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Research Article

Understanding the Mechanism and Selectivities of the Reaction of Meta-Chloroperbenzoic Acid and Dibromocarbene with β-Himachalene: A DFT Study

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This study was performed to understand the site selectivity in the reaction between β-himachalene and meta-chloroperbenzoic acid (m-CPBA) in the first step followed by the addition of dibromocarbene (CBr_2) to the main monoepoxidation product P_α formed in the first reaction. Calculations were performed using the Becke three-parameter hybrid exchange functional and the Lee–Yang–Parr correlation functional (B3LYP) with the 6-311 + G (d, p) basis set. Transition states were located by QST2, and their highlighting was validated by the existence of only one imaginary frequency in the Hessian matrix. The action of m-CPBA on β-himachalene was analyzed on the two double bonds of β-himachalene whose theoretical calculations show that the attack affects the most substituted double bond on α side containing hydrogen of ring junction. The obtained P_α product thereafter treated with dibromocarbene leads via an exothermic reaction to the six-membered ring double bond position of α-monoepoxide. The major products $P_{\alpha\alpha}$ are kinetically and thermodynamically favored with a high stereoselectivity in perfect correlation with the experimental observations.

1. Introduction

Aromatic plants contain a variety of essential oils in their wood, leaves, fruits, bark, seeds, and/or roots. These oils exhibit antiseptic, cytotoxic, antibacterial, and antioxidant activities allowing them many applications in perfume, agrofood, cosmetic, and pharmaceutical industries [1]. For example, *Cedrus atlantica* essential oil is essentially composed of α-, β-, and γ-himachalene [2]. β-Himachalene is an optically active bicyclic sesquiterpene representing approximately 50% of the essential oils isolated by fractional distillation of the essential oil of the Atlas and Himalayan cedar [3]. The structure of β-himachalene includes two double bonds, one in six-membered ring double bond and the other in seven-membered ring double bond.

In order to obtain new therapeutic agents in medicinal chemistry and new compounds with interesting olfactory properties in perfumery, β-himachalene has been epoxidized by m-chloroperbenzoic acid. Indeed, when these reactants are used in stoichiometric proportions, only the seven-membered ring double bond of β-himachalene is attacked, producing a majority of the α-stereoisomer referred to as P_α (Figure 1). When treated with dibromocarbene, these later leads, via an exothermic reaction, to two products $P_{\alpha\alpha}$ and

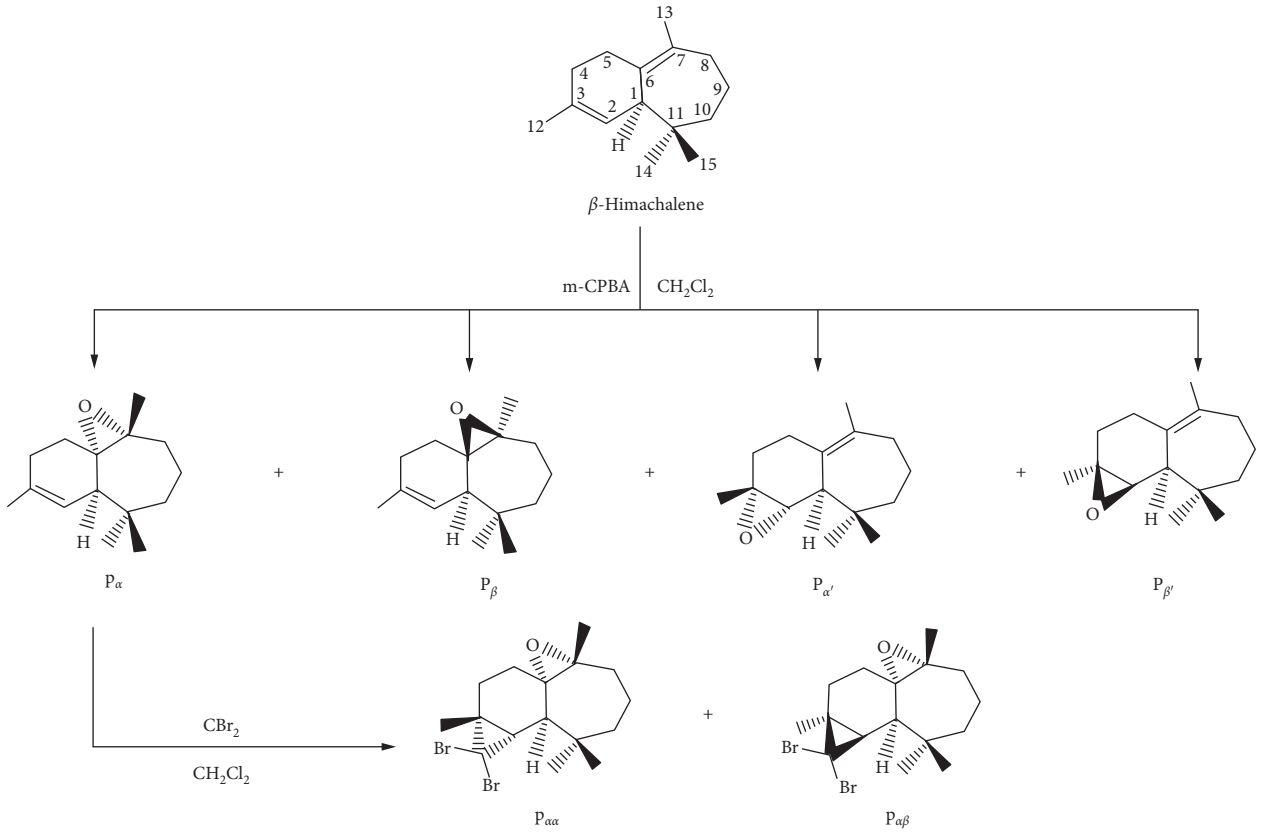

Figure 1: Addition scheme reactions of m-CPBA and dibromocarbene to β-himachalene.

$P_{\alpha\beta}$ (Figure 1) formed at the α and β sides of the six-membered ring double bond of P_α, respectively. The product $P_{\alpha\alpha}$ is kinetically and thermodynamically favored with a high stereoselectivity. The quantum chemistry can provide very reliable information and verify results already found through the experiment.

This work aims to understand the site selectivity of the β-himachalene reaction with m-CPBA and CBr_2. The computational calculations are performed using the digital chemistry software (Gaussian 09W) which is recognized by its advanced capabilities in the electronic modelling of chemical structures. The DFT method is chosen, which is the most relevant method in quantum chemistry and allows the study of the electronic structure in principle in an exact way, with the 6-311 + G (d, p) basis set, which gives more precise results. This work is divided into two parts: the first is dedicated to the ep-oxidation of β-himachalene by m-CBPA and the second part will treat the cyclopropanation reaction between the major product P_α resulting from the first reaction and dibromocarbene according to the reaction sequences proposed in Figure 1.

2. Theoretical and Computational Methods

2.1. Global and Local Reactivity Indices. Conceptual density functional theory (CDFT) [4, 5] has provided powerful tools in the study of chemical reactivity by defining many descriptors such as the electronic chemical potential μ [6], the electrophilicity ω [7] and the nucleophilicity N [8] indices, and local condensed indices such as the Parr functions (P_k^+,P_k^-) [9, 10] and the Fukui functions (f_k^+, f_k^-) [11, 12].

The nucleophilic/electrophilic nature of the reactants is evaluated through the electrophilicity ω and nucleophilicity N indices, where the value of ω is found from the electronic chemical potential μ and the global hardness η [6, 13]. These parameters are calculated from the energies of the highest occupied molecular orbital (E_{HOMO}) and lowest unoccupied molecular orbital (E_{LUMO}) according to the following equations:

$$\mu = \frac{E_{\mathrm{HOMO}} + E_{\mathrm{LUMO}}}{2}, \tag{1}$$

$$\eta = E_{\mathrm{LUMO}} - E_{\mathrm{HOMO}}. \tag{2}$$

From equations (1) and (2), we can also calculate the global electrophilicity index ω (equation (3)), defined as the energy stabilization due to charge transfer [7]:

$$\omega = \frac{\mu^2}{2\eta}. \tag{3}$$

The nucleophilicity index N (equation (4)) is calculated from the difference of the HOMO energy of the reactant and tetracyanoethylene (TCE) as a reference [8]:

$$N = E_{\mathrm{HOMO}}(\mathrm{Nu}) - E_{\mathrm{HOMO}}(\mathrm{TCE}). \quad (4)$$

The local electrophilicity ω_k [14] and nucleophilicity N_k [15] indices are calculated by the following equations, respectively:

$$\omega_k = \omega \times P_k^+, \quad (5)$$

$$N_k = N \times P_k^-, \quad (6)$$

where electrophilic P_k^+ and nucleophilic P_k^- Parr functions are obtained by analysis of the Mullikan atomic spin density (ASD) of the radical anion and radial cation of the reactants, which allow for the characterization of the electrophilic and nucleophilic centers of a molecule [10, 16].

The Fukui function (FF) is calculated using the procedure proposed by Yang and Mortier [11] based on a finite difference method: f_k^+ for nucleophilic attack (equation (7)), f_k^- for electrophilic attack (equation (8)), and f_k^0 for radical attack (equation (9)):

$$f_k^+ = \rho_k(N+1) - \rho_k(N), \quad (7)$$

$$f_k^- = \rho_k(N) - \rho_k(N-1), \quad (8)$$

$$f_k^0 = \frac{\rho_k(N+1) - \rho_k(N-1)}{2}, \quad (9)$$

where $\rho_k(N)$, $\rho_k(N-1)$, and $\rho_k(N+1)$ are the gross electronic populations of the site k in neutral, cationic, and anionic systems, respectively.

2.2. Computational Details. All computations of geometry optimization were executed using the Gaussian 09W programs [17]. The geometries of the products were fully optimized through DFT calculations using the hybrid functional B3LYP [18, 19] with the 6-311 + G (d, p) basis set [20]. The transition states, resultant to the two α and β reaction sides, were located at the same level by QST2. Their existence was validated by the existence of one and only one imaginary frequency in the Hessian matrix. The intrinsic reaction coordinate (IRC) [21] was performed and plotted to show that the TS is well connected to both minima of reagents and products. The values of enthalpy, entropy, and free energy were calculated from the analysis of the electronic structures of the stationary points and the bond orders (Wiberg indices) using the natural bond orbital method (NBO).

3. Results and Discussion

3.1. Analysis of the Reactivity Indices of the Reactants in the Base State

3.1.1. Prediction of Nucleophilic/Electrophilic Character. Table 1 summarizes the electronic chemical potential μ, chemical hardness η, global electrophilicity ω, and nucleophilicity N of β-himachalene and m-CPBA calculated at B3LYP/6-311 + G (d, p) level (eV). The table indicates that the electronic chemical potential of β-himachalene, $\mu = -2.99$ eV, is higher than that of m-CPBA, $\mu = -4.74$ eV. This means that there is a global electron density transfer (GEDT) [22] of β-himachalene to m-CPBA. The m-CPBA presents an electrophilicity (ω) index of 2.14 eV and a nucleophilicity (N) index of 1.77 eV, and those corresponding to the β-himachalene are 0.76 eV and 3.19 eV, respectively. There results suggest that m-CPBA behaves as an electrophile, while the β-himachalene behaves as a nucleophile.

Table 1: Electronic chemical potential (μ), chemical hardness (η), electrophilicity (ω), and nucleophilicity (N) of β-himachalene and m-CPBA (eV).

Reactants	μ	η	ω	N
β-Himachalene	−2.99	5.90	0.76	3.19
m-CPBA	−4.74	5.23	2.14	1.77

3.1.2. Prediction of Site Selectivity. The most favored interaction between two polar centers is related to the local indices (ω_k and N_k). The most favored product is associated with the highest local electrophilicity index ω_k of the electrophile and the highest local nucleophilicity index N_k of the nucleophile. From Figure 2, it is clear that the oxygen atom O^* of m-CPBA is the most electrophilic active site ($\omega_{O*} = 0.29$ eV). We can observe from the surface map illustrated in Figure 3 that the $C_6 = C_7$ double bond ($N_{C6} = 0.64$, $N_{C7} = 0.70$ eV) is very nucleophilic than $C_2 = C_3$ ($N_{C2} = 0.10$, $N_{C7} = 0.26$ eV). In addition, the analysis of the nucleophilic P_k^- Parr functions at the reactive sites of β-himachalene indicates that the C_6 and C_7 carbon atoms, with P_k^- values of 2.23 and 3.04, respectively, are more nucleophilically active than the C_2 and C_3 carbon atoms, with P_k^- values of 1.42 and 0.69, respectively. This result confirms that the attack is preferentially done on the double bond $C_6 = C_7$ in good agreement with experimental observations [23].

In the same perspective, the Fukui functions (f_k^+, f_k^-) are helpful and enable us to distinguish clearly between nucleophilic and electrophilic attacks. However, they have a positive value at sites liable to nucleophilic attack and a negative value at sites liable to electrophilic attack. The values of local reactivity descriptors calculated using the DFT method for natural population analysis- (NPA-) derived charges of the molecule studied are shown in Table 2.

3.1.3. Structural Analysis of the Transition States of the Cyclopropanation Reaction. The study of the stereoselectivity of $C_6 = C_7$ and $C_2 = C_3$ bonds indicates that the attack of the seven-membered ring double bond of β-himachalene is preferred. The thermodynamic energies and relative energies were calculated and are presented in Table 3. The analysis of the energies of the reactants, the products obtained, TS_α,TS_β, $TS_{\alpha'}$, and $TS_{\beta'}$ transition state energies at the C_6=C_7 and C_2=C_3 double bonds, respectively, of β-himachalene, and the difference in transition energy shows that the attack is kinetically preferred at α side of the double bond of the seven-membered ring. The activation energies corresponding to the attack at the two sides of the

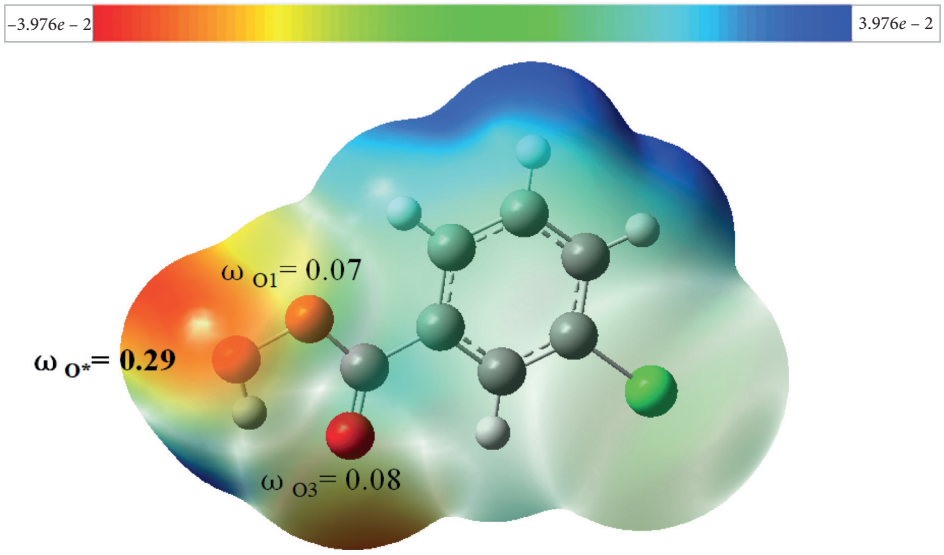

Figure 2: The density map and electrophilicity index of m-CPBA.

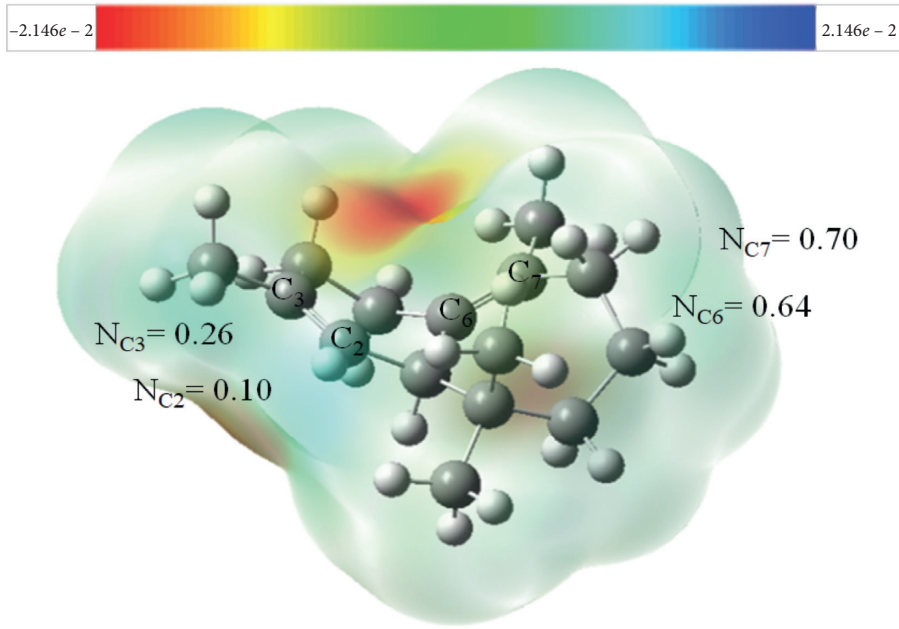

Figure 3: The density map and nucleophilicity index of β-himachalene.

Table 2: Local reactivity properties of reagents calculated using the DFT method for NPA-derived charges.

	f_k^+	f_k^-	P_k^+	P_k^-	ω_k^+	ω_k^-
C_2	0.0045	0.0318	0.0593	1.4291	1.4291	0.0242
C_3	0.0043	0.0826	0.1076	0.6973	0.0033	0.0629
C_6	0.0201	0.2022	0.2976	2.2363	0.0153	0.1539
C_7	0.0340	0.2214	0.3024	3.0426	0.0259	0.1686

$C_6 = C_7$ double bond of β-himachalene are 17.5 kcal·mol^{-1} at β and 13.8 kcal·mol^{-1} at α and those corresponding to the attack on both sides of the $C_2 = C_3$ double bond are of the order of 14.2 and 17.8 kcal·mol^{-1} at α' and β', respectively, showing that the formation of α isomers is kinetically preferred to the formation of β isomers. The formation of P_α, P_β, $P_{\alpha'}$, and $P_{\beta'}$ is an exothermic reaction, with −53.3, −45.8, −51.9, and −45.4 kcal·mol^{-1}, respectively. The examination of m-CPBA epoxidation of the β-himachalene using the data given in Table 3 indicates that the energy barrier corresponding to the approach to the α side is lower than that corresponding to the other sides. This result allows us to

Table 3: Thermodynamic energies of the reaction between β-himachalene and m-CPBA calculated using DFT/6-311 + G (d, p).

	E (a.u.)	ΔE (kcal/mol)	H (a.u)	ΔH (kcal/mol)	G (a.u.)	ΔG (kcal/mol)	ν (cm^{-1})
m-CPBA	−955.721212	—	−955.602614	—	−955.649316	—	
β-Himachalene	−586.183305	—	−585.813259	—	−585.870499	—	
TS_α	−1541.882123	13.8	−1541.393050	14.3	−1541.480039	24.9	−375.75
TS_β	−1541.876139	17.5	−1541.386179	18.6	−1541.472639	29.6	−416.05
$TS_{\alpha'}$	−1541.880225	14.2	−1541.390097	14.5	−1541.478986	25.2	−376.66
$TS_{\beta'}$	−1541.869299	17.8	−1541.381268	18.9	−1541.470977	30.3	−418.89
P_α	−661.413885	−53.3	−661.037817	−52.4	−661.095788	−51.0	
P_β	−661.401320	−45.8	−661.024962	−44.3	−661.083388	−43.6	
$P_{\alpha'}$	−661.413022	−51.9	−661.036573	−50.7	−661.094555	−49.8	
$P_{\beta'}$	−661.401101	−45.4	−661.024790	−44.1	−661.077968	−42.3	

conclude that the α-attack is kinetically and thermodynamically favored and that the C_6=C_7 double bond of β-himachalene is more reactive than the other C_2=C_3, and this is in good agreement with the experimental results [23].

3.1.4. Analysis of the IRC of the Reaction between β-Himachalene and M-CPBA. The molecular system during the reaction between β-himachalene and m-CPBA was studied by calculating the intrinsic reaction coordinate (IRC) in order to show that the transition state is indeed linked to the two minima (reactants and products). The plots of the total energy E vs intrinsic reaction coordinate (IRC) corresponding to all possible pathways are shown in Figure 4. This figure indicates that the reaction takes place by one-step mechanism characterized by the formation of the first bond followed by closure of the cycle without the formation of a stable intermediary reactant. The analysis of the IRC calculated using DFT at B3LYP/6-311 + G (d, p) basis set shows that whatever quantity of m-CPBA is used in the interaction with β-himachalene, the transition states are reached without going through a stable intermediary stage.

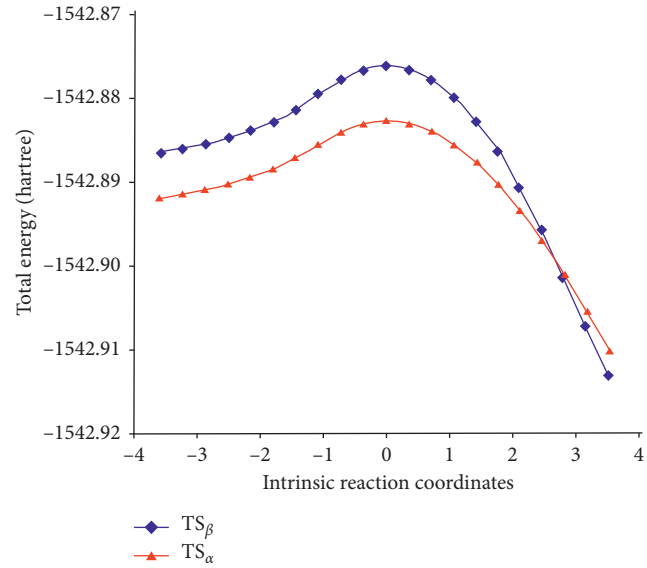

Figure 4: IRC of the reaction between β-himachalene and m-CBPA calculated using DFT at B3LYP/6-311 + G (d, p) level. Structural analysis of the transition states of the reaction.

3.1.5. Structural analysis of the transition states of the reaction. The optimized geometries of the TS_α, TS_β, TS_α, and $TS_{\beta'}$ transition states associated with the reaction between β-himachalene and m-CBPA are shown in Figure 5. The asynchronicity of bond formation in this reaction can be measured as the difference between the two lengths of the two σ bonds formed, namely, Δd given in Å:

$$\Delta d = \left| d_{O^*-C_6} - d_{O^*-C_7} \right|, \quad (10)$$

$$\Delta d = \left| d_{O^*-C_2} - d_{O^*-C_3} \right|, \quad (11)$$

where $d_{O^*-C_6}$, $d_{O^*-C_7}$, $d_{O^*-C_2}$, and $d_{O^*-C_3}$ are the length of the bond between the oxygen atom and carbon atoms C_6, C_7, C_2, and C_3, respectively. It was found that the asynchronicity of stereoisomer is $\Delta d = 0.16$ Å at TS_α, while at TS_β, the asynchronicity of stereoisomer is $\Delta d = 0.31$ Å. On the other hand, the asynchronicity of the stereoisomer was 0.16 Å at $TS\alpha'$ and 0.23 Å $TS_{\beta'}$.

3.2. Analysis of intramolecular Chemical Descriptors of the Reaction between P_α and Dibromocarbene. After the determination of the chemoselectivity and stereoselectivity of the reaction between β-himachalene and m-CBPA, we subsequently studied the cyclopropanation reaction between the major product (P_α) and dibromocarbene. The electronic chemical potential (μ), chemical hardness (η), electrophilicity index (ω), global nucleophilicity index (N), and maximum charge transfer ΔN_{max} calculated for P_α and dibromocarbene are shown in Table 4. This table indicates that the electrophilic index of dibromocarbene (4.46 eV) is greater than that of P_α (0.83 eV). This result suggests that dibromocarbene behaves as an electrophile, while P_α behaves as a nucleophile. This behavior is confirmed by the global nucleophilic indices of the reactants. The chemical hardness of P_α is 6.38 eV. This value is greater than that of dibromocarbene (3.41 eV). Also, the electronic chemical potential of P_α (−3.26 eV) is greater than that of dibromocarbene (−5.52 eV). This result indicates that electrons are transferred from P_α to dibromocarbene.

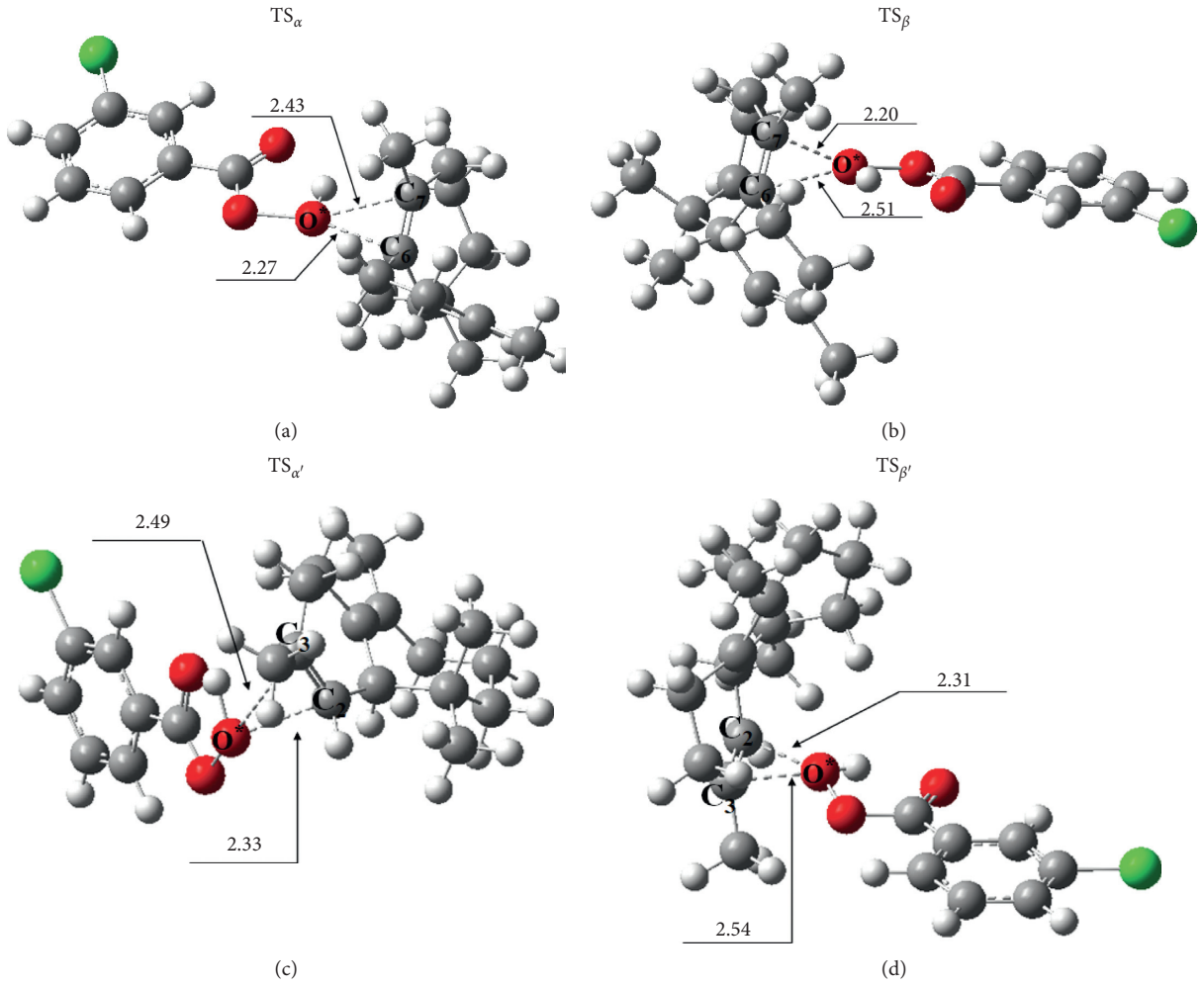

Figure 5: Optimized geometries of the transition states TS$_\alpha$, TS$_\beta$, TS$_{\alpha'}$, and TS$_{\beta'}$ of the β-himachalene and m-CBPA (the distances are given in Å).

Table 4: Electronic chemical potential (μ), chemical hardness (η), electrophilicity (ω), and nucleophilicity (N) of the major product (P$_\alpha$) and CBr_2 calculated at B3LYP/6-311 + G (d, p) level (eV).

	P$_\alpha$	CBr_2
μ	−3.26	−5.52
H	6.38	3.41
ω	0.83	4.46
N	2.68	1.91
ΔN_{max}	−0.51	−1.61

3.2.1. Kinetic Study. The stereoselectivity of the addition of dibromocarbene to the major product (P$_\alpha$) obtained from the first reaction of β-himachalene with m-CPBA was examined in both α and β sides of P$_\alpha$. The calculated energies of the reactants, the obtained products (TS$_{\alpha\alpha}$ and TS$_{\alpha\beta}$) at the $C_2 = C_3$ double bond of P$_\alpha$, and the difference in transition energies are listed in Table 5. From this table, we can deduce that the transition state energy of the β side of double bond $C_2 = C_3$ (8.9 kcal/mol) is located above the transition state energy of the α side (4.1 kcal/mol). The formation of the products P$_{\alpha\alpha}$ and P$_{\alpha\beta}$ occurred via exothermic reaction with −49.3 and −44.4 kcal/mol, respectively, and is strongly exergonic, by −31.7 and −26.9 kcal/mol, respectively. These values indicate that the reaction between P$_\alpha$ and dibromocarbene is energetically exothermic. We also notice that the energy barrier corresponding to the approach to the α side is less than the corresponding one to the β side (Figure 6). These results allow us to conclude that α-attack is kinetically and thermodynamically favored. It also explains the great stereoselectivity observed experimentally.

3.2.2. Structural Analysis of the Transition States of the Epoxy Reaction. The analysis of the geometries of the transition states associated with the reaction between P$_\alpha$ and dibromocarbene (Figure 7) shows that the lengths of the bonds formed by stereoisomer 1 are 2.26 Å at $d_1(C^* - C_3)$ and 2.59 Å at $d_2(C^* - C_2)$ for TS$_{\alpha\alpha}$. However, those formed by stereoisomer 2 are 2.75 Å at $d_1(C^* - C_3)$ and 2.38 Å at $d_2(C^* - C_2)$ for TS$_{\alpha\beta}$, where C^* is the carbon atom of dibromocarbene.

The asynchronicity of bond formation in this reaction, measured as the difference between the two lengths of the two σ bonds formed (Δd), is given by

Table 5: Thermodynamic energies of the cyclopropanation reaction between P_α and dibromocarbene calculated using the DFT method at B3LYP/6-311 + G (d, p) basis set.

	E (a.u.)	G (a.u.)	H (a.u.)	ΔE (kcal/mol)	ΔG (kcal/mol)	ΔH (kcal/mol)
P_α	−661.413801	−661.095710	−661.037800			
CBr_2	−5186.296500	−5186.321500	−5186.288610			
$TS_{\alpha\alpha}$	−5847.703721	−5847.389	−5847.318702	4.1	17.6	4.8
$TS_{\alpha\beta}$	−5847.696000	−5847.381512	−5847.310901	8.9	22.4	9.7
$P_{\alpha\alpha}$	−5847.788923	−5847.467800	−5847.400001	−49.3	−31.7	−46.1
$P_{\alpha\beta}$	−5847.781200	−5847.460222	−5847.392300	−44.4	−26.9	−41.3

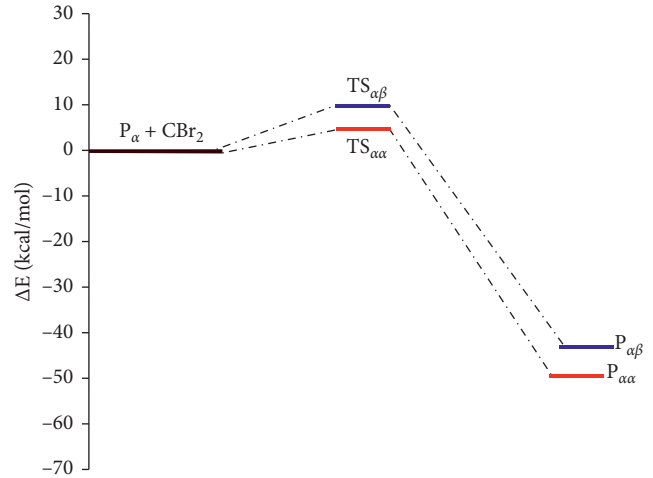

Figure 6: Energy profile of reaction between P_α and dibromocarbene.

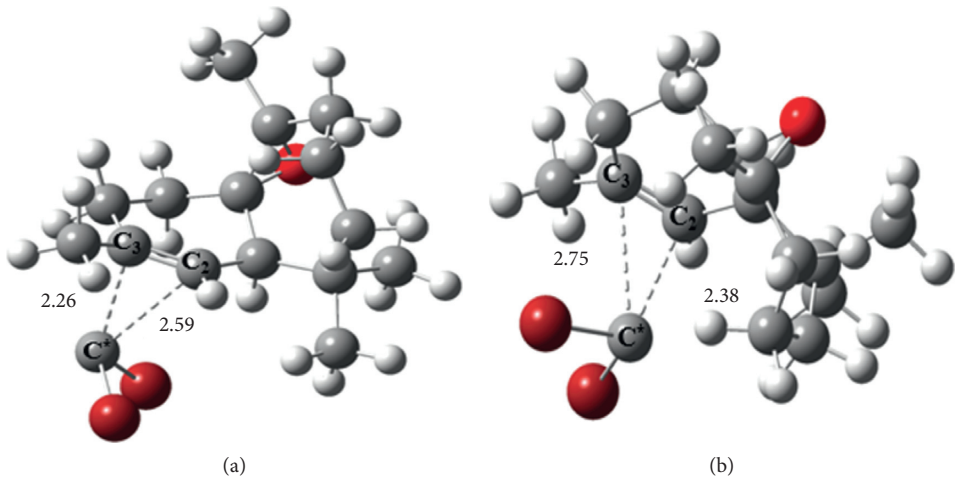

Figure 7: Bond lengths (Å) of the transition states of the reaction between P_α and CBr_2. (a) $TS_{\alpha\alpha}$. (b) $TS_{\alpha\beta}$.

$$\Delta d = |d_1 - d_2|. \quad (12)$$

It was found that the asynchronicity of the stereoisomer 1 is $\Delta d = 0.33$ Å at $TS_{\alpha\alpha}$. However, the asynchronicity of the stereoisomer 2 is $\Delta d = 0.37$ Å at $TS_{\alpha\beta}$. From these transition states, we can conclude that the favored stereoisomer is more asynchronous than the other.

4. Conclusions

The reaction of meta-chloroperbenzoic acid and dibromocarbene with β-himachalene was studied using the DFT method at the B3LYP/6-311 + G (d, p) level. The results confirm that this theory gives a conceptual framework to the study of the reactivity and selectivity of the chemical reaction

through local and global descriptors. The latter allows one to show that the double bond of the seven-membered ring of β-himachalene is more reactive with a high stereoselectivity with m-CPBA through its α face than the six-membered one forming the major product P_α. The reaction of the latter with CBr_2 takes place according to an exothermic mechanism in a single step in which the product $P_{\alpha\alpha}$ is kinetically and thermodynamically favored over $P_{\alpha\beta}$ according to the energetic parameters of the transition states in good agreement with experimental observations.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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