

Understanding the Regioselectivity and Reactivity of β -Himachalene Using Zeroual Function as a new Regioselectivity Descriptor

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ABSTRACT: In this work we used density functional theory (DFT) B3LYP/6-31G*(d) to study the stoichiometric reaction between the β -himachalene and dibromocarbene. We have shown that β -himachalene behaves as a nucleophile, while dibromocarbene behaves as an electrophile; that the chemical potential of dibromocarbene is superior to that of β -himachalene in absolute terms; and that β -himachalene reacts with an equivalent quantity of dibromocarbene to produce only one products **P₁: (1S,3R,8S) -2,2- dibromo -3,7,7,10 -tetramethyltricyclo [6,4,0,0^{1,3}] dodec-9-ene** (referred to here as P₁). P₁ is formed at the only α side of the C₆=C₇ double bond of β -himachalene. This reaction is exothermic, stereoselective and chemospecific, and is controlled by charge transfer and we proposed electrophilic Z_k^+ and nucleophilic Z_k^- Zeroual functions allows explaining the total regioselectivity found in β -himachalene, while electrophilic Z_k^- functions indicate that the double bond C₆=C₇ of the β -himachalene is the most nucleophilic than the double bond C₂=C₃. Although the proposed Zeroual functions give a similar local reactivity as the Parr functions, both are derived from conceptually different reactivity models. The local reactivity given by the Zeroual electrophilic and nucleophilic functions is in agreement with experimental results.

KEYWORDS: [1+2] cycloaddition; B3LYP/6-31G*(d); charge transfer; chemospecificity; density functional theory (DFT); exothermic reaction, stereoselectivity, α -elimination.

1 INTRODUCTION

Trihalomethanes, such as tribromomethane (bromoform), are quite reactive toward strong base. The base, such as hydroxide, removes the hydrogen of HCB₃ as a proton much more rapidly than it attacks the carbon in the S_N₂ manner. The carbanion so formed, Cl₃C[⊖], is unstable and loses chloride ion to form a highly reactive neutral intermediate, :CBr₂, called **dibromocarbene**. This intermediate has only six valence electrons around carbon and therefore is strongly electrophilic. The formation of :CBr₂ from HCB₃ by the α -elimination reactions from the *same* carbon atom. Similarly the reaction of β -himachalene [1] with an equivalent quantity of dibromocarbene (*Prepared from the α -elimination reaction*) leads chemospecifically to the single cyclopropane (1S,3R,8S)-2,2-dibromo-3,7,7,10-tetramethyltricyclo[6,4,0,0^{1,3}]dodec-9-ene (referred to here as P₁). The structure of this product has been determined by spectroscopy (Hydrogen-1 nuclear magnetic resonance, Carbon-13 nuclear magnetic resonance and mass spectroscopy) [2] and its stereochemistry confirmed by X-ray diffraction [3]. Figure 1 represents results obtained experimentally. The objective of this research was to create the new descriptors to describe the regioselectivity (Zeroual fonctions), and compared with Parr Fonctions.

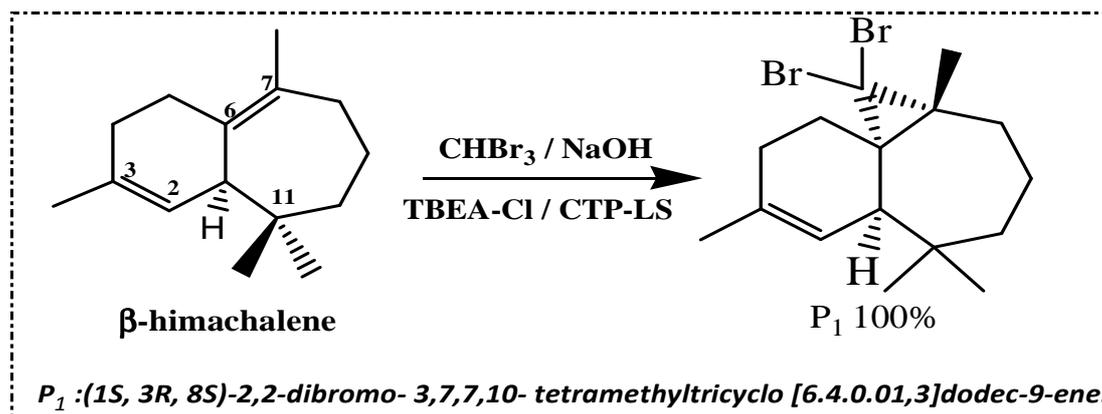


Fig. 1. Cyclopropanation Reaction between the β -himachalene and dibromocarbene

2 COMPUTATIONAL METHODS

DFT computations were carried out using the B3LYP [4], [5] hybrid meta functional, together with the standard 6-31G* basis set [6]. The optimizations were carried out using the Bery analytical gradient optimization method [7], [8]. The stationary points were characterized by frequency computations in order to verify that TSs have one and only one imaginary frequency. The IRC paths [9] were traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism using the second order Gonzalez-Schlegel integration method [10], [11]. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method [12], [13]. All computations were carried out with the Gaussian 09 suite of programs [14]. The global electrophilicity index, ω , is given by the following expression [15], $\omega = \frac{\mu^2}{2\eta}$, in terms of the electronic chemical potential μ and the chemical hardness η . Both quantities may be approached in terms of the one-electron energies of the frontier molecular orbitals HOMO and LUMO, as $\mu \approx \frac{E_{HOMO} + E_{LUMO}}{2}$ and $\eta \approx E_{LUMO} - E_{HOMO}$, respectively [16], [17]. Recently, we introduced an empirical (relative) nucleophilicity index [18], [19], N , based on the HOMO energies obtained within the Kohn-Sham scheme [20], and defined as $N = E_{HOMO}(\text{Nu}) - E_{HOMO}(\text{TCE})$. Nucleophilicity is referred to tetracyanoethylene (TCE), because it presents the lowest HOMO energy in a long series of molecules already investigated in the context of polar cycloadditions. This choice allows us to conveniently handle a nucleophilicity scale of positive values.

The local electrophilicity indices ω_k [21], and the local nucleophilicity indices N_k [22], at the atomic site k defined in terms of the related condensed Zeroual functions, Z_k^+ and Z_k^- , as

$$\omega_k = \omega \cdot Z_k^+ \quad \text{and} \quad N_k = N \cdot Z_k^-$$

Where Z_k^+ and Z_k^- they are the electrophilic and nucleophilic Zeroual functions respectively, obtained through the analysis of the Mulliken atomic spin density of the radical anion, the radical cation and the radical neutral of the studied molecules.

$$Z_k^- = [D_k(N) - D_k(N - 1)]$$

$$Z_k^+ = [D_k(N + 1) - D_k(N)]$$

Where $D_k(N)$, $D_k(N - 1)$ and $D_k(N + 1)$ are of the Mulliken atomic spin density of the site k in neutral, cationic, and anionic systems, respectively, and we compared with Parr functions. [23], [24], [25], [26], [27], [28], [29], [30], [31], [32].

3 RESULTS AND DISCUSSIONS

3.1 ANALYSIS OF THE GLOBAL REACTIVITY INDEXES FOR DIBROMOCARBENE AND β -HIMACHALENE

The μ , η , ω , N and $\Delta\omega$ values for a dibromocarbene and the β -himachalene used in cycloaddition reaction most of them having a known electrophilic/nucleophilic character are displayed in Table 1. The molecules are given in decreasing order of the N value. At the top of this table appears β -himachalene, which is classified as a strong nucleophile ($N=3.427$ eV), while at dibromocarbene ($N= 0.21$ eV). The chemical hardness of the β -himachalene (6,488 eV) is superior to the chemical hardness of the dibromocarbene (3,460 eV) and the electronic chemical potential of the β -himachalene (-2,499 eV) is higher to that of

the dibromocarbène (-5,319 eV), what shows that the electron transfer takes place from the β -himachalene to dibromocarbene and we shows that dibromocarbene is strongly electrophilic than β -himachalene.

Table 1. B3LYP/6-31G* electronic chemical potential μ , chemical hardness η , global electrophilicity ω , global nucleophilicity N indices and $\Delta\omega$, in eV.

	μ	η	ω	N	$\Delta\omega$
β -himachalene	-2,499	6,488	0,696	3,427	3,411
Dibromocarbene	-5,332	3,460	4,107	2,469	

3.2 ANALYSIS OF THE LOCAL REACTIVITY INDEXES FOR DIBROMOCARBÈNE AND β - HIMACHALENE

Polar Diels–Alder (P-DA) reactions involving asymmetrically substituted reagents take place through high asymmetric transition state structures (TSs).[33] Several studies have established that the most favourable regioisomeric reactive channel is that involving the most favourable local electrophilic and nucleophilic interactions. This behaviour is well predicted by the analysis of the local electrophilicity ω_k and the nucleophilicity N_k indices derived from the Zeroual functions. (Figure 2)

Despite the similarity of the electrophilic and nucleophilic local activations given for the Parr and Zeroual functions for the β -himachalene given in Table 2.

Table 2. Electrophilic and nucleophilic Zeroual functions of the β -himachalene (see atom numbering in figure 2)

	$D_k(N - 1)$	$D_k(N + 1)$	$D_k(N)$	P_k^-	Z_k^-
C2	0,14	0,08	0,01	0,14	-0,04
C3	0,09	0,13	-0,005	0,09	-0,095
C6	0,25	0,27	0,92	0,25	0,67
C7	0,27	0,28	0,92	0,27	0,65

Table 2 shows that the Zeroual functions agree with the Parr functions as the observed electrophilic/nucleophilic behaviour does correspond to changes in charge distribution, as proposed by the Zeroual functions. On the other hand, the Parr functions yield the same pattern for the electrophilic and nucleophilic local activation as Zeroual functions. Thus, the Zeroual functions correctly suggested that the C6 and C7 carbon is more nucleophilic centre than C2 and C3, in clear agreement with the experimental results. Similar results are obtained with the Parr functions.

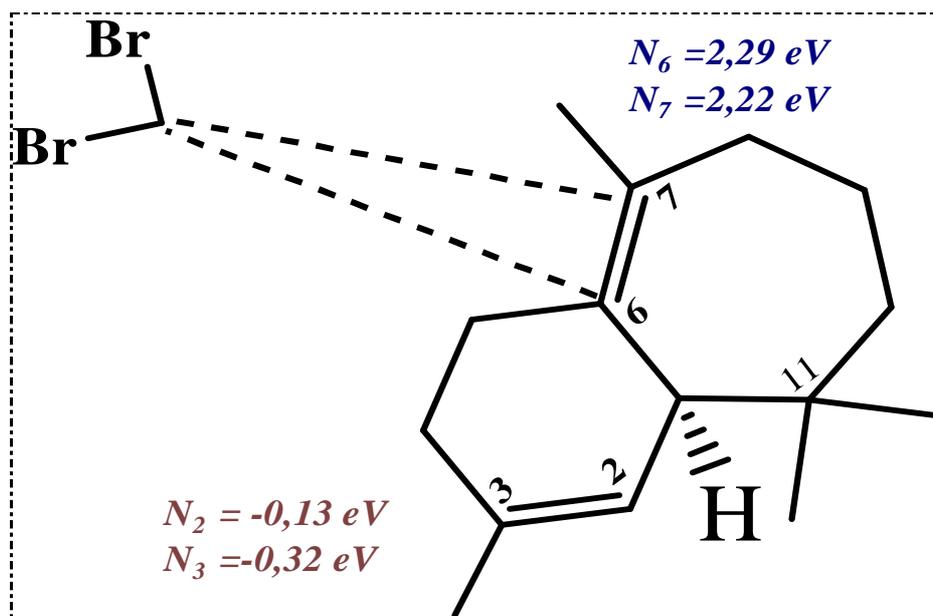


Fig. 2. Illustration of the favorable interactions using local nucleophilicities (N_k calculated from Zeroual functions)

The figure 2 shows that an unexpected result is found at the nucleophilic intermediate β -himachalene, to nucleophilic Z_k^- Zeroual functions that the double bond $C_6=C_7$, is more nucleophilically activated than the double bond $C_2=C_3$. Consequently, the more favourable nucleophilic/electrophilic interactions will be between the double bond $C_6=C_7$ of the β -himachalene and the carbon of dibromocarbene this regioselectivity experimentally observed.

3.3 KINETIC STUDY OF STEREOSELECTIVITY OF THE DOUBLE BOND $C_6=C_7$

A late highlight that the attack of the double bond $C_6=C_7$ alpha side of β -himachalene is preferred, we determined the energy of the reactants, the energy of the products obtained, the α , β TS energy and difference ($TS_\beta-TS_\alpha$). (Table 3)

Table 3. Total (E, a.u) and Relative (ΔE , kcal/mol) Energies of the Stationary Points Involved in the Addition Reaction to the β -himachalene and dibromocarbene.

	E (u.a)	$\Delta E^*(\text{kcal/mol})$ ($E - E_R$)	$\Delta(TS_\beta-TS_\alpha)$ (kcal/mol)
Réactifs (β -himachalene + CBR_2)	-5767,430	-----	8,16
E_{TS_α}	-5767,424	3,76	
E_{TS_β}	-5767,411	11,92	
Produit P_1 (α side)	-5767,534	-65,26	
Produit P_2 (β side)	-5767,509	-49,57	

Table 3 shows that:

- The transition state energy of the β side of double bond $C_6=C_7$ is located in front 8.16 kcal/mol below the transition state energy of the α side.
- The formation of products P1 and P2 are exothermic by -65.26 and -49.57 kcal/mol respectively and thermodynamically favorable.
- The difference between the activation energies of products P1 and P2 is of order 8.16 kcal/ mol indicating that the formation of alpha isomer is kinetically favored than isomer beta this result is *agreement with the experimental results*.

Using the data given in Table 3, we can sketch the energy profile of the reaction (Figure 3). This shows that:

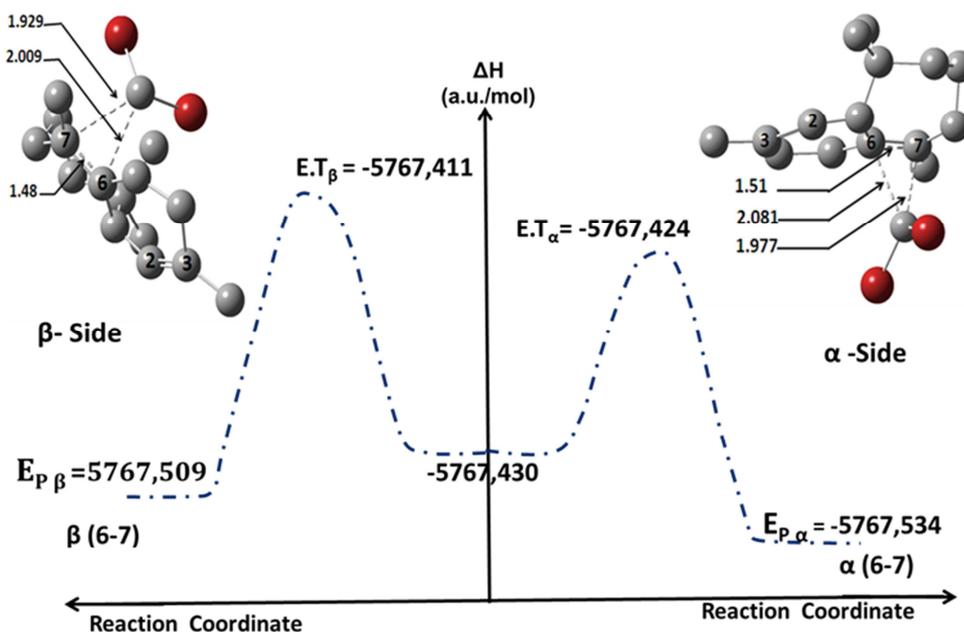


Fig. 3. Profile of the reaction between the β -himachalene and dibromocarbene

- The transition state energies at the two sides of the $C_6=C_7$ double bond of β -himachalene are -5767.424 a.u./mol at α and -5767.411 a.u./mol at β . The difference between them is 0.013 a.u./mol.
- The difference between the activation energies of P_2 and P_3 is around 8.16 Kcal/mol, showing that the formation of α isomers is kinetically preferred to the formation of β isomers. This result is in agreement with experimental results.
- The formation of P_2 and P_3 is exothermic, by -65.26 and -49.57 Kcal/mol respectively.
- The formation of P_2 and P_3 is thermodynamically favorable.

The geometry of the transition states TS_α and TS_β is shown in Figure 3. The lengths of the C_6-CBr_2 , C_7-CBr_2 and C_6-C_7 bonds corresponding to TS_α and TS_β are:

- The α side of the C_6-C_7 bond: (C_6-CBr_2)=2.081 Å, (C_7-CBr_2)=1.977 Å and (C_6-C_7)=1.51 Å;
- The β side of the C_6-C_7 bond: (C_6-CBr_2)=2.009 Å, (C_7-CBr_2)=1.929 Å and (C_6-C_7)=1.48 Å.

These transition states correspond to the formation of concerted bonds.

4 CONCLUSION

Using the DFT method with B3LYP/6-31G*(d) to calculate total and relative energies, transition state energies and interatomic distances of the [1+2] cycloaddition reaction between β -himachalene and dibromocarbene we have shown that:

- The stereoselectivity and chemoselectivity observed at the α -side of the $C_6=C_7$ bond is confirmed by the α and β -Side transition states.
- The values of total and relative energies of both reactions are negative, implying that the reactions are exothermic.
- The energy difference between the HOMO of β -himachalene and the LUMO of dibromocarbene and between the LUMO of β -himachalene and the HOMO of dibromocarbene is greater than 2 eV, indicating that the reaction mechanism is controlled by charge transfer.
- The interatomic distances calculated for the [1+2] cycloaddition demonstrate that the reaction is concerted.

Finally, analysis of the recently proposed electrophilic Z_k^+ and nucleophilic Z_k^- Zeroual functions allows explaining the total regioselectivity found in β -himachalene; while electrophilic Z_k^- functions indicate that the double bond $C_6=C_7$ of β -himachalene is the most nucleophilic.

Although the proposed Zeroual functions give a similar local reactivity as the Parr functions, both are derived from conceptually different reactivity models. The local reactivity given by the Zeroual electrophilic and nucleophilic functions is in agreement with experimental results.

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