic Structures for the IMDA Reactions of Compounds 1, 2 and 3

Three reactions were studied (see Scheme 3). The first one was a non-activated IMDA reaction associated with a

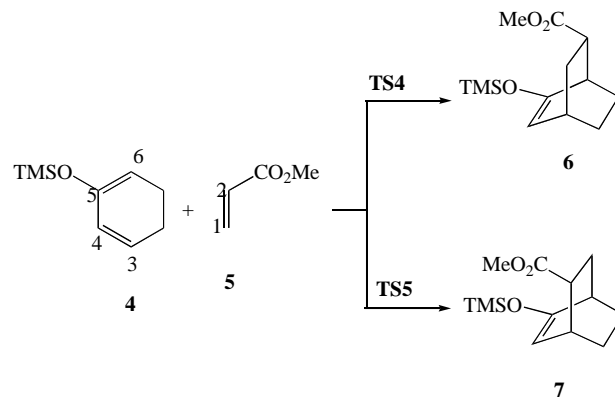


Scheme 3.

non-polar process (see the IMDA reaction of **1** in Scheme **3a**). The second and third reactions are IMDA polar processes with substitutions at both D and Dp fragments (see the IMDA reactions **2** and **3** in Scheme **3b**) [4]. For each one of these IMDA reactions two regiochemical channels, the *fused* (TSf) and the *bridged* (TSb) modes, were studied. Experimentally, the substitution present on compound **3** affords a non-expected regiochemistry, due to a restriction produced by the tether and the reaction proceeds at high temperature (180 °C) [4].

For the IMDA reaction of compound **1**, the activation energies associated with the two regioisomeric channels are 26.0 (**TS1f**) and 34.3 (**TS1b**) kcal/mol. Therefore, the *fused* mode is favoured over the *bridged* one by 8.3 kcal/mol. Compounds **2** and **3** present a change of the position of substituents. The energy profiles corresponding to the three IMDA reactions are shown in Fig. (1). The substitution produces a decrease in activation energy. The activation energy associated with the *fused* TS2f, 17.0 kcal/mol, is 7.7 kcal/mol lower to that associated with TS3f, 24.7 kcal/mol. The larger activation energy associated with the IMDA of compound **3** could be related to the specific disposition of the substituents, which does not favour the polar process.

This fact is confirmed by the analysis of the two regioisomeric channels associated with the intermolecular DA reaction between the activated diene **4** and methyl acrylate **5** shown in Scheme **4**. Thus, while the substitution pattern of **TS3f** is similar to that present at **TS4**, the one at **TS2f** corresponds to that at **TS5**. Note that for the intermolecular DA reaction between **4** and **5**, the more favourable regioisomeric approach mode *via* **TS4** is 16.3 kcal/mol lower in energy than that *via* **TS5**.



Scheme 4.

Finally, the energy profile analysis shows that in all cases the *fused* modes are favoured over the *bridged* ones by about 10 kcal/mol, due to the strain produced by the tether at the latter (see Fig. 1). These energy differences indicate a similar strain at the three-bridged channels.

Fig. (2) shows the geometry of the TSs involved in the three IMDA reactions. The lengths of the two forming bonds indicate that these TSs correspond to asynchronous bond-forming processes. The extent of the asynchronicity can be measured by considering the difference between the lengths of the two forming bonds at the TSs. For compound **1** the asynchronicity is 0.28 at **TS1f** and 0.52 at **TS1b**. For polar IMDA reactions of compounds **2** and **3** these values are 0.86 at **TS2f**, 0.95 at **TS2b**, 0.21 at **TS3f** and 0.05 at **TS3b**. These values show that the unlike substitution at compounds **2** and **3** causes a distinct asynchronicity at the TSs. In these intramolecular processes the results show that the

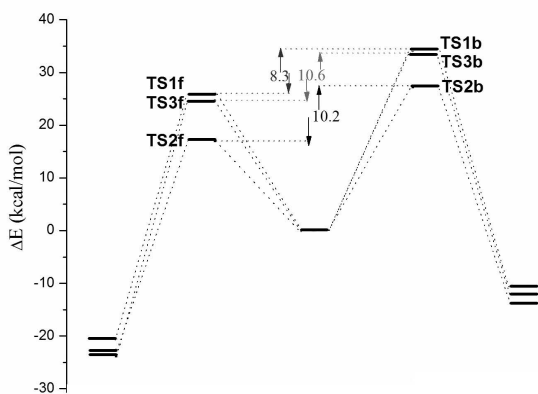
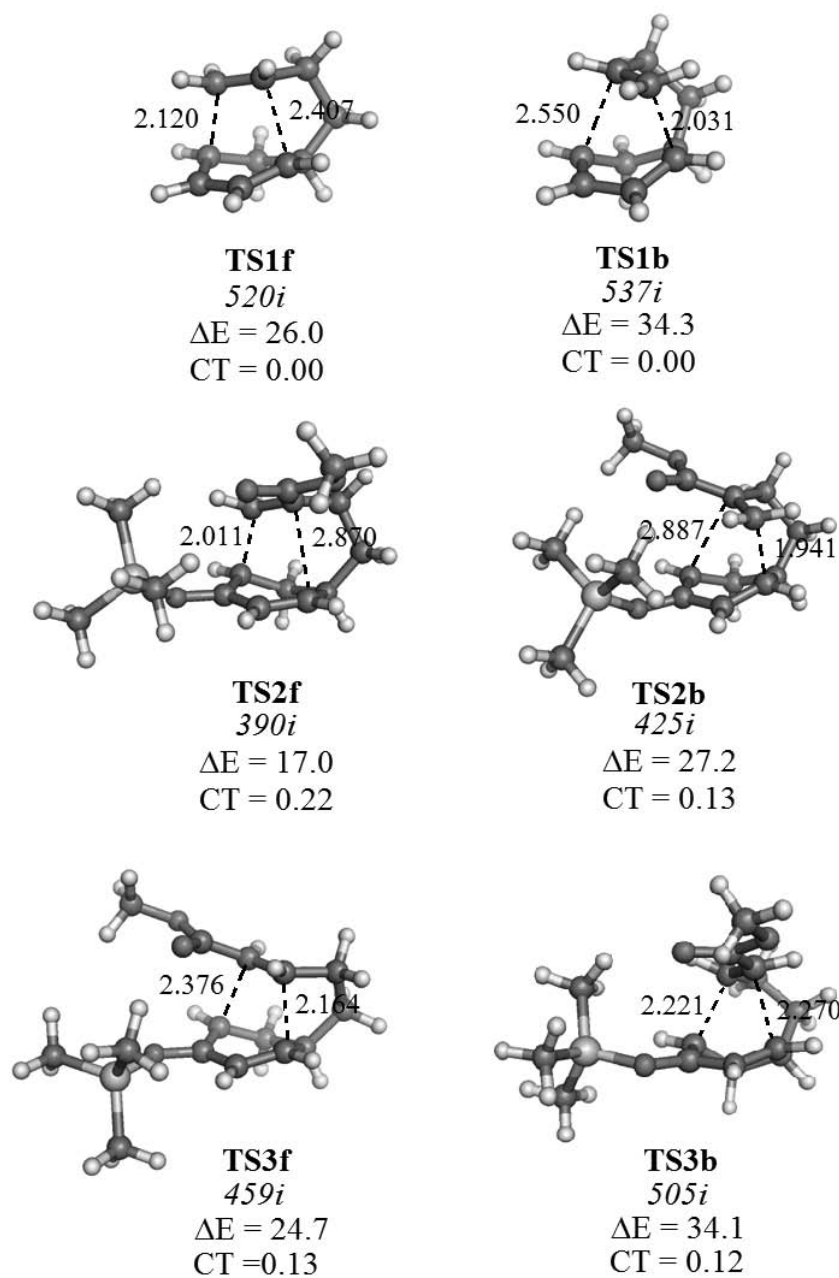


Fig. (1). Energy profile for IMDA reactions.



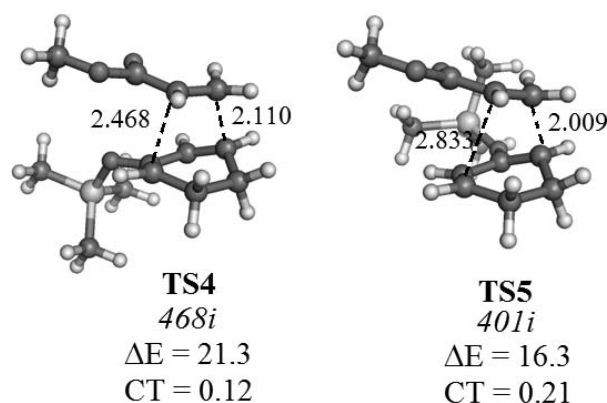
**Fig. (2).** Geometries *endo* transition states for IMDA reaction. The imaginary frequencies are given in cm<sup>-1</sup> and bond distances in Å units. Relative activation energy (ΔE) in kcal/mol and charge transfer (CT) in *e*.

asynchronicity of the bond-formation cannot be related to the activation energy of the process [15].

Fig. (3) shows the geometry of the TSs involved in the intermolecular DA reaction between **4** and **5**. The asynchronicity of bond formation is 0.36 at **TS4** and 0.82 at **TS5**. For these intermolecular processes, the more favourable reactive channel takes place along the more asynchronous TS, favouring the CT by a polar process.

The polar character of these DA reactions was evaluated analyzing the CT at the TSs. We performed a natural

population analysis (NPA) along the intrinsic reaction coordinate (IRC) associated with IMDA processes, and then they were compared with the CT at the intermolecular counterpart. Fig. (4a) illustrates variations in CT along the IRC for IMDA processes. Fig. (4b) shows the variations in CT for intermolecular DA processes. For non-polar IMDA processes the CT along the IRC did not present any variation. Polar processes show a similar tendency in both reaction types (DA and IMDA reactions). It can be seen that the CT pattern is essentially the same for intermolecular and



**Fig. (3).** Geometries *endo* transition states for DA reaction. The imaginary frequencies are given in cm<sup>-1</sup> and bond distances in Å units. Relative activation energy (ΔE) in kcal/mol and charge transfer (CT) in e.

intramolecular processes. A substantial CT is observed in the vicinity of the corresponding TS structure. Our results show that most DA reactions analyzed in this study have a *one-step, two-stage* mechanism through high asynchronous TSs. Along the first stage of the reaction, the CT increases to reach the formation of the first C-C sigma bond. At the second stage of the reaction, there is a decrease of the CT as a consequence of a back-donation along the formation of the second C-C sigma bond [5]. Finally, Fig. (4) shows that for these polar DA reactions, the maximum CT at the most favourable regioisomeric channels takes place after passing the TSs, while for the non-favoured TSs it appears at the TS region.

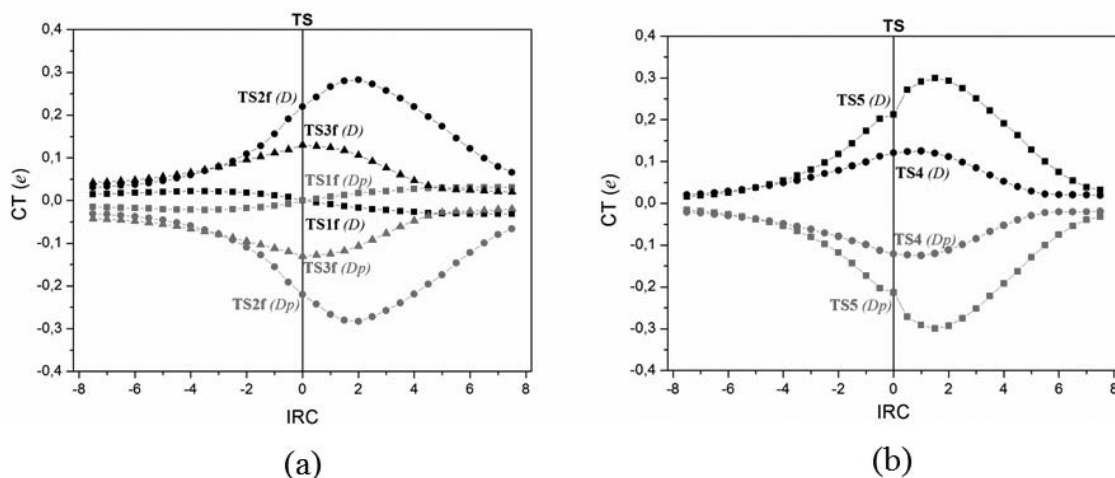
### b) Reactivity Indices Analysis for IMDA Reactions

The conceptual DFT has been used to explain the feasibility of polar DA reactions [5]. In this context, the electrophilicity index classifies the electrophilicity of a series of Ds and Dps involved in intermolecular DA reactions within a unique relative scale [6]. In addition, the

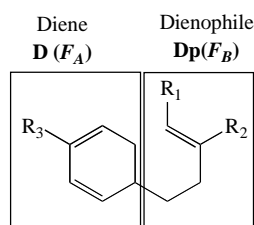
relationship between Δω at the ground state of the reagents and CT at the TSs, that is the polar character of the reactions, is directly related to the decrease at the energy barrier. In order to analyze the polar character of IMDA reactions, we have recently introduced a series of related indices, namely the fragment's electrophilicity and nucleophilicity indices, ω<sub>F</sub>, and N<sub>F</sub>, [8] and the invariance of the electrophilicity index ω<sub>Ω</sub>[9].

The electronic properties for compounds **1-3** are summarized in Table 1. The global electrophilicity and nucleophilicity indices of these compounds are 0.93 and 3.50 eV for **1**, 1.20 and 3.84 eV for **2** and 1.17 and 3.68 eV for **3**, respectively. While compound **1** is classified as a marginal electrophile within the electrophilicity scale [6], compounds **2** and **3** are classified as moderate electrophiles. Note that all three compounds are described as good nucleophiles following the N index in Table 1.

The fragment's electrophilicity and nucleophilicity indices on the other hand have been used to analyze the polar interactions in IMDA reactions [8]. Compound **1** presents



**Fig. (4).** Charge transfer along of the reaction coordinates (a) IMDA processes (b) DA processes.

**Table 1.** Global Properties of Fragments Embedded in Different Chemical Environments Present in IMDA Processes. Electronic Chemical Potential  $\mu$  and Chemical Hardness  $\eta$  in a.u. and Electrophilicity  $\omega$  in eV Units

- 1**  $R_1 = R_2 = R_3 = H$   
**2**  $R_1 = H; R_2 = CO_2Me; R_3 = OTMS$   
**3**  $R_1 = CO_2Me; R_2 = H; R_3 = OTMS$

	$\mu$	$\eta$	$\omega$	$N$	$\omega_D$	$\omega_{Dp}$	$N_D$	$N_{Dp}$
1	-0.1130	0.1870	0.93	3.50	0.91	0.02	3.45	0.05
2	-0.1167	0.1548	1.20	3.84	0.03	1.17	3.69	0.14
3	-0.1183	0.1632	1.17	3.68	0.01	1.16	3.66	0.02
	$\mu_A$	$\eta_A$	$\omega_A$		$\mu_B$	$\eta_B$	$\omega_B$	
1	-0.1118	0.1854	0.91		-0.1251	0.2561	0.83	
2	-0.1042	0.1764	0.83		-0.1155	0.1602	1.13	
3	-0.1061	0.1868	0.82		-0.1106	0.1444	1.15	

both electrophilic and nucleophilic patterns concentrated in the same D fragment ( $\omega_D = 0.91$  eV and  $N_D = 3.45$  eV). Compound **1** is classified as a marginal electrophile, and as a consequence it is expected to proceed by a non-polar IMDA reaction. This result is in clear agreement with the low CT found at **TS1f** and **TS1b**. Note that the FMO prescription will fail in these IMDA processes since the HOMO and LUMO levels are centred in the same D fragment within the molecule [8]. Compounds **2** and **3** present an electrophilic pattern concentrated in the Dp fragment,  $\omega_D = 1.17$  eV for **2** and 1.16 eV for **3**, while the nucleophilic pattern is concentrated in the D fragment,  $N_D = 3.69$  and 3.66 eV, for compounds **2** and **3** respectively. With the  $\omega_D$  and  $N_D$  at hand, the dual indices E1 and E2 defined in Eqs (3) and (4) may be obtained. These indices may be used to estimate the direction of the electronic flux. For compounds **2** and **3**: E1 = 5.13 and 4.82; E2 = 0.17 and 0.03, respectively. Therefore, for these compounds, E1 > E2 indicates that in these IMDA reactions the CT will take place from D to Dp: these reactions present a diene-dienophile electron flux (DDpF) mechanism [8].

For an IMDA reaction, the invariance of the electrophilicity index  $\omega_\Omega$  [9] accounts for the transferability of fragment's electrophilicity indices in comparison with the isolated molecules;  $\omega = 0.83$  eV for **4** and  $\omega = 1.49$  eV for **5**. In compounds **2** and **3** the values of the  $\omega_\Omega$  index of the D fragments are 0.83 and 0.82 eV, and the values of the Dp fragments are 1.13 and 1.15 eV, respectively. The decrease of the  $\omega_\Omega$  values of the Dp fragments at **2** and **3** may be traced to the electron-release character of the methylene chain present in these compounds. The fragment's electrophilicity difference  $\Delta\omega_\Omega = |\omega_{Dp} - \omega_D|$  is used to estimate the CT at the TSs associated with IMDA reactions. For compound **2** and **3** these values are 0.30 eV and 0.33 eV,

respectively. These values are higher in comparison with the value 0.08 eV for compound **1**.

Finally, the transferability index  $\omega_f/\omega$  accounts for the degree of projection of the global propriety onto fragments. Compounds **2** and **3** show a high degree of transferability of the fragment's electrophilicity ( $\omega_{Dp}/\omega$ ) in the Dp fragment [8], 97.5 and 99.1 per cent, respectively, due to the strong electron-withdrawing effect promoted by the carboxymethyl substituent. In addition, these compounds also present the nucleophilicity patterns concentrated in the D fragments. The degree of transferability of the fragment's nucleophilicity ( $N_D/N$ ) is 96.0 and 99.4 per cent, respectively.

In summary, this fragment analysis, which is in clear agreement with the CT performed at the corresponding TSs, reinforces the fact that the IMDA processes for **2** and **3** are mainly controlled by the presence of the electron-withdrawing methoxy carbonyl substituents present in the Dp fragment.

## CONCLUDING REMARKS

Three IMDA reactions associated with the formation of *fused* and *bridged* tricyclodecane skeletons have been studied at the B3LYP/6-31G(d) level of theory. In addition, the intermolecular DA process mode has also been considered to compare both processes. First, we have shown that the strain effect produced by the tether creates an increase of the activation energy, and therefore the torsion associated with the different regioisomeric channels determines the favoured reaction mechanism. The analysis of the electronic properties at the TSs shows that both reaction modes (the DA and the IMDA) present the same electronic behaviours, but the difference lies in the geometric factors

introduced by the chain of union between D and Dp in the IMDA reactions. Analysis of the reactivity indices defined within the conceptual DFT allows for the establishment of the electronic flux for compound **2** and **3** as a DDPF type. For compound **1** the small  $\Delta\omega_{\Omega}$  value shows that the IMDA process will have a non-polar character, whereas for compounds **2** and **3**, the high  $\Delta\omega_{\Omega}$  values indicate that these IMDA processes will proceed *via* a polar mechanism with substantial CT at the TS, which will decrease the activation energy. The larger activation energy associated with the IMDA of compound **3** relative to that for compound **2** could be related to the specific disposition of the substituents in the former that does not favour the polar process along the intramolecular mode.

## ACKNOWLEDGEMENTS

This work was supported by FONDECYT Grant 1070715. LRD thanks the Spanish Government for financial support through project CTQ2009-11027/BQU. Support from project 130922 from USM is also acknowledged.

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