ORIGINAL PAPER

Theoretical study of stereoselectivity of the [1 + 2] cycloaddition reaction between (1S,3R,8S) -2,2-dichloro-3,7,7,10-tetramethyltricyclo[6,4,0,0$^{1.3}$]dodec-9-ene and dibromocarbene using density functional theory (DFT) B3LYP/6-31G*(d)

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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 product (1S,3R,8S)-2,2-dichloro-3,7,7,10-tetramethyltricyclo[6,4,0,0$^{1.3}$]dodec-9-ene (referred to here as P_1) and dibromocarbene. We have shown that P_1 behaves as a nucleophile, while dibromocarbene behaves as an electrophile; that the chemical potential of dibromocarbene is superior to that of P_1 in absolute terms; and that P_1 reacts with an equivalent quantity of dibromocarbene to produce two products: (1S,3R,8R,9S,11R)-10,10-dibromo-2,2-dichloro-3,7,7, 11-tetramethyltetracyclo[6,5,0,0$^{1.3}$,0$^{9.11}$] tridecane (referred to here as P_2) and (1S,3R,8R,9R,11S)-10,10-dibromo-2,2-dichloro-3,7,7,11-tetramethyltetracyclo[6,5,0,0$^{1.3}$,0$^{9.11}$] tridecane (referred to here as P_3). P_2 and P_3 are formed at the α and β sides, respectively, of the $C_2=C_3$ double bond of P_1. This reaction is exothermic, stereoselective and chemospecific, and is controlled by charge transfer. Regioselectivity of the reaction was interpreted using the Lee-Yang-Parr functional.

Keywords 1+2 cycloaddition · β-himachalene · B3LYP/ 6-31G*(d) · Charge transfer · Chemospecificity · Density

functional theory · Exothermic reaction · Regioselectivity · Stereoselectivity

Introduction

The reaction of carbenes with olefins to form cyclopropanes can be classified as a cycloaddition reaction. Carbenes are prepared by reactions known as α-elimination reactions, originally developed for halogen derivatives. In the presence of a base, chloroform loses one hydrogen atom, producing an unstable anion. Similarly, the reaction of β-himachalene—a major component of the essential oil of *Cedrus Atlantica*, the Atlas Cedar—with an equivalent quantity of dichlorocarbene leads chemospecifically to the single cyclopropane (1S,3R, 8S)-2,2-dichloro-3,7,7,10-tetramethyltricyclo[6,4,0, 0$^{1.3}$]dodec-9-ene (referred to here as P_1) [1–3]. The structure of this product has been determined by spectroscopy (^{1}H nuclear magnetic resonance, ^{13}C nuclear magnetic resonance and mass spectroscopy) and its stereochemistry confirmed by X-ray diffraction [4]. Figure 1 represents results obtained experimentally.

P_1 is then treated with bromoform in the presence of sodium hydroxide in dichloromethane as a solvent (Fig. 1), leading to the formation of two products: (1S,3R,8R,9S,11R)-10, 10-dibromo-2,2-dichloro-3,7,7,11-tetramethyltetracyclo[6,5, 0,0$^{1.3}$.0$^{9.11}$]tridecane, referred to here as P_2, and (1S,3R,8R, 9R,11S)-10,10-dibromo-2,2-dichloro-3,7,7,11-tetramethyltetracyclo[6,5,0,0$^{1.3}$.0$^{9.11}$] tridecane, referred to here as P_3. The structures of these two products have been determined using spectroscopy (nuclear magnetic resonance, ^{1}H and ^{13}C) and the stereochemistry of P_3 has been confirmed by X-ray diffraction [5].

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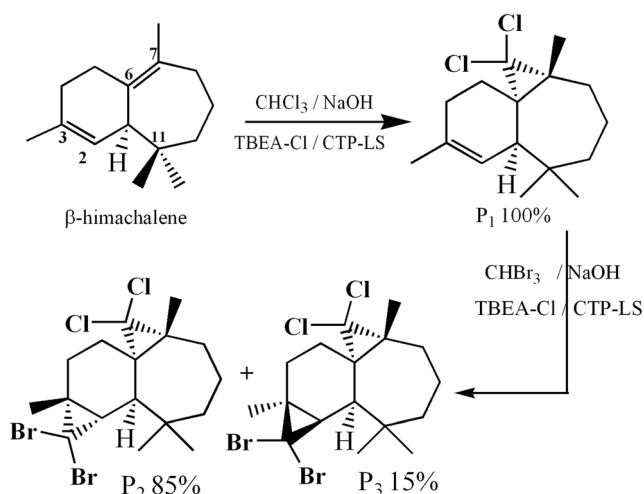
Fig. 1 Reactions leading to the dichlorinated product P_1 and the dichlorinated dibromates P_2 and P_3 (see text for definitions of products)

In this work, we used density functional theory (DFT) with base B3LYP/6-31G*(d) to study these reactions, and compared theoretical results with results obtained experimentally [1–5].

Chemical concepts and reactivity indices

Domingo et al. [6] have proposed that the assumption that a weakly electrophilic molecule is necessarily strongly nucleophilic holds good for simple molecules. High nucleophilicity corresponds to low ionization potential and vice versa. These researchers used the HOMO (highest occupied molecular orbital) energies obtained using the Kohn-Sham method. The relative empirical nucleophilicity (N) is defined as $N = (E_{HOMO(Nu)} - E_{HOMO(TCE)})$ [7].

In order to determine the reactive sites of a molecule when attacked by an electrophile, nucleophile or radical, chemists use net charge to determine which interactions are most likely. However, it is well known that net charges calculated at different sites on a molecule do not provide a good description of the interactions between molecules, particularly in the case of reactions controlled by frontier orbitals, so-called soft–soft interactions. As an alternative to calculating charge, recent studies [8, 9] have shown the value of applying HSAB theory

Table 1 Intramolecular chemical descriptors (eV) for β-himachalene and dichlorocarbene, taking the highest occupied molecular orbital (HOMO) energy of tetracyanoethylene as a reference [ε HO(TCE)= −0.3503 (a.u.)= −9.5322 (eV)]. *LUMO* Lowest unoccupied molecular orbital

	ε(HOMO) (eV)	ε(LUMO) (eV)	μ (eV)	ω (eV)	N (eV)
β-Himachalene	−5.6925	0.6938	−2.4993	0.4890	3.4274
Dichlorocarbene	−7.3578	−3.5510	−5.4544	3.9075	1.7621

Table 2 Local electrophilicity and local nucleophilicity indices and atomic spin density of β-himachalene and dichlorocarbene

	Atom	P^+	P^-
Dichlorocarbene	CCl_2	0.97	0.67
β-Himachalene	C_2	0.08	0.14
	C_3	0.13	0.09
	C_6	0.27	0.25
	C_7	0.28	0.27

(hard and soft acids and bases) at a local level when studying interactions between molecules, since use of net charges to predict reactivity may lead to predictions that are in contradiction with experimental results [10–12].

Computational methods

All calculations were carried out in Gaussian 09 [13] using DFT with the functional hybrid B3LYP and base 6-31G*(d) [14–16].

All structures were completely optimized and the nature of each stationary point was determined through frequency calculation. All transition states correspond to first order saddle points, i.e., to a single imaginary frequency.

Results and discussion

Analysis of intramolecular chemical descriptors
for the stoichiometric reaction between β-himachalene
and dichlorocarbene

The HOMO and LUMO energies of the reactants, electronic chemical potential (μ), electrophilicity index (ω) and global
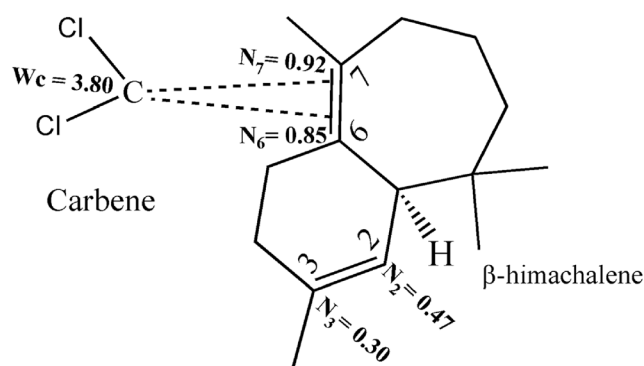
Fig. 2 Interaction between the reactive sites in the stoichiometric reaction between dichlorocarbene and β-himachalene

Table 3 Intramolecular chemical descriptors (eV) for P_1 and dibromocarbene, taking the HOMO energy of tetracyanoethylene as a reference [ε HO(TCE)= −0,3503 (a.u.)= −9.5322 (eV)]

	ε(HOMO) (eV)	ε(LUMO) (eV)	μ (eV)	η (eV)	ω (eV)	N (eV)	ΔN_{max}
P_1	−6.262	0.078	−3.091	6.341	0.753	3.269	0.487
Dibromocarbene	−7.062	−3.601	−5.332	3.460	4.107	2.469	1.540

nucleophilicity index (N) for β-himachalene and dichlorocarbene are shown in Table 1. From these results we can see that:

- The electronic chemical potential of β-himachalene (−2.4993 eV) is greater than that of dichlorocarbene (−5.4544 eV), which implies that the transfer of electrons takes place from β-himachalene to dichlorocarbene.
- The electrophilicity index of dichlorocarbene (3.9075 eV) is greater than that of β-himachalene (0.4890 eV). Consequently, in this cycloaddition, dichlorocarbene behaves as an electrophile while β-himachalene behaves as a nucleophile.
- The global nucleophilic indices of the reactants confirm that dibromocarbene is an electrophile and that β-himachalene is a nucleophile.

Local electrophilicity index, local nucleophilicity index and atomic spin density of the reactants

The local electrophilicity index [17, 18] and local nucleophilicity index [19, 20] were evaluated using the following expressions: $\omega_k = \omega.P^+$ and $N_k = N.P^-$ such that P^+ and P^- are the electrophilic and nucleophilic Parr functions, respectively [21–23].

Local electrophilicity, ω_k, for the carbenes and local nucleophilicity, N_k, for the atoms C_2, C_3, C_6 and C_7 of β-himachalene, calculated using the Parr functions (atomic spin density) are shown in Table 2 and represented in Fig. 2.

These results show that the most favored interaction takes place between the carbon atom of the carbene (with the highest value of ω_k) and the C_6 and C_7 atoms of β-himachalene (with the highest value of N_k). Consequently, the regioselectivity observed is predicted correctly by the Parr function. In order to demonstrate that the attack on the $C_6=C_7$ double bond of β-himachalene is preferred, we studied the stereoselectivity of this bond and found that the α side is preferred [24].

Analysis of intramolecular chemical descriptors of the reaction between P_1 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_1 and

Fig. 3 Interaction between frontier orbital of P_1 and dibromocarbene
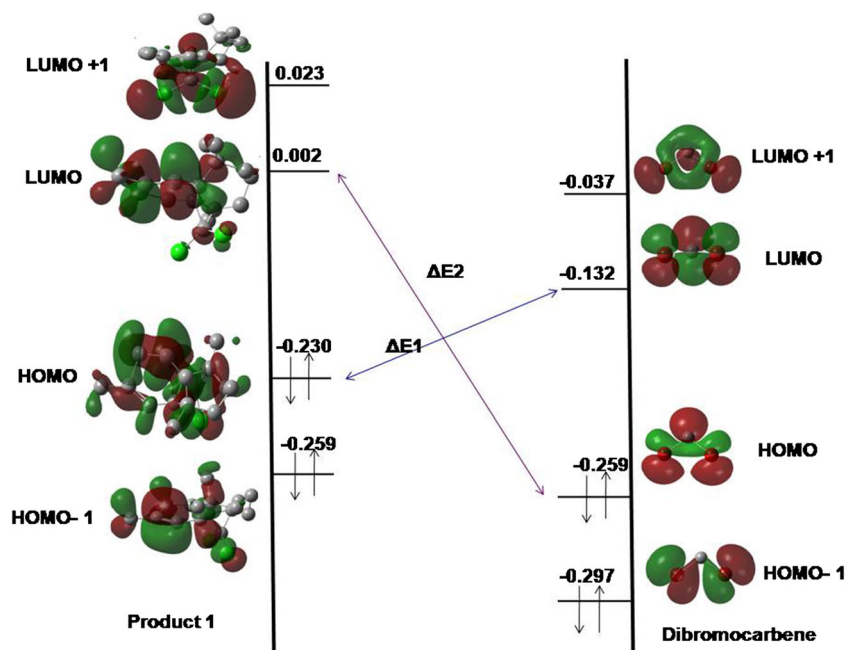
Table 4 Total energy B3LYP/6-31G*(d) (E in a.u.) and relative energies ΔE^*(kcal mol^{-1}) for the stationary points of the stoichiometric reaction between P_1 and dibromocarbene

	E (a.u.)	ΔE^* (kcal mol^{-1}) (E–E$_R$)	$\Delta(T_{S\beta}–T_{S\alpha})$ (kcal mol^{-1})
Reactants (P_1+CBr$_2$)	−6,725.909		27.421
E$_{TS\,\alpha}$	−6,725.801	67.330	
E$_{TS\,\beta}$	−6,725.758	94.752	
P$_2\,\alpha$	−6,725.991	−51.450	
P$_3\,\beta$	−6,725.998	−55.847	

dibromocarbene are shown in Table 3. From these results we can see that:

- The electrophilic index of dibromocarbene (4.107 eV) is greater than that of P_1 (0.753 eV). Consequently, in this cycloaddition, dibromocarbene behaves as an electrophile while P_1 behaves as a nucleophile.
- The global nucleophilic indices of the reactants confirm that dibromocarbene is an electrophile and that P_1 is a nucleophile.
- The maximum charge transfer of dibromocarbene (1.540) is greater that of P_1 (0.487) and the difference between the electrophilic indices of the reactants is $\Delta\omega$=3.354 eV, indicating the very high polarity of this cycloaddition.
- The chemical hardness of P_1 (6.341 eV) is greater than that of dibromocarbene (3.460 eV) and the electronic chemical potential of P_1 (−3.091 eV) is greater than that of dibromocarbene (−5.332 eV), showing that electrons are transferred from P_1 to dibromocarbene.

Figure 3 represents the interaction between frontier orbitals of P_1 and dibromocarbene in a [1+2] cycloaddition reaction. The energy difference between the HOMO of P_1 and the LUMO of dibromocarbene is 2.661 eV and the difference between the HOMO of dibromocarbene and the LUMO of P_1 is 7.140 eV. The HOMO of P_1 is close to the LUMO of dibromocarbene, confirming that P_1 is nucleophilic and dibromocarbene is electrophilic.

Kinetic study

Calculation of the energies of the reactants, the energies of the products obtained, TS$_\alpha$ and TS$_\beta$ transition energies at the C$_2$=C$_3$ double bond of P_1 and the difference in transition energy show that the attack is kinetically preferred at the α side (Table 4). Using the data given in Table 4, we can sketch the energy profile of the reaction (Fig. 4). This shows that:

- The activation energies corresponding to the attack at the two sides of the C$_2$=C$_3$ double bond of P_1 are 94.75 kcal mol^{-1} at β and 67.33 kcal mol^{-1} at α.
- The difference between the activation energies of P_2 and P_3 is around 27.42 kcal mol^{-1}, 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 −51.450 and −55.847 kcal mol^{-1}, respectively.
- The formation of P_2 and P_3 is thermodynamically favorable.

Fig. 4 Energy profile of the stoichiometric reaction between P_1 [(1S, 3R, 8S)-2,2-dichloro-3,7,7,10- tetramethyltricyclo [6.4.0.0^{1,3}]dodec-9-ene] and dibromocarbene (distances in Å) (TE=transition energy)
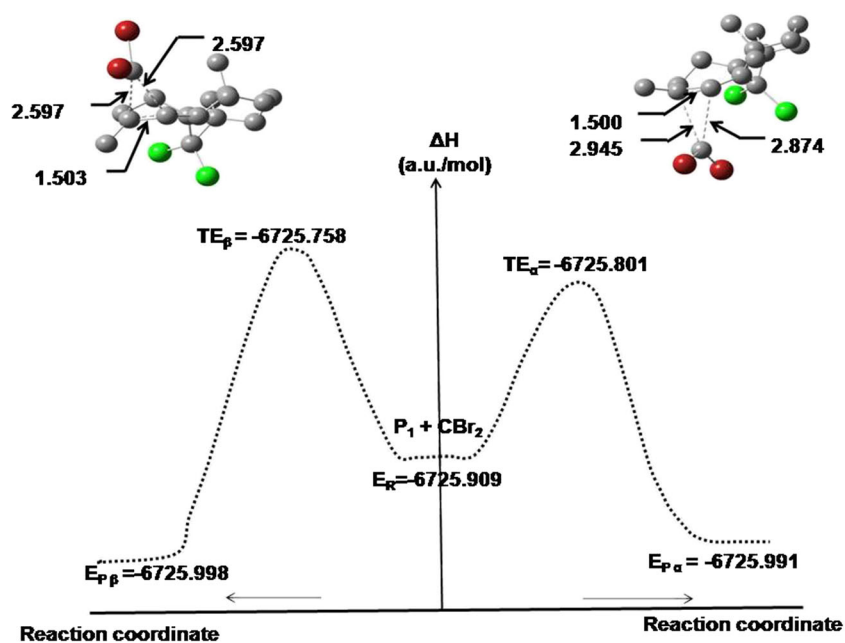
The geometry of the transition states TS_α and TS_β is shown in Fig. 4. The lengths of the C_3–CBr_2 and C_2–C_3 bonds corresponding to TS_α and TS_β are:

- The α side of the C_2–C_3 bond: ⓒ$_2$–CBr_2)=2.874 Å, ⓒ$_3$–CBr_2)=2.945 Å and ⓒ$_2$–C_3)=1.5 Å;
- The β side of the C_2–C_3 bond: ⓒ$_2$–CBr_2)=2.597 Å, ⓒ$_3$–CBr_2)=2.597 Å and ⓒ$_2$–C_3)=1.503 Å.

These transition states correspond to the formation of concerted bonds.

Conclusions

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 dichlorocarbene on the one hand and between the product of this first reaction (($1S$, $3R$, $8S$)-2,2-dichloro-3,7,7,10-tetramethyltricyclo[6.4.0.0$^{1.3}$]dodec-9-ene, referred to as P_1) and dibromocarbene on the other, we have shown that:

- The stereoselectivity and chemoselectivity observed at the α side of the C_2=C_3 bond is confirmed by the α and β transition states, and the formation of the product P_2 (($1S,3R,8R,9S,11R$)-10,10-dibromo-2,2-dichloro-3,7,7,11-tetramethyltetracyclo[6,5,0,0$^{1.3}$,0$^{9.11}$] tridecane) is kinetically preferred to formation of P_3 (($1S,3R,8R,9R,11S$)-10,10-dibromo-2,2-dichloro-3,7,7,11-tetramethyltetracyclo[6,5,0,0$^{1.3}$,0$^{9.11}$] tridecane). P_2 is formed in greater quantity than P_3.
- 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 P_1 and the LUMO of dibromocarbene and between the LUMO of P_1 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.
- The fact that product P_2 (formed at the α side) is kinetically favored is due to the presence of two methyl groups linked to the C_{11} of β-himachalene (steric hindrance).

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