

Elucidation of the chemo- and stereoselectivity of [1+2] cycloaddition reactions between α -cis-himachalene and dichlorocarbene using a multiphilic descriptor

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Abstract

A theoretical study of the mechanism and selectivity of [1+2] cycloaddition reactions between α -cis-himachalene and dichlorocarbene was performed using DFT B3LYP/6-311+G(d, p). Analysis of the global electrophilicity indices shows that α -cis-himachalene behaves as a nucleophile, while dichlorocarbene behaves as an electrophile. In line with the local philicity concept, we propose a multiphilic descriptor. This descriptor is capable of simultaneously explaining the nucleophilicity and electrophilicity of the atomic sites in the molecule. The double bond of the six-membered ring is attacked when stoichiometric quantities of α -cis-himachalene and dichlorocarbene are used, while the other double bond is attacked by dichlorocarbene only when it is used in excess. The calculation of activation and reaction energies indicates that the α cycloadducts are favored both kinetically and thermodynamically

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1. Introduction

This work forms part of our studies into the uses of essential oil of the Atlas Cedar (*Cedrus Atlantica*)¹⁻², used as a raw material in the perfume industry. This oil has been the object of various important studies which focused on the isolation, identification, and reactivity of its constituents³⁻⁷. The essential oil of the Atlas Cedar is primarily constituted (75%) of three sesquiterpenic bicyclic hydrocarbons: α -cis-himachalene, β -himachalene and γ -cis-himachalene. Each one of them differs from the others only by the seven-membered ring double bond position⁶. The reactivity of these sesquiterpenes has been extensively studied⁸⁻¹¹. 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 industry¹²⁻¹⁴. In our study we looked at the action of two different quantities of dichlorocarbene on α -cis-himachalene, and analysed the chemo- and stereoselectivity of these reactions. A stoichiometric quantity of dichlorocarbene led to an attack at the six membered ring double bond producing a majority of the α -stereoisomer, referred to here as P_α (the α side is that which contains the C_1 -H of the bond and the β side is the opposite), and a minority of the β -stereoisomer, referred to as P_β , while an excess of dichlorocarbene led to an attack at the seven-membered ring double bond of α -cis-himachalene producing a majority of the $\alpha\alpha$ -stereoisomer, referred to as $P_{\alpha\alpha}$, and a minority of the $\alpha\beta$ -stereoisomer, referred to as $P_{\alpha\beta}$ (Figure 1).

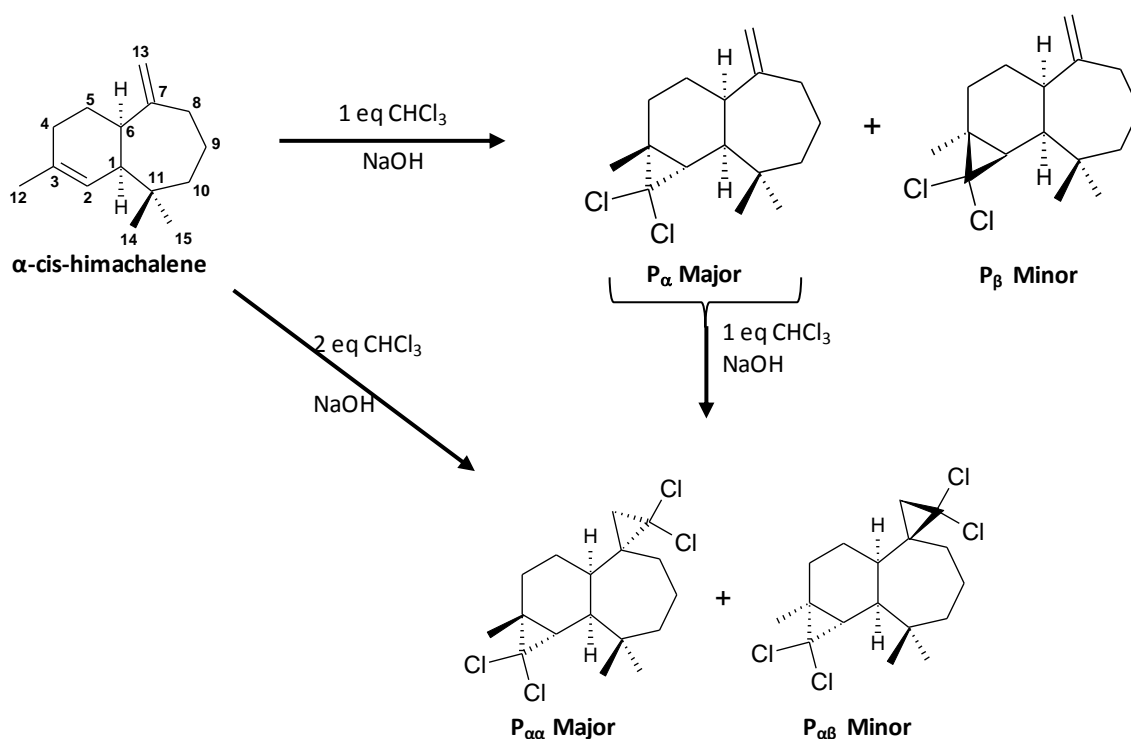


Figure 1. Mechanism of the reaction between α -cis-himachalene and dichlorocarbene

2. Theoretical and Computational Methods

2.1 Global reactivity indices

Conceptual density functional theory (DFT) is a valuable tool for understanding the chemical reactivity and site selectivity of molecular systems¹⁵. We used chemical potential, global hardness, global softness, electronegativity and electrophilicity in order to predict chemical reactivity of the compounds studied. In this paper we give the formal

definitions of all these descriptors and working equations for their use, and we review in some detail various applications of both global and local reactivity descriptors in the context of chemical reactivity and site selectivity.

Electronegativity χ ¹⁶ and hardness η ¹⁷⁻¹⁸ are described within the framework of conceptual DFT¹⁵. Electronegativity is the negative of chemical potential defined as follows for an N-electron system with total energy E and external potential $v(r)$ ¹⁹,

$$\mu = -\chi = \left(\frac{\partial E}{\partial N} \right)_{v(r)} \quad (1)$$

where μ is the chemical potential^{15, 20}. Hardness η is defined as the corresponding second derivative²¹,

$$\eta = \left(\frac{\partial^2 E}{\partial N^2} \right)_{v(r)} = \left(\frac{\partial \mu}{\partial v(r)} \right)_N \quad (2)$$

Using a finite difference method, working equations for the calculation of μ and η may be given as¹⁵:

$$\mu = -\frac{(I+A)}{2} \quad (3)$$

$$\eta = I - A \quad (4)$$

where I and A are the ionization potential and electron affinity, respectively. If ϵ_{HOMO} and ϵ_{LUMO} are the energies of the highest occupied and lowest unoccupied molecular orbitals respectively, then the above equations can be rewritten²² using Koopmans' theorem²³, as

$$\mu = \frac{\epsilon_{\text{HOMO}} + \epsilon_{\text{LUMO}}}{2} \quad (5)$$

$$\eta = \epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}} \quad (6)$$

In this work, μ and η are calculated using equations 5 and 6. The electrophilicity index, as defined by Parr et al.²⁴, is given by

$$\omega = \frac{\mu^2}{2\eta} \quad (7)$$

This quantity can be considered as a measure of the electrophilic power of a system. Recently, Domingo et al.²⁵ introduced an empirical (relative) nucleophilicity index, Nu , based on the highest occupied molecular orbital energies obtained within the Kohn–Sham scheme²⁶ and defined as:

$$Nu = \epsilon_{\text{LUMO}}(Nu) - \epsilon_{\text{HOMO}}(\text{TCE}) \quad (8)$$

This nucleophilicity scale takes tetracyanoethylene as a reference. This choice allows us to handle a nucleophilicity scale with only positive values²⁵.

2.2 Local reactivity indices

Fukui Function (FF)²⁷⁻²⁹ is one of the widely used local density functional descriptors to model chemical reactivity and site selectivity and is defined as the derivative of the electron density $\rho(r)$ with respect to the total number of electrons N in the system, at constant external potential $v(r)$:

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N} \right)_{v(r)} = \left(\frac{\partial \mu}{\partial v(r)} \right)_N \quad (9)$$

The condensed FF are calculated using the procedure proposed by Yang and Mortier³⁰, based on a finite difference method:

$$f_k^+[N] = p_k[N+1] - p_k[N] \quad \text{for nucleophilic attack (10a)}$$

$$f_k^-[N] = p_k[N] - p_k[N-1] \quad \text{for electrophilic attack (10b)}$$

$$f_k^0[N] = (p_k[N+1] - p_k[N-1]) \quad \text{for radical attack (10c)}$$

where $p_k[N]$; $p_k[N-1]$ and $p_k[N+1]$ are the electronic populations of the site k in neutral, cationic, and anionic systems, respectively. Chattaraj et al.³¹ have introduced the concept of generalized philicity. It contains almost all information about hitherto known different global and local reactivity and selectivity descriptors, in addition to the information regarding electrophilic/nucleophilic power of a given atomic site in a molecule. It is possible to define a

local quantity called philicity associated with a site k in a molecule with the help of the corresponding condensed- to-atom variants of FF, f_k^α as

$$\omega_k^\alpha = f_k^\alpha \omega \quad (11)$$

where ($\alpha = + ; - ; 0$) represents local philic quantities describing nucleophilic, electrophilic and radical attacks respectively. Equation (11) predicts that the most electrophilic site in a molecule is the one which gives the highest value of ω_k^+ . When two molecules react, which one will act as an electrophile (nucleophile) will depend on which has a higher (lower) electrophilicity index. Recently the usefulness of the electrophilicity index in studying the toxicity of polychlorinated biphenyls, benzidine and chlorophenol has been assessed in detail³²⁻³⁴.

Global softness S is defined as the inverse of hardness³⁵. Local softnesses³⁶ used to describe the reactivity of individual atoms in a molecule are defined as follows:

$$s_k^\alpha = f_k^\alpha S \quad (13)$$

where ($\alpha = + ; - ; 0$) represents local softness in the case of nucleophilic, electrophilic and radical attacks respectively. Based on local softness, relative nucleophilicity (s_k^-/s_k^+) and relative electrophilicity (s_k^+/s_k^-) indices have also been defined and their usefulness to predict reactive sites also been addressed³⁹. The quantum chemical model used to calculate wave function, the type of population analysis used to obtain the partial charges and the basis set employed in the molecular orbital calculations are important parameters, which significantly influence the Fukui functions²⁹.

The condensed dual descriptor has been defined as $f_k^{(2)}(r) = [f^+(r) - f^-(r)]$ ³⁷⁻³⁸. If $f_k^{(2)}(r) > 0$ for a given site, then a nucleophilic attack is more likely, whereas if $f_k^{(2)}(r) < 0$ there is a greater likelihood of electrophilic attack³⁷⁻³⁹. The associated dual local softness have also been defined as⁴⁰:

$$\Delta s_k = S(f^+ - f^-) = s_k^+ - s_k^- \quad (15)$$

2.3 Computational details

The quantum chemistry calculations reported here were carried out using the DFT B3LYP³⁹ exchange-correlation functional method, together with the standard 6-311+G** basis set⁴¹. The optimizations were performed using the Berny analytical gradient optimization method⁴². DFT B3LYP/6-311+G** was also used to study the transition states and to characterize the stationary points to verify that each transition state had one and only one imaginary frequency. The intrinsic reaction coordinate (IRC) path was traced in order to check the energy profiles connecting each transition state to the two associated minima of the proposed mechanism. The electronic populations used for the calculation of local reactivity indices were computed using natural population analysis (NPA). All calculations were performed using the Gaussian 09W suite of programs⁴³.

3. Results and Discussion

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

3.1.1 Prediction of the regioselectivity

The reactivity indices calculated using conceptual DFT are powerful tools for analyzing the polar/nonpolar character of reactions similar to those we are studying here⁴⁴⁻⁴⁵. Table 1 shows the calculated values of static global properties, namely chemical electron potential μ , chemical hardness η , global electrophilicity ω and global nucleophilicity N . The electronic chemical potential μ of α -cis-himachalene is greater than that of dichlorocarbene, while the global electrophilicity index ω of dichlorocarbene is greater than that of α -cis-himachalene. These results confirm that α -cis-himachalene is a nucleophile and that dichlorocarbene is an electrophile, which implies that charge transfer takes place from α -cis-himachalene to dichlorocarbene. The energy gap between the HOMO of α -cis-himachalene and the LUMO of dichlorocarbene is 2.5543 eV, while the energy gap between the HOMO of dichlorocarbene and the LUMO of α -

cis-himachalene is 7.7582 eV. This result confirms that α -cis-himachalene behaves as a nucleophile, while dichlorocarbene is an electrophile. The localisation of the HOMO and LUMO of α -cis-himachalene and dichlorocarbene are shown in Figure 2

Table 1. Electronic chemical potential μ , hardness η , global electrophilicity ω and global nucleophilicity N of α -cis-himachalene and dichlorocarbene (eV)

	μ	η	ω	N
α-cis-himachalene	-3,0606	6,5326	0,7170	3,0417
Dichlorocarbene	-5,6626	3,7799	4,2414	1,8161

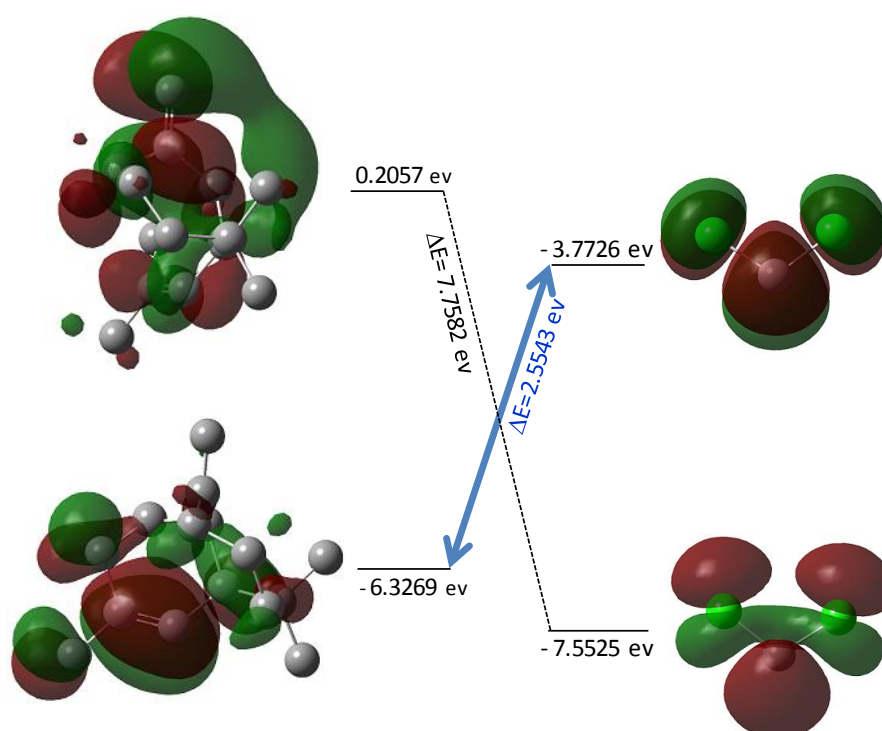


Figure 2. Energy gap between HOMO and LUMO in the reaction of α -cis-himachalene with dichlorocarbene (eV)

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

The local (regional) electrophilicity index introduced by Domingo et al.⁴⁶ helps in identify the relevant electrophilic sites within a static reactivity picture. In the absence of a precise definition of local nucleophilicity we will assume that the most nucleophilic site at the nucléophilie moiety will be the one presenting the highest value of the Fukui function for an electrophilic attack, f_k^- . The local electrophilicity/nucleophilicity character of reagents, however, may also be of significant utility in predicting the stereoselectivity patterns that can be expected for a given reaction. The formation of the first new can be justified by the interaction between the more electrophilic site of the dichlorocarbene and the more nucleophilic site of the α -cis-himachalene. The nucleophilic Fukui indices f^- for the atoms C₂ and C₃ of α -cis-himachalene are higher than for C₇ and C₁₃, but the f^- value of the C₂ atom is almost same as that of the C₃ atom, making it difficult to determine whether these atoms behave as electrophiles or not. In this situation, the dual descriptors $f_k^{(2)}(r)$, Δs_k and multiphilic descriptor $\Delta\omega_k$ are helpful. All these descriptors enable us to distinguish

clearly between nucleophilic and electrophilic attacks at a particular site, inasmuch as they have a positive value at sites liable to nucleophilic attack and a negative value at sites liable to electrophilic attack. The multiphilic descriptor $\Delta\omega_k$ is particularly useful in this respect. The values of local reactivity descriptors calculated using DFT B3LYP/6-311+G** method for NPA derived charges of the molecule studied are shown in Table 2.

Table 2. Local reactivity properties of certain molecules calculated using DFT B3LYP/6-311+G** for NPA derived charges.

Atom	f_k^+	f_k^-	ω_k^+	ω_k^-	S_k^+	S_k^-	Δf_k	$\Delta\omega_k$	ΔS_k
C ₁	-0.0037	-0.0408	-0.0027	-0.0292	-0.0003	-0.0031	0.0370	0.0265	0.0028
C ₂	0.1535	0.1878	0.1100	0.1346	0.0117	0.0144	-0.0343	-0.0246	-0.0026
C ₃	0.1315	0.1968	0.0943	0.1411	0.0101	0.0151	-0.0653	-0.0468	-0.0050
C ₄	-0.0102	-0.0430	-0.0073	-0.0308	-0.0008	-0.0033	0.0328	0.0235	0.0025
C ₅	-0.0052	-0.0109	-0.0037	-0.0078	-0.0004	-0.0008	0.0057	0.0041	0.0004
C ₆	0.0002	-0.0025	0.0002	-0.0018	0.0000	-0.0002	0.0027	0.0019	0.0002
C ₇	0.0460	0.0342	0.0330	0.0245	0.0035	0.0026	0.0117	0.0084	0.0009
C ₈	-0.0073	-0.0104	-0.0053	-0.0074	-0.0006	-0.0008	0.0030	0.0022	0.0002
C ₉	-0.0015	-0.0004	-0.0011	-0.0003	-0.0001	0.0000	-0.0012	-0.0008	-0.0001
C ₁₀	-0.0024	0.0020	-0.0017	0.0014	-0.0002	0.0002	-0.0044	-0.0031	-0.0003
C ₁₁	-0.0079	0.0031	-0.0056	0.0022	-0.0006	0.0002	-0.0109	-0.0078	-0.0008
C ₁₂	-0.0106	-0.0429	-0.0076	-0.0308	-0.0008	-0.0033	0.0324	0.0232	0.0025
C ₁₃	0.1159	0.1223	0.0831	0.0877	0.0089	0.0094	-0.0065	-0.0046	-0.0005
C ₁₄	0.0038	-0.0041	0.0027	-0.0030	0.0003	-0.0003	0.0080	0.0057	0.0006
C ₁₅	-0.0033	-0.0080	-0.0024	-0.0058	-0.0003	-0.0006	0.0048	0.0034	0.0004
C*	0.2733	0.1972	1.1591	0.8364	0.0361	0.0261	0.0761	0.3227	0.0101

* C carbon atom of dichlorocarbene

We see from Table 2 that the negative value of the condensed dual descriptor $f^{(2)}(\mathbf{r})$ is particularly marked at the site C₃, implying that this will be the preferred site for an electrophilic attack, while the C₇ atom is the preferred site for nucleophilic attack. The most favored stereoisomer is that which is associated with the higher dual descriptor $f^{(2)}(\mathbf{r})$ of the electrophile and the lower dual descriptor $f^{(2)}(\mathbf{r})$ of the nucleophile. We determined $f^{(2)}(\mathbf{r})$ for α -cis-himachalene and dichlorocarbene 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. We deduce that the most favored interaction will take place between the C₃ atom of α -cis-himachalene and the C* carbon atom of dichlorocarbene, followed by closure of the cycle with the formation of the second C*-C₂ bond. The interaction between the nucleophile α -cis-himachalene and the electrophile dichlorocarbene is therefore competitive.

3.2 Study of the mechanism of the reaction between α -cis-himachalene and dichlorocarbene

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

The activation energy of transition state TS _{α} (corresponding to the α side) is 3.9415 kcal/mol, i.e. 15.7704 kcal/mol below TS _{β} (corresponding to the β side) showing that the α -stereoisomer is kinetically preferred to the β -stereoisomer in the stoichiometric reaction. An excess of dichlorocarbene results in two transition states: TS _{$\alpha\alpha$} (corresponding to the

α side of C₂-C₃ and C₇-C₁₃) with an activation energy of 10.8735 kcal/mol, i.e. 12.0621 kcal/mol below TS _{$\alpha\beta$} (corresponding to the α side of C₂-C₃ and β side of C₇-C₁₃), indicating that the $\alpha\alpha$ -stereoisomer is kinetically preferred to the $\alpha\beta$ -stereoisomer.

3.2.2 Analysis of the IRC of the reaction between α -cis-himachalene and dichlorocarbene

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 σ 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 α -cis-himachalene and dichlorocarbene 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 2. IRC calculation shows that this reaction follows a concerted mechanism in a single step but in two phases⁴⁷. Analysis of the IRC calculated using DFT/B3LYP/6-311+G** shows that whatever quantity of dichlorocarbene is used in the interaction with α -cis-himachalene, the transition states are reached without going through a stable intermediary stage. Tables 3 and 4 show that after making thermal corrections for the thermodynamic energies, the free activation enthalpies of TS _{α} and TS _{β} increase by 17.9913 kcal/mol and 30.3263 kcal/mol respectively, while the free activation enthalpies of TS _{$\alpha\alpha$} and TS _{$\alpha\beta$} increase by 24.4189 kcal/mol and 25.9224 kcal/mol respectively. These high values are a result of the unfavorable activation entropies associated with the process. The products P _{α} and P _{β} obtained for a stoichiometric quantity of the reactants are strongly exothermic, by -50.1524 kcal/mol and -40.2202 kcal/mol respectively. Consequently, P _{α} is thermodynamically preferred to P _{β} . In the second reaction (excess of dichlorocarbene), products P _{$\alpha\alpha$} and P _{$\alpha\beta$} are also exothermic, by -52.3487 kcal/mol and -47.2659 kcal/mol respectively, indicating that P _{$\alpha\alpha$} is thermodynamically preferred to P _{$\alpha\beta$} .

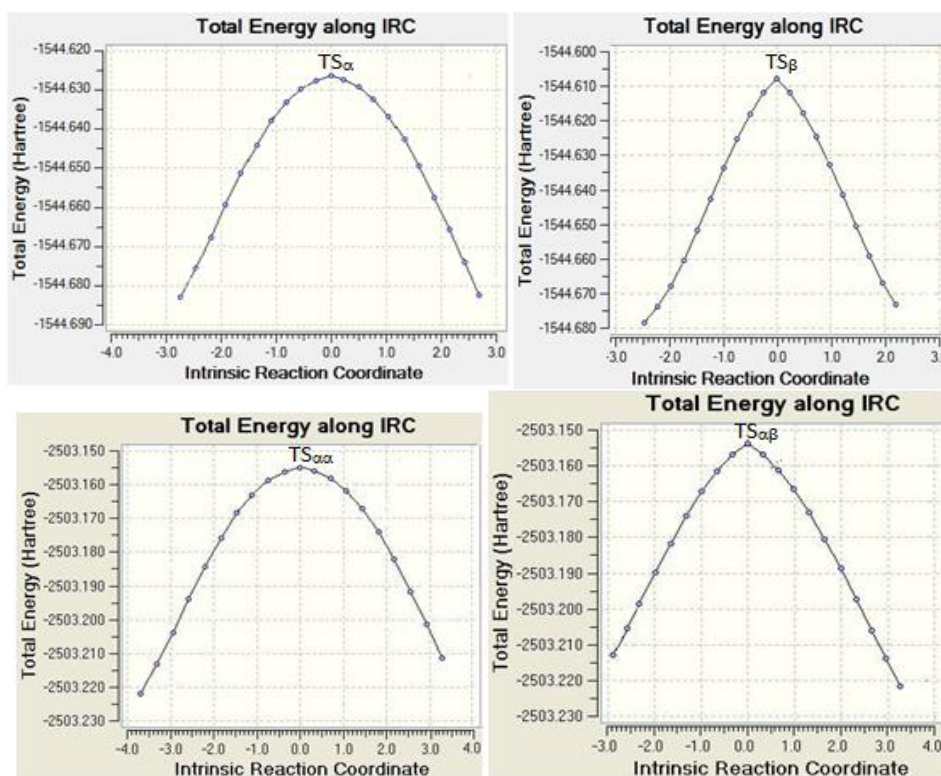


Figure 3. IRC of the reaction between α -cis-himachalene and dichlorocarbene calculated using DFT B3LYP/6-311+G**

Table 3. Thermodynamic energies of the reaction between α -cis-himachalene and one equivalent of dichlorocarbene calculated using DFT B3LYP/6-311+G **

	α -cis-hima-chalene	Dichloro-carbene	TS $_{\alpha}$	TS $_{\beta}$	P $_{\alpha}$	P $_{\beta}$
E (a.u.)	-586.1795	-958.4536				
ΔE (kcal/mol)			3.9415	15.7704	-53.5990	-43.6795
H (u.a)	-585.8081	-958.4452	-1544,2453	-1544,2275	-1544,3332	-1544,3174
ΔH (kcal/mol)			4.9837	16.1515	-50.1524	-40.2202
G (u.a)	-585.8640	-958.4753	-1544,3107	-1544,2910	-1544,3966	-1544,3806
ΔG (kcal/mol)			17.9913	30.3263	-35.9193	-25.8616
ν (cm $^{-1}$)			-658.5314	-501.0580		

Table 4. Thermodynamic energies of the reaction between α -cis-himachalene and two equivalents of dichlorocarbene calculated using DFT B3LYP/6-311+G **

	P $_{\alpha}$	Dichloro-carbene	TS $_{\alpha\alpha}$	TS $_{\alpha\beta}$	P $_{\alpha\alpha}$	P $_{\alpha\beta}$
E (a.u.)	-1544.7185	-958.4536				
ΔE (kcal/mol)			10.8735	12.0621	-55.4868	-50.5199
H (a.u.)	-1544.3332	-958.4452	-2502.7596	-2502.7574	-2502.8618	-2502.8537
ΔH (kcal/mol)			11.7840	13.1463	-52.3487	-47.2659
G (a.u.)	-1544.3966	-958.4753	-2502.8330	-2502.8306	-2502.9328	-2502.9242
ΔG (kcal/mol)			24.4189	25.9224	-38.1727	-32.8175
ν (cm $^{-1}$)			-502.3281	-657.5062		

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 α -cis-himachalene and dichlorocarbene (Figure 4) shows that 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 $\Delta d = |d_{C^* - C_3} - d_{C^* - C_2}|$.

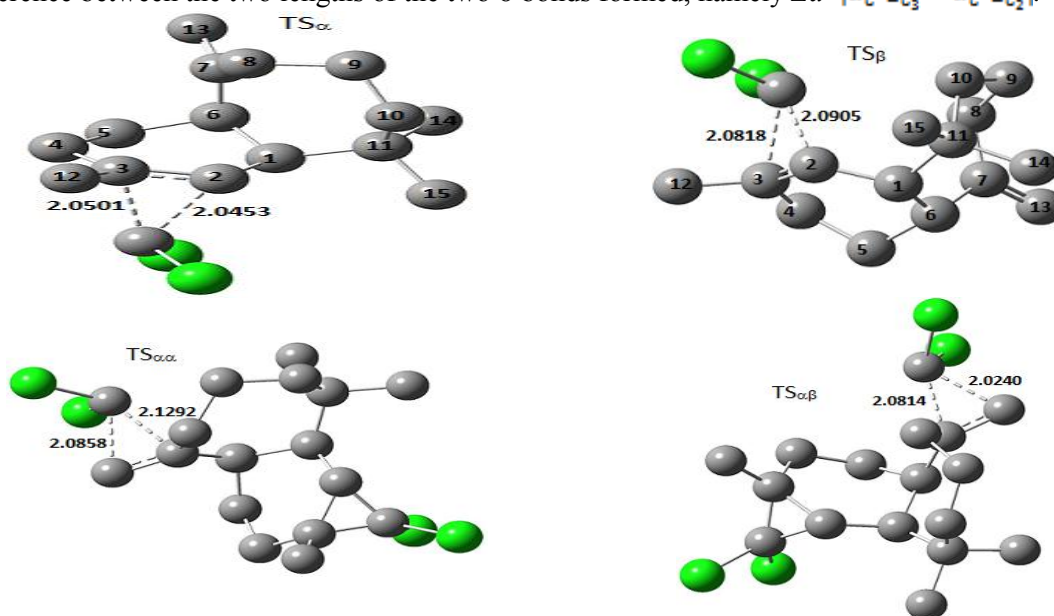


Figure 4. Bond lengths (Å) of the transition states of the reaction between α -cis-himachalene and dichlorocarbene.

Asynchronicity of chemoisomer 1 is $\Delta d=0.0304$ Å at TS1 and $\Delta d=0.128$ Å at TS2, while asynchronicity of chemoisomer 2 is $\Delta d=0.0231$ Å at TS3 and $\Delta d=0.0197$ Å at TS4. We can conclude that the transition states associated with the two chemoisomeric pathways show that the favored regioisomers are more asynchronous than the others.

4. Conclusion

The chemoselectivity and stereoselectivity for the [1+2] cycloaddition reactions between α -cis-himachalene and dichlorocarbene were studied using density functional theory (DFT) B3LYP/6-311+G**. The study shows that DFT-based reactivity indexes appear to be reliable predictors of stereoselectivity and reaction pathways in the case of competitive cycloaddition reactions. We have shown that the most favorable interaction takes place between the C₃ atom of the α -cis-himachalene and the C* atom of the dichlorocarbene, followed by closure of the cycle with the formation of the second C*-C2 bond.

Our results confirm the importance of the selected descriptors, namely, multiphilic descriptor and nucleophilicity excess in analyzing the overall reactivity trends in molecular systems.

References

- 1 - R. Hammal, A. Benharref, A. El Hajbi, Int. J. of Innovation and Applied Studies, **2014**, 6, 734-745.
- 2 - R. Hammal, A. Zeroual, A. Benharref, A. El Hajbi, J. Nat. Prod. Plant Resources, **2015**, 5 (2):6-12.
- 3 - A. S. Pfau, P. Plattner, Helvetica Chimica Acta, **1934**, 17, 129-157.
- 4 - G. S. Krishna, S. Dev, PC Guha, Indian Chem. Soc., **1952**, 29, 721-730.
- 5 - J. B. Berdenberg, H. Erdtmann, Acta Chem. Scand., **1961**, 15, 685-686.
- 6 - M. Plattier, P. Teisseire, Recherches, **1974**, 19, 131-144.
- 7 - T. C. Joseph, S. Dev, Tetrahedron, **1968**, 24, 3809-3827.
- 8 - S. C. Bisary, S. Dev, Tetrahedron **1968**, 24, 3869.
- 9 - R. Shankaranyan, S. Krishmappa, S. Dev, Tetrahedron, **1977**, 33, 885.
- 10 - M. Plattier, P. Rouiller, P. Teisseire, Recherches 19 (1974) 145.
- 11 - J. Daunis, R. Jacquier, H. Lopez, Ph. Viallefont, J. Chem. Res. (1981) 639.
- 12 - A. Benharref, A. Bernardini, S. Fkih Tetouani, R. Jacquier, Ph. Viallefont, J. Chem. Res. (1981) 4329.
- 13 - A. Benharref, A. Chekroun, J.P. Lavergne, Bull. Soc. Chim. Fr. 128 (1991) 739.
- 14 - E. Lassaba, H. El Jamili, A. Chekroun, A. Benharref, A. Chiaroni, C. Riche, J. P. Lavergne, Synth. Commun. **1998**, 28, 2641.
- 15 - R. G. Parr, W. Yang, Density Functional Theory of Atoms and Molecules, Oxford University Press: Oxford, **1989**.
- 16 - L. Pauling, The Nature of the Chemical Bond, 3rd ed., Cornell University Press: Ithaca, New York, **1960**.
- 17 - R. G. Pearson, Chemical Hardness: Applications from Molecules to Solids, Wiley-VCH: Weinheim, **1997**.
- 18 - K. D. Sen, D. M. P. Mingos, Structure and Bonding: Chemical Hardness, Vol. 80, Springer: Berlin, **1993**.
- 19 - R. G. Parr, R. A. Donnelly, M. Levy, W. E. Palke, J. Chem. Phys., **1978**, 68, 3801.
- 20 - W. Kohn, L. Sham, J. Phys. Rev. A, **1965**, 140, 1133.
- 21 - R. G. Parr, R. G. Pearson, J. Am. Chem. Soc., **1983**, 105, 7512.
- 22 - R. G. Pearson, Inorg. Chem., **1988**, 27, 734.
- 23 - T. A. Koopmans, Physica, **1933**, 1, 104.
- 24 - R. G. Parr, L. Von Szentpaly, S. Liu, J. Am. Chem. Soc., **1999**, 121, 1922.
- 25 - L. R. Domingo, E. Chamorro, P. Perez, J. Org. Chem., **2008**, 73, 4615.

- 26 - W. Kohn, L. Sham, J. Phys. Rev. A, **1965**, 140, 1133.
- 27 - R. G. Parr, W. Yang, J. Am. Chem. Soc., **1984**, 106, 4049.
- 28 - K. Fukui, Science, **1987**, 218, 747.
- 29 - P. W. Ayers, M. Levy, Theor. Chem. Acc., **2000**, 103, 353.
- 30 - W. Yang, W. J. Mortier, J. Am. Chem. Soc., **1986**, 108, 5708.
- 31 - P. K. Chattaraj, B. Maiti, U. Sarkar, J. Phys. Chem. A, **2003**, 107, 4973.
- 32 - R. Parthasarathi, J. Padmanabhan, V. Subramanian, B. Maiti, P. K. Chattaraj, J. Phys. Chem. A, **2003**, 107, 10346.
- 33 - R. Parthasarathi, J. Padmanabhan, V. Subramanian, B. Maiti, P. K. Chattaraj, Current Sci., **2004**, 86, 535.
- 34 - J. Padmanabhan, R. Parthasarathi, V. Subramanian, P. K. Chattaraj, Chem. Res. Tox., **2006**, 19, 356.
- 35 - W. Yang, R. G. Parr, Proc. Natl. Acad. Sci. U.S.A., **1985**, 82, 6723.
- 36 - C. Lee, W. Yang, R. G. Parr, J. Mol. Struct. (Theochem), **1988**, 163, 305.
- 37 - C. Morell, A. Grand, A. Toro-Labbé, Chem. Phys. Lett., **2006**, **425** (4–6): 342-346.
- 38 - J. Gázquez, **The hard and soft acids and bases principle**, J. Phys. Chem. A, **1997**, **101**: 4657-4659.
- 39 - J. L. Gázquez, In *Chemical Reactivity Theory: A Density Functional View*; ed. by P. K. Chattaraj; CRC Press - Taylor & Francis Group: Boca Raton, **2009**, pp. 7-21.
- 40 - R. Parthasarathi, J. Padmanabhan, M. Elango, V. Subramanian, P. K. Chattaraj, Chem. Phys. Lett., **2004**, 394, 225.
- 41 - W. J. Hehre, L. R. Schleyer, J. A. Pople, Ab initio Molecular Orbital Theory, Wiley: New York, **1986**
- 42 - H. B. Schlegel, J. Comput. Chem., **1982**, 3, 214.
- 43 - M. J. Frisch et al., Gaussian 09, Gaussian Inc., Wallingford CT, **2009**.
- 44 - L. R. Domingo, M. J. Aurell, P. Perez, R. Contreras, Tetrahedron, **2002**, 58, 4417.
- 45 - P. Perez, L. R. Domingo, A. Aizman, R. Contreras, In *Theoretical Aspects of Chemical Reactivity*; ed. by A. Toro-Labbe; Elsevier Science: New York, **2007**.
- 46 - L. R. Domingo, M. J. Aurell, P. Perez, R. Contreras, J. Phys. Chem. A, **2002**, 106, 6871.
- 47 - L. R. Domingo, M. T. Picher, P. Arroyo, J. A. Sáez, J. Org. Chem., **2006**, 71, 9319-9330.