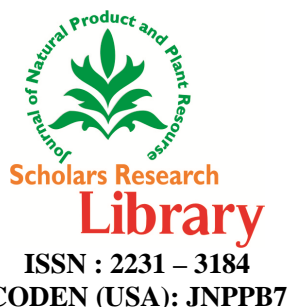




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### Exploration of regioselectivity phenomenon in [1+2] cycloaddition reactions between $\alpha$ -trans-himachalene and dibromocarbene on the basis of the reactivity indices theory

Redouan Hammal<sup>1\*</sup>, Abdellah Zeroual<sup>1</sup>, Ahmed Benharref<sup>2</sup> and Abdeslam El Hajbi<sup>1</sup>

<sup>1</sup>Physical Chemistry Laboratory, Chemistry Department, Faculty of Science, Chouaïb Doukkali University, BP 20, 24000 ElJadida, Morocco

<sup>2</sup>Laboratory of Biomolecular Chemistry, Natural Substances and Reactivity (URAC 16), Cadi Ayyad University, Semlalia Faculty of Science, BP 2390, 40000 Marrakech, Morocco

#### ABSTRACT

In this work, the mechanism and selectivity of the 1,2-cycloaddition of  $\alpha$ -trans-himachalene with dibromocarbene are studied using the DFT method at the B3LYP/6-311G(d,p) computational level. We have shown that  $\alpha$ -trans-himachalene behaves as a nucleophile, while dibromocarbene behaves as an electrophile. Analysis of the global and local electrophilicity and nucleophilicity indices allows an explanation about the regio- and chemoselectivity of this cycloaddition. The asynchronous concerted mechanism of this reaction is analyzed by the potential energy surface. The product (1R, 2S, 4R, 7S)-3,3-dibromo-8-methylene-4,12,12-trimethyl-tricyclo [5.5.0.0<sup>2,4</sup>] dodecane is more favored by stoichiometric reaction between dibromocarbene and  $\alpha$ -trans-himachalene, resulting from the attack of the most substituted double bond at the  $\alpha$  side (referred to here as P<sub>1</sub>( $\alpha$ )), while the product (1R, 2S, 4R, 7S, 8R)-3,3,13,13-tetrachloro-4,12,12-trimethyl-tricyclo [5.5.0.0<sup>2,4</sup>] -spiro[2<sup>8</sup>] tetradecane is preferred by the reaction between two equivalents of dibromocarbene with  $\alpha$ -trans-himachalene, resulting from the attack of the exocyclic double bond at the  $\beta$  side of  $\alpha$ -trans-himachalene (referred to here as P<sub>2</sub>( $\beta$ )). The stationary points were characterized by frequency calculations in order to verify that the transition states had one and only one imaginary frequency. These results are in good agreement with experimental outcomes.

**Keywords:** 1,2-cycloaddition, nucleophilicity, electrophilicity,  $\alpha$ -trans-himachalene, reactivity index, DFT.

#### INTRODUCTION

This work follows on from our study of the reactivity of the essential oil of the Atlas Cedar, *Cedrus atlantica*, [1] which is used in perfumery and cosmetics. A number of studies have investigated the isolation and identification of this oil, and the reactivity of its constituents [2-6].

The essential oil of the Atlas Cedar is principally composed (75%) of three bicyclic sesquiterpenic hydrocarbons, namely  $\alpha$ -cis-himachalene,  $\beta$ -himachalene and  $\gamma$ -cis-himachalene. When these are treated with hydrochloric acid in acetic acid, followed by dehydrogenation in a basic environment,  $\alpha$ -trans-himachalene is formed [7-9]. The reactivity of these sesquiterpenes has been studied [10-12]. Studies have also been carried out on the reactivity of the himachalenes (hemisynthesis) in order to obtain new compounds with olfactory properties of interest to the perfume industry [13-15]. In our study we looked at the action of two different quantities of dibromocarbene on  $\alpha$ -trans-himachalene, and analysed the chemo-, regio and stereoselectivity of these reactions. A stoichiometric quantity of dibromocarbene led to an attack at  $\alpha$  side of the most substituted double bond, while an excess of dibromocarbene

led to an attack at  $\beta$  side of the exocyclic double bond of  $\alpha$ -trans-himachalene. This shows that the endocyclic double bond of the  $\alpha$ -cis- and  $\alpha$ -trans-himachalene behaves in the same way as the exocyclic double bond [1].

By carrying out theoretical calculations regarding the behaviour of  $\alpha$ -trans-himachalene in the presence of dibromocarbene we have been able to predict chemoselectivity using frontier orbital theory, and to analyse regio- and stereoselectivity using reactivity indices and activation energies of the transition states. Experiments have shown that the action of a stoichiometric quantity of dibromocarbene on  $\alpha$ -trans-himachalene produces a majority of the regioisomer  $\alpha$ , referred to here as  $P_1(\alpha)$ , and a minority of the regioisomer  $\beta$ , referred to as  $P_1(\beta)$ . Reaction between  $\alpha$ -trans-himachalene and an excess of dibromocarbene leads to the formation a majority of the regioisomer  $\beta$ , referred to as  $P_2(\beta)$ , and a minority of the regioisomer  $\alpha$ , referred to as  $P_2(\alpha)$  (Figure 1).

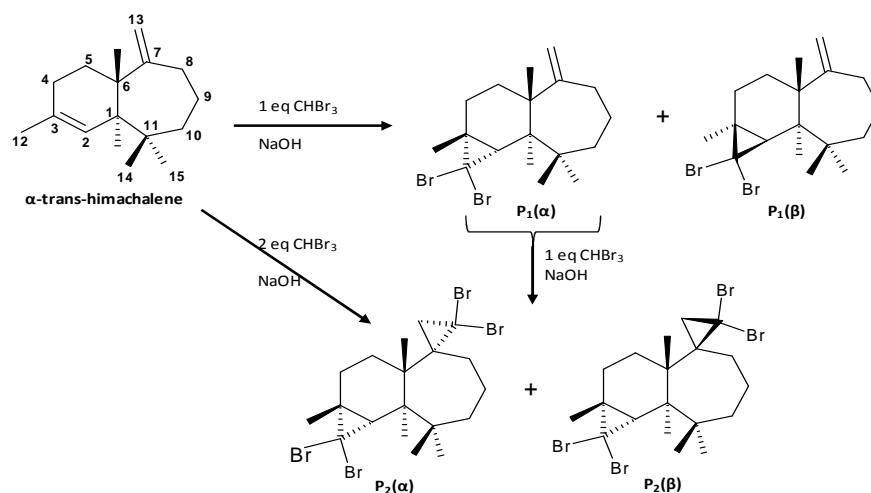


Fig. 1 Reaction between dibromocarbene and  $\alpha$ -trans-himachalene

## 2. Method of calculation

We studied the mechanism and equilibrium geometries of the reaction between  $\alpha$ -trans-himachalene and dibromocarbene, together with the transition states corresponding to the two approaches at the  $\alpha$  and  $\beta$  sides, using DFT/B3LYP/6-311G(d, p) [16-17]. We identified the transition states and confirmed their existence by the presence of a single imaginary frequency in the Hessian matrix. We calculated and plotted the intrinsic reaction coordinate (IRC) [18] in order to show that the transition state is indeed linked to the two minima (reactants and product). We analysed the electronic structures of the stationary points and the bond orders (Wiberg indices) [19] using natural bond order method (NBO) [20-21]. We calculated the values of enthalpies, entropies and free energies using standard statistical thermodynamics. All calculations were carried out using the DFT/B3LYP/6-311G(d, p) method in Gaussian 09 [22].

In order to demonstrate the nucleophilic/ electrophilic nature of the reactants, we calculated the electronic chemical potential  $\mu$  and the global hardness  $\eta$ . These two values can be calculated from the energies of the HOMO and LUMO frontier molecular orbitals, with  $\mu = (E_{HOMO} + E_{LUMO})/2$  and  $\eta = (E_{LUMO} - E_{HOMO})$  [23]. The global electrophilicity index  $\omega = (\mu^2/2\eta)$  [24] is also defined as the energy stabilisation due to charge transfer [25]. The nucleophilicity index  $N$  is expressed as a function of the HOMO energy of tetracyanoethylene (TCE) as  $N = E_{HOMO(Nu)} - E_{HOMO(TCE)}$  [26].

Reactivity indices were calculated from the HOMO and LUMO energies in the fundamental state of the molecules using DFT/B3LYP/6-311G(d, p). The static local electrophilicity  $\omega_k$  [27] and nucleophilicity indices  $N_k$  [24] are reliable predictors of the most favoured electrophile-nucleophile interaction for the formation of a chemical bond between two atoms. The expressions  $\omega_k = \omega \cdot P_k^+$  and  $N_k = N \cdot P_k^-$  [28] correspond respectively to the local electrophilicity index  $\omega_k$  and the local nucleophilicity index  $N_k$ .  $P_k^+$  and  $P_k^-$  are obtained by analysing the Mulliken spin density of the anion and the cation [28].

## 3. Analysis of results

### 3.1 Analysis of the reactivity indices of the reactants in the base state

#### 3.1.1 Predicting the Normal Electron Demand (NED) / Inverse Electron Demand (IED) characteristics of the reaction

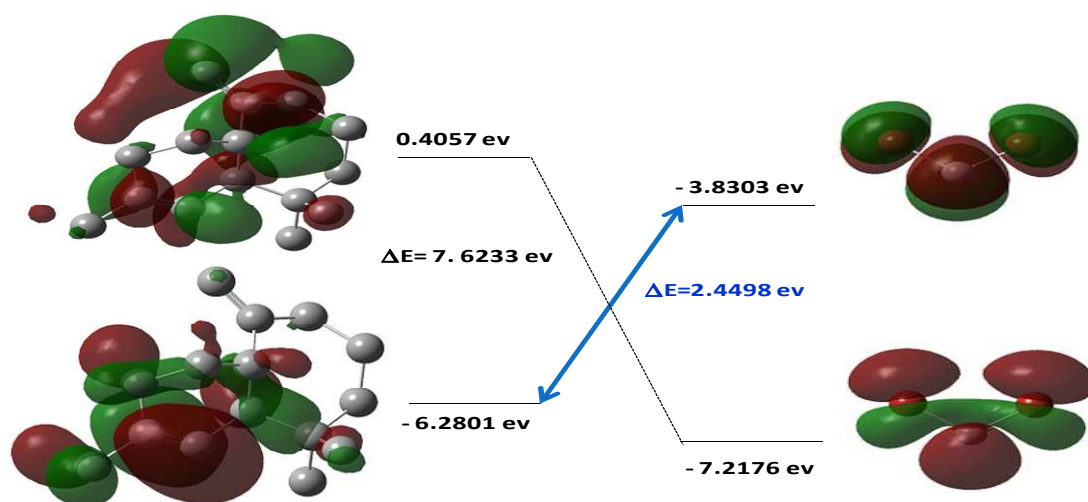
We used frontier molecular orbital theory to predict whether the reaction between  $\alpha$ -trans-himachalene and dibromocarbene can be characterised as NED (Normal Electron Demand) or IED (Inverse Electron Demand).

Global and local indices as defined by conceptual DFT [29] are effective tools for studying the reactivity of polar interactions.

Chemical electron potential  $\mu$ , chemical hardness  $\eta$ , global electrophilicity  $\omega$  and global nucleophilicity  $N$  are the global properties of  $\alpha$ -trans-himachalene and dibromocarbene which allow us to analyse the reactivity at various sites on these reactants. The energy gap between the HOMO of  $\alpha$ -trans-himachalene and the LUMO of dibromocarbene is 2.4498 eV, while the energy gap between the HOMO of dibromocarbene and the LUMO of  $\alpha$ -trans-himachalene is 7.6233 eV (Table 1). This result shows that  $\alpha$ -trans-himachalene behaves as a nucleophile, while dibromocarbene is an electrophile. The localisation of the HOMO and LUMO of  $\alpha$ -trans-himachalene and dibromocarbene are shown in Figure 2.

**Table 1 Energy gap between HOMO and LUMO in the reaction of  $\alpha$ -trans-himachalene with dibromocarbene (eV)**

	HOMO	LUMO	$ E_{\text{HOMO}}^{\text{(A)}} - E_{\text{LUMO}}^{\text{(B)}} $	$ E_{\text{LUMO}}^{\text{(A)}} - E_{\text{HOMO}}^{\text{(B)}} $
$\alpha$ -trans-himachalene (A)	-6.2801	0.4057	2.4498	7.6233
Dibromocarbene (B)	-7.2176	-3.8303		



**Fig. 2 Interaction between the orbital borders HOMO and LUMO of the  $\alpha$ -trans-himachalene and dibromocarbene calculated by DFT/B3LYP/6-311G(d,p)**

Table 2 shows that the electronic chemical potential  $\mu$  of  $\alpha$ -trans-himachalene is greater than that of dibromocarbene, while the global electrophilicity index  $\omega$  of dibromocarbene is greater than that of  $\alpha$ -trans-himachalene. These results confirm that  $\alpha$ -trans-himachalene is a nucleophile and that dibromocarbene is an electrophile, which implies that charge transfer takes place from  $\alpha$ -trans-himachalene to dibromocarbene. The significant difference in electrophilicity ( $\Delta\omega = 3.8590$  eV) between  $\alpha$ -trans-himachalene and dibromocarbene shows a high NED polarity for this reaction.

**Table 2 Electronic chemical potential  $\mu$ , hardness  $\eta$ , global electrophilicity  $\omega$  and global nucleophilicity  $N$  of  $\alpha$ -trans-himachalene and dibromocarbene (eV)**

	$\mu$	$\eta$	$\omega$	$N$
$\alpha$ -trans-himachalene	-2.9372	6.6858	0.6452	3.0885
Dibromocarbene	-5.5239	3.3873	4.5042	2.1511

### 3.1.2 Using electrophilicity and nucleophilicity indices to predict the regio- and stereoselectivity of the reaction

According to the polar model proposed by Chattaraj [30], the local philicity indices ( $\omega_k$  and  $N_k$ ) are reliable indicators for predicting the most favoured interaction between two polar centers. The most favored regioisomer is that which is associated with the highest local electrophilicity index  $\omega_k$  of the electrophile and the highest local nucleophilicity index  $N_k$  of the nucleophile. We determined  $N_k$  for  $\alpha$ -trans-himachalene and  $\omega_k$  for dibromocarbene in order to predict the most likely electrophile/nucleophile interaction throughout the reaction pathway, in order to elucidate the chemo- and stereoselectivity of the reaction. The carbon of dibromocarbene is the most electrophilic active site ( $\omega_C=2.1064$  eV). The  $C_2$  and  $C_3$  carbon atoms of the endocyclic double bond of  $\alpha$ -trans-himachalene are more nucleophilic and more active than those of the  $C_7$  and  $C_{13}$  atoms of the exocyclic double bond. Furthermore,

the C<sub>3</sub> carbon atom is the most nucleophilic site of the  $\alpha$ -trans-himachalene ( $N_{C_3}=0.8429$  eV). Figure 3 shows the most active sites of  $\alpha$ -trans-himachalene and dibromocarbene.

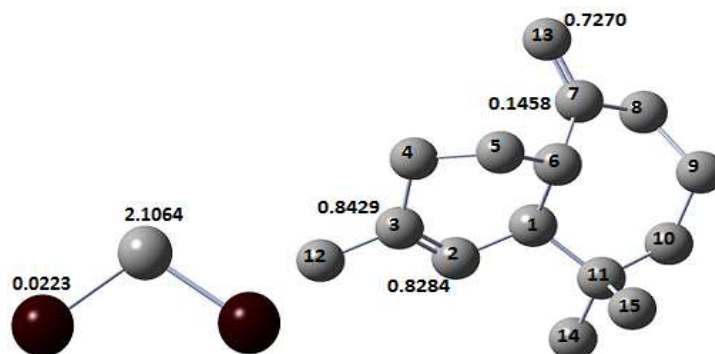


Fig. 3 Local nucleophilicity  $N_k$  (eV) of  $\alpha$ -trans-himachalene and local electrophilicity  $\omega_k$  (eV) of dibromocarbene.

We can therefore deduce that the most favored interaction will take place between the C<sub>3</sub> atom of  $\alpha$ -trans-himachalene and the C carbon atom of dibromocarbene, followed by closure of the cycle with the formation of the second C-C<sub>2</sub> bond. The interaction between the nucleophile  $\alpha$ -trans-himachalene and the electrophile dibromocarbene is therefore competitive.

The major products obtained from this reaction are indeed linked to the two active C=C sites of  $\alpha$ -trans-himachalene. Figure 4 shows that the attack leads to the formation of two chemoisomers, each of which consists of two regioisomers  $\alpha$  and  $\beta$ .

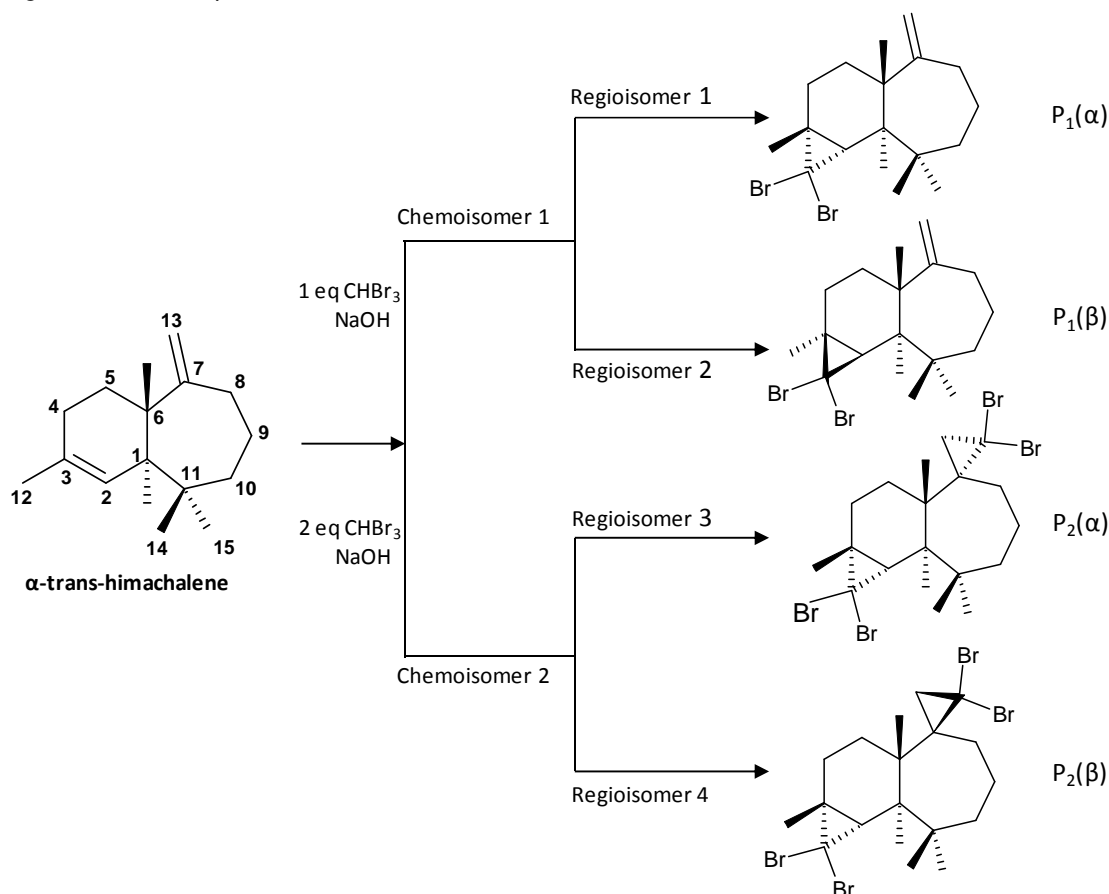


Fig. 4 Reaction of  $\alpha$ -trans-himachalene with dibromocarbene showing chemoselectivity

### 3.2 Study of the mechanism of the reaction between $\alpha$ -trans-himachalene and dibromocarbene

#### 3.2.1 Analysis of the potential energy surface and prediction of the reaction mechanism

The activation energy of transition state TS<sub>1</sub> (corresponding to the  $\alpha$  side) is 4.7461 kcal/mol, i.e. 6.5269 kcal/mol below TS<sub>2</sub> (corresponding to the  $\beta$  side) showing that the  $\alpha$  regioisomer is kinetically preferred to the  $\beta$  regioisomer

in the stoichiometric reaction. An excess of dibromocarbene results in two transition states: TS<sub>3</sub> (corresponding to the  $\alpha$  side) with an activation energy of 8.1474 kcal/mol, i.e 6.3107 kcal/mol below TS<sub>4</sub> (corresponding to the  $\beta$  side), indicating that the regioisomer corresponding to the  $\beta$  side is kinetically preferred to the  $\alpha$  regioisomer.

### 3.2.2 Analysis of the IRC of the reaction between $\alpha$ -trans-himachalene and dibromocarbene

The cycloaddition reaction may have one of two main mechanisms, concerted or stepwise. The concerted mechanism involves a single step with asynchronous formation of two bonds, or a single step with two phases, characterized by the formation of the first bond  $\sigma$  followed by the closure of the cycle without the formation of a stable intermediary reactant, while the two-step mechanism involves an intermediary reactant. We studied the molecular system as it develops during the reaction between  $\alpha$ -trans-himachalene and dibromocarbene by calculating IRC in order to show that the TS is indeed linked to the two minima (reactants and products).

The plots  $E=f(IRC)$  corresponding to all possible pathways are shown in figure 5. IRC calculation shows that this reaction follows a concerted mechanism in a single step but in two phases [31]: chemoisomer 1 corresponds to the formation of the C-C<sub>3</sub> bond, followed by closure of the cycle with the C-C<sub>2</sub> bond, while chemoisomer 2 corresponds to the formation of the C-C<sub>13</sub> bond, followed by closure of the cycle with the C-C<sub>7</sub> bond. Analysis of the IRC calculated using DFT/B3LYP/6-311G(d, p) shows that whatever quantity of dibromocarbene is used in the interaction with  $\alpha$ -trans-himachalene, the transition states are reached without going through a stable intermediary stage.

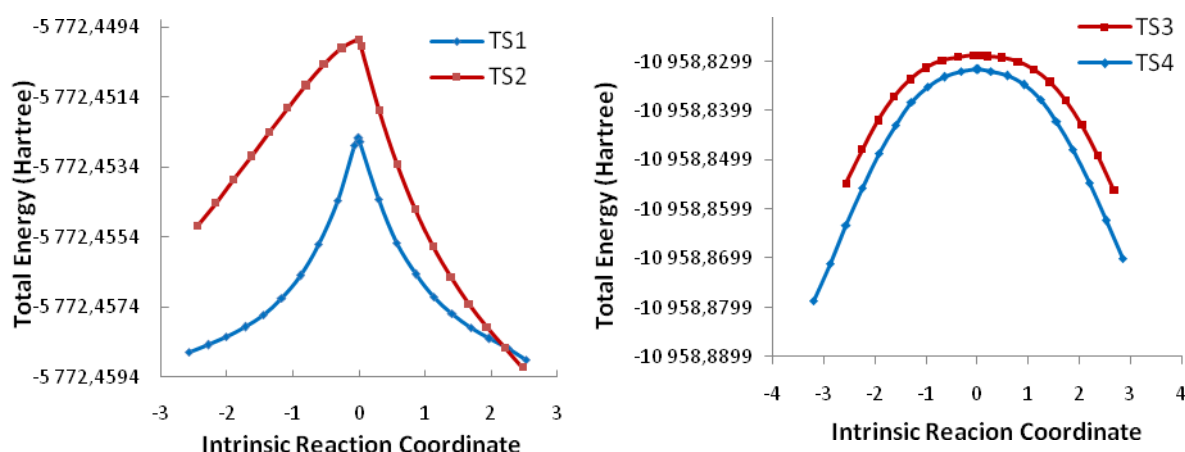


Fig. 5 IRC of the reaction between  $\alpha$ -trans-himachalene and dibromocarbene calculated using B3LYP/6-311G (d, p)

Tables 3 and 4 show that after making thermal corrections for the thermodynamic energies, the free activation enthalpies of TS<sub>1</sub> and TS<sub>2</sub> increase by 17.5169 kcal/mol and 21.2368 kcal/mol respectively, while the free activation enthalpies of TS<sub>3</sub> and TS<sub>4</sub> increase by 21.4997 kcal/mol and 19.8557 kcal/mol respectively. These high values are a result of the unfavorable activation entropies associated with the process.

Table 3 Thermodynamic energies of the reaction between  $\alpha$ -trans-himachalene and one equivalent of dibromocarbene calculated using DFT/6-311G (d, p)

	Les réactifs		TS <sub>1</sub>	TS <sub>2</sub>	P <sub>1</sub> ( $\alpha$ )	P <sub>1</sub> ( $\beta$ )
	$\alpha$ -trans-himachalene	Dibromocarbene				
E (u.a)	-586,1680	-5186,2921	-5772,4526	-5772,4497	-5772,5494	-5772,5397
$\Delta E$ (Kcal/mol)	-	-	4,7462	6,5270	-56,0140	-49,9013
H (u.a)	-585,7965	-5186,2843	-5772,0733	-5772,0687	-5772,1648	-5772,1549
$\Delta H$ (Kcal/mol)	-	-	4,6455	7,5615	-52,7823	-46,5637
S (cal/mol.K)	119,1160	69,0900	145,0350	142,3370	139,4010	140,9990
$\Delta S$ (cal/mol.K)	-	-	-43,1710	-45,8690	-48,8050	-47,2070
G (u.a)	-585,8531	-5186,3171	-5772,1422	-5772,1363	-5772,2311	-5772,2219
$\Delta G$ (Kcal/mol)	-	-	17,5169	21,2368	-38,2316	-32,4893
$\nu$ (cm <sup>-1</sup> )	-	-	-317,3498	-248,8933	-	-

The products P<sub>1</sub>( $\alpha$ ) and P<sub>1</sub>( $\beta$ ) obtained for a stoichiometric quantity of the reactants are strongly exothermic, by -56.0140 kcal/mol and -49.9013 kcal/mol respectively. Consequently, P<sub>1</sub>( $\alpha$ ) is thermodynamically preferred to P<sub>1</sub>( $\beta$ ). In the second reaction (excess of dibromocarbene), products P<sub>2</sub>( $\alpha$ ) and P<sub>2</sub>( $\beta$ ) are also exothermic, by -51.2683 kcal/mol and -47.8241 kcal/mol respectively, indicating that P<sub>2</sub>( $\alpha$ ) is thermodynamically preferred to P<sub>2</sub>( $\beta$ ).



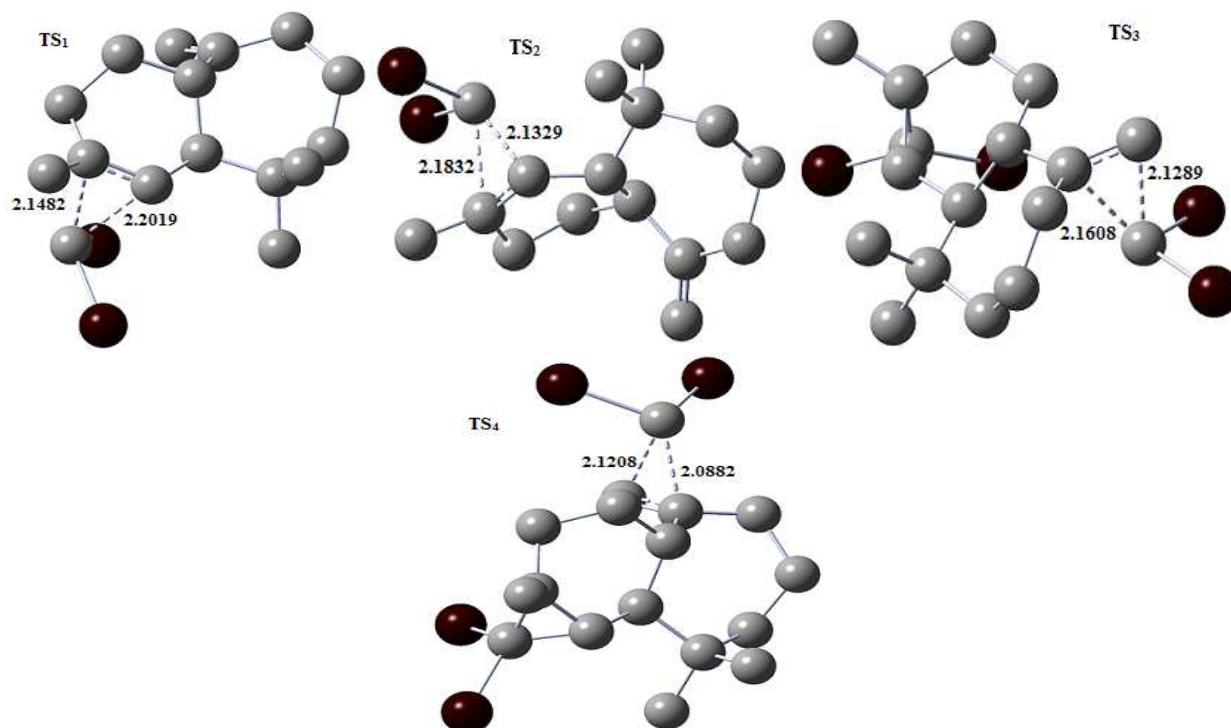
**Table 4** Thermodynamic energies of the reaction between  $\alpha$ -trans-himachalene and two equivalents of dibromocarbene calculated using DFT/6-311G (d, p)

	Les réactifs		TS <sub>3</sub>	TS <sub>4</sub>	P <sub>2</sub> ( $\alpha$ )	P <sub>2</sub> ( $\beta$ )
	P <sub>1</sub> ( $\alpha$ )	Dibromocarbene				
E (u.a)	-5772,5494	-5186,2921	-10958,8285	-10958,8315	-10958,9232	-10958,9177
$\Delta E$ (Kcal/mol)	-	-	8,1474	6,3107	-51,2683	-47,8241
H (u.a)	-5772,1648	-5186,2842	-10958,4346	-10958,4376	-10958,5259	-10958,5206
$\Delta H$ (Kcal/mol)	-	-	9,0757	7,2289	-48,2090	-44,8393
S (cal/mol.K)	139,401	69,09	166,8210	166,1420	160,8430	160,7890
$\Delta S$ (cal/mol.K)	-	-	-41,6700	-42,3490	-47,6480	-47,7020
G (u.a)	-5772,2311	-5186,3171	-10958,5139	-10958,5165	-10958,6023	-10958,5969
$\Delta G$ (Kcal/mol)	-	-	21,4997	19,8557	-34,0029	-30,6162
$\nu$ (cm-1)	-	-	-407,6035	-433,0462	-	-

### 3.2.3 Structural analysis of the transition states of the reaction

Analysis of the geometries of the transition states associated with the reaction between  $\alpha$ -trans-himachalene and dibromocarbene (Figure 6) shows that the lengths of the bonds formed by chemoisomer 1 are 2.2019 Å at  $d_1$ (C-C<sub>2</sub>) and 2.1482 Å at  $d_2$ (C-C<sub>3</sub>) for TS<sub>1</sub>, and 2.1329 Å at  $d_1$ (C-C<sub>2</sub>) and 2.1832 Å at  $d_2$ (C-C<sub>3</sub>) for TS<sub>2</sub>, while those formed by chemoisomer 2 are 2.1608 Å at  $d_1$ (C-C<sub>7</sub>) and 2.1289 Å at  $d_2$ (C-C<sub>13</sub>) for TS<sub>3</sub>, and 2.1208 Å at  $d_1$ (C-C<sub>13</sub>) and 2.0882 Å at  $d_2$ (C-C<sub>7</sub>) for TS<sub>4</sub>.

The asynchronicity of bond formation in this reaction can be measured as the difference between the two lengths of the two  $\sigma$  bonds formed, namely  $\Delta d = d_1 - d_2$ . Asynchronicity of chemoisomer 1 is  $\Delta d = 0.0537$  Å at TS<sub>1</sub> and  $\Delta d = 0.0503$  Å at TS<sub>2</sub>, while asynchronicity of chemoisomer 2 is  $\Delta d = 0.0319$  Å at TS<sub>3</sub> and  $\Delta d = 0.0326$  Å at TS<sub>4</sub>. We can conclude that the transition states associated with the two chemoisomeric pathways show that the favored regioisomers are more asynchronous than the others.



**Fig. 6** Bond lengths (Å) of the transition states of the reaction between  $\alpha$ -trans-himachalene and dibromocarbene.

## CONCLUSION

The chemo-, regio- and stereoselectivity of the reaction between  $\alpha$ -trans-himachalene and dibromocarbene was studied using DFT/B3LYP/6-311G(d, p). Analysis of the global electrophilicity and nucleophilicity indices showed that  $\alpha$ -trans-himachalene behaves as a nucleophile, while dibromocarbene behaves as an electrophile. The regioselectivity found experimentally was confirmed by local indices of electrophilicity and nucleophilicity  $\omega_k$  and  $N_k$ .

Calculation of activation energies, analysis of the potential energy surface and IRC calculation shows that this reaction follows a concerted asynchronous mechanism and that whatever quantity of dibromocarbene is used, the favored electrophile-nucleophile reaction takes place at the  $\alpha$  side of the double bond of  $\alpha$ -trans-himachalene, leading to the formation of a dibromate product (1R, 2S, 4R, 7S)-3,3-dibromo-8-methylene-4,12,12-trimethyl-tricyclo [5.5.0.0<sup>2,4</sup>] dodecane when the reaction is stoichiometric, and a tetrabromate product (1R, 2S, 4R, 7S, 8R)-3,3,13,13-tetrachloro-4,12,12-trimethyl-tricyclo [5.5.0.0<sup>2,4</sup>] -spiro[2<sup>8</sup>] tetradecane when there is an excess of dibromocarbene.

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