Computational Study of the Mechanism
and Reactivity of β-Himachalene
in Presence of Carbenes Using DFT

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ABSTRACT: *The reactivity of the bicyclic sesquiterpene β-himachalene which is considered one of the main constituents of the essential oil of the Atlas cedar (Cedrus atlantica) and its derivatives have been studied extensively, in order to prepare new biological products. The title compound, $C_{17}H_{26}Br_2$ was synthesized from the β-himachalene with :CBr₂, in dichloromethane (DCM) and with :CH₂ cycloaddition reaction, in diethyl ether. Density functional theory (DFT) calculations at the B3LYP/6-311+G(d,p) computational level account for the total chemo- and regioselectivity, in complete agreement with the experimental outcomes.*

KEYWORDS: *β-himachalene; Cedrus atlantica; Cycloaddition reactions reactivity descriptors; Density Functional Theory.*

INTRODUCTION

In the context of the valorization of essential oil of the Atlas Cedar (*cedrus atlantica*), this work is part of our ongoing program [1-3]. This oil has been the object of various important studies which focused on the isolation, identification, and reactivity of its constituents.

Analysis of essential oil from *cedrus atlantica* revealed the presence of twenty-five compounds, representing 97.48 % of the total composition. The major group of compounds, the main one being α-himachalene (35.34%) followed by β-himachalene (13.62%), γ-himachalene (12.6%),
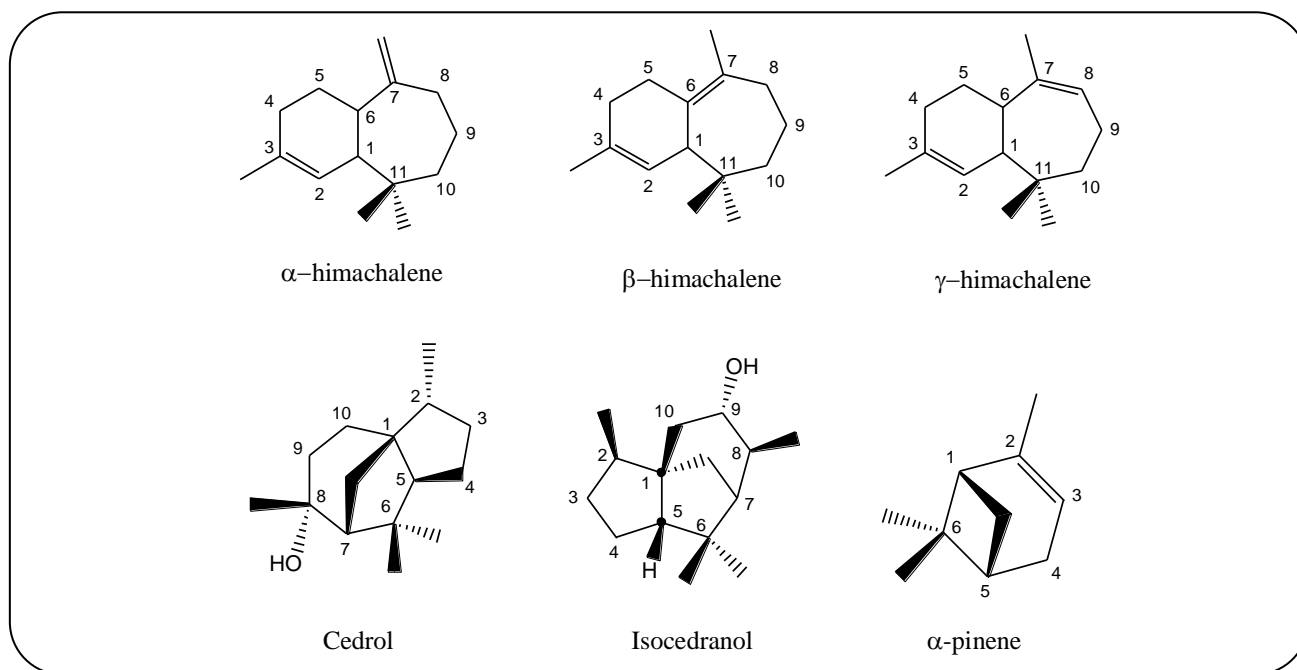
Fig. 1: The main compounds of essential oil from cedrus atlantica.

cedrol (10.32%), isocedranol (5.52%) and α-pinene (5.5%) [4]. Indeed, our group has studied himachalenes reactivity (hemisynthesis) in order to obtain new compounds which could be considered important intermediates for access to the bioactive molecules [5, 6].

The knowledge of the reactivity of a molecule is an essential concept; it is of crucial interest because it allows understanding of interactions that are operating during a reaction mechanism. In particular electrostatic interactions have been successfully explained by the use of molecular electrostatic potential [7,8].

However, since 2005 a descriptor of local reactivity whose name is simply a dual descriptor [9] has allowed to rationalize reaction mechanisms in terms of overlapping nucleophilic regions with electrophilic regions in order to get a maximum stabilization thus leading to final products or intermediates. All those favorable nucleophilic–electrophilic interactions have been explained as a manifestation of the Principle of Maximum Hardness. In addition, chemical reactions have been understood in terms of the hard and soft acids and bases principle [10], a principle that has been used even with the aim of replacing the use of the molecular orbital theory to understand the whole chemistry [11]. In the present work, the reactivity of β-himachalene (Fig. 1) using the reactivity indices defined within conceptual Density Functional Theory (DFT) at the B3LYP/6-311+G(d,p) basis set [12-15] was investigated.

COMPUTATIONAL DETAILS

The B3LYP functional [16] was used together with the 6-311+G(d,p) basis set in the Density Functional Theory calculations using the Gaussian 09 series of programs[17]. Although, we note that the anionic and cationic systems, required in the calculations of the local index were kept at the same geometry as the neutral system. The optimizations at this level of theory were performed using the Berny analytical gradient optimization method [18]. The stationary points were characterized by calculations of frequency (performed at the same level of theory) to verify that the TSs had one and only imaginary frequency. The Intrinsic Reaction Coordinate (IRC) path was traced to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism. The electronic structures of critical points were analyzed by using the Natural Bond Orbital (NBO) method [19,20].

The global electron density transfer (GEDT) [21, 22] was computed by the sum of the natural atomic charges (q), obtained by a Natural Population Analysis (NPA), of the atoms belonging to each framework (f) at the TSs; that is, $EDT(f) = \sum_{q \in f} q$; Positive values mean a flux from the considered framework to the other one.
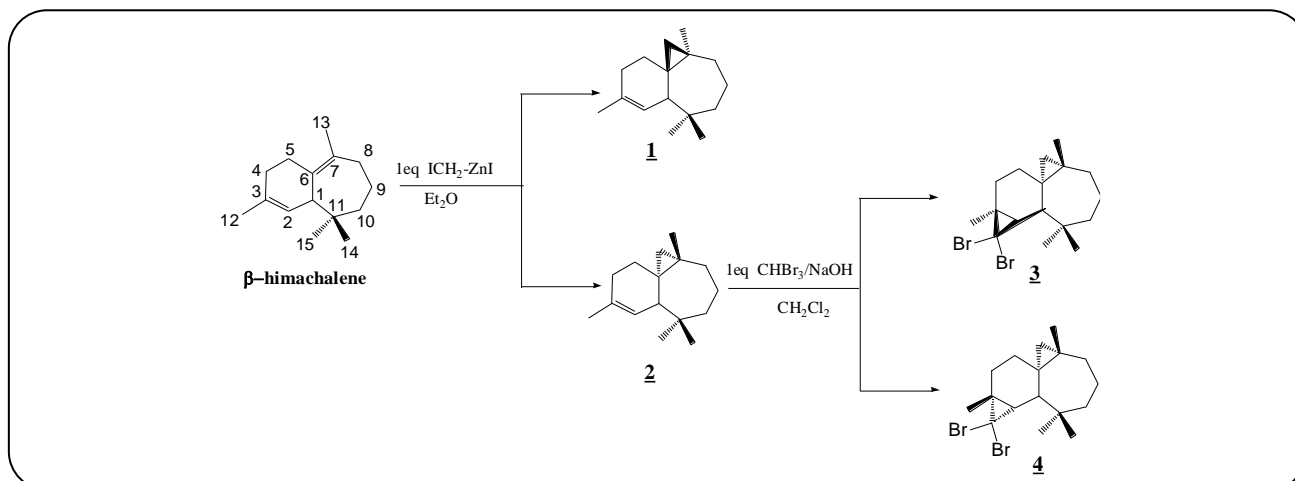
Scheme 1: Reaction of β-himachalene with $\cdot CH_2$ and $\cdot CBr_2$.

RESULTS AND DISCUSSION

In order to obtain new compounds with interesting olfactory properties in perfumery and to explain the chemo-, regio-, and stereo-selectivity experimentally observed to synthesize of (1S,3S,8R,9S,11R)-10,10-Dibromo-3,7,7,11-tetramethyltetracyclo-[6.5.0.0^{1,3}.0^{9,11}] tridecane, the action of an equivalent of ICH2-ZnI on β-himachalene isolated from *cedrus atlantica* essential oil is studied through a rigorous quantum chemical analysis of the changes in the electron density as well as the energies associated with these changes along the cycloaddition reaction path. The treatment at room temperature of β-himachalene with a stoichiometric amount of ICH$_2$-ZnI in diethyl ether provides compound **2** with a good yield.

The same experimental protocol was carried out for the **2** compound. Thus, the cycloaddition reaction on the latter, using CHBr$_3$ in dichloromethane (DCM) leads to the two products **3** and **4** with respective yields of 15 and 85%. As a result, the reaction is regiospecific and stereoselective (Scheme 1).

Global reactivity indices defined within conceptual DFT are powerful tools to explain the reactivity indices in cycloaddition reactions. Thus, in order to predict the reactivity of β-himachalene in presence of ($\cdot CH_2$) and ($\cdot CBr_2$), The global indices, namely, the electronic chemical potential,μ, the chemical hardness, η, the electrophilicity ω and the nucleophilicity *N*, gathered in Table 1 are analyzed, and the present analysis has been performed at the B3LYP/6-311+G(d,p) computational level.

The electronic chemical potential μ [23] of $\cdot CH_2$, -5.492eV, is lower than that of β-himachalene -3.148 eV, indicating that along a polar cycloaddition reaction path, the global electron density transfer will take place from the β-himachalene toward the $\cdot CH_2$. This polarity was confirmed by the GEDT value computed at the transition states TSs of the reaction; the larger the GEDT at the TS, the more polar the reaction. On the other hand, the electrophilicity ω indices [24] of β-himachalene is 0.839 eV and 4.419 eV of $\cdot CH_2$, and the nucleophilicity N indices [25-27], 3.269 eV of β-himachalene and 2.169 eV of $\cdot CH_2$. These results show that the β-himachalene is a strong and very good nucleophilie, while, $\cdot CH_2$ is a strong electrophile.

In order to predict the most favorable initial electrophile/nucleophile interaction in this cycloaddition reaction, Domingo proposed the nucleophilic P$_k^-$ and electrophilic P$_k^+$ Parr functions [28], analysis of the Atomic Spin Density (ASD) at the radical cation and the radical anion, as a powerful tool in the study of the local reactivity in polar or ionic processes. Therefore, the formation of the first new single bond always involves the most electrophilic center of the electrophile and the most nucleophilic center of the nucleophile.

Fig. 2 shows the Mulliken atomic spin densities of the radical cation and anion, together with the nucleophilic P_k^- and P_k^+ Parr functions of β-himachalene. Analysis of the nucleophilic P_k^- Parr functions at the reactive sites of β-himachalene indicates that both the C6 carbon atom, with a P_k^- value of 0.343, and the C7 carbon atom, with

Table 1. B3LYP/6-311+G(d,p) electronic chemical potential μ, chemical hardness η, electrophilicity ω,
nucleophilicity N, in eV, of β-himachalene, (·CH₂) and (·CBr₂)

Compounds	μ	η	ω	N
β-himachalene	-3.148	5.903	0.839	3.269
$\cdot CH_2$	-5.492	3.413	4.419	2.169
$\cdot CBr_2$	-5.606	3.379	4.651	2.074
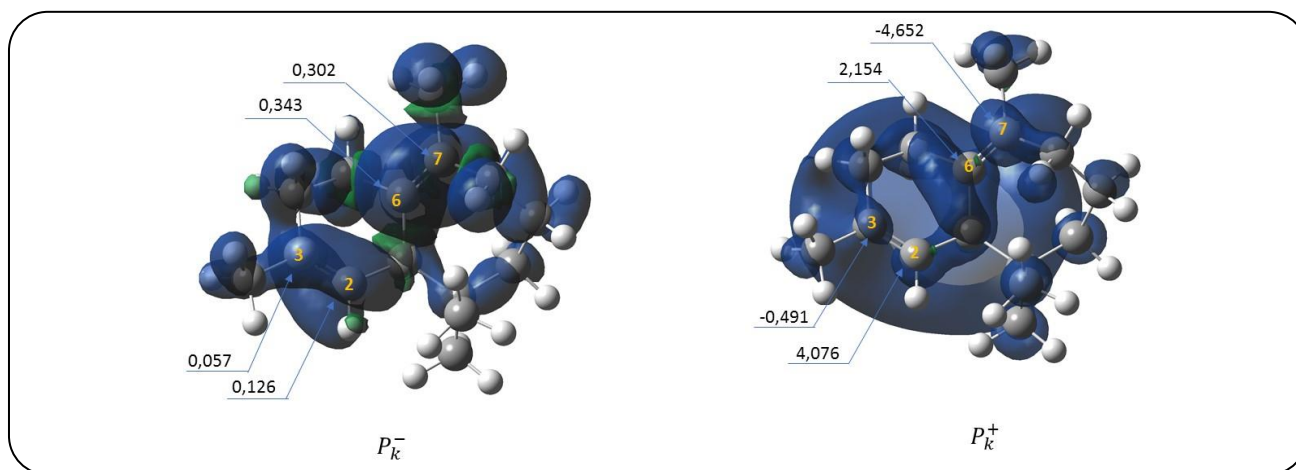
Fig. 2: Three-dimensional representations of the atomic spin densities (ASP) of the radical cation and anion, together
with the nucleophilic P_k^- and P_k^+ Parr functions of β-himachalene.

P_k^- the value of 0.302, are nucleophilically activated, the latter more than the former. These results indicate that the most reactive fragment of β-himachalene is the C6-C7 double bond elucidates for the total chemoselectivity experimentally observed (Scheme 1). Therefore, the most nucleophilic center of β-himachalene, is C6 carbon atom.
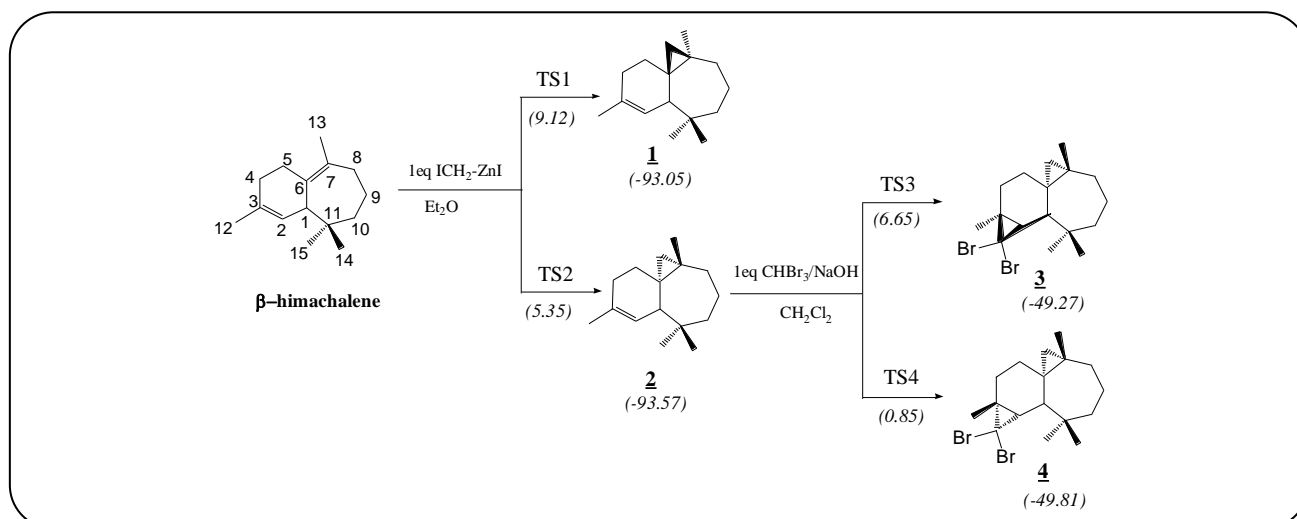
The cycloaddition of β-himachalene with ·CH₂, (CA-1) and ·CBr₂, (CA-2), respectively were performed by DFT calculations using the B3LYP functional together with the 6-311+G(d,p) basis set. Analysis of the stationary points associated with the two cycloadditions, CA-1 in diethyl ether and CA-2 in DCM reaction paths shows this reaction path is characterized by a one-step mechanism. Relative energies in diethyl ether and in DCM are given in Scheme 2.

Along the CA-1 reaction path, the 1 and 2 cycloadducts being strongly exothermic are found below the reagents by 93.05 and 93.57 kcal/mol, respectively, thus, 3 and 4 cycloadducts are also strongly exothermic by 49.27 and 49.81 kcal/mol, respectively for CA-2. Some appealing conclusions can be drawn from these energy results, the most favorable reaction path associated with the CA-1 reaction in diethyl ether, which is associated with the

formation of product 2 via TS2, presents an activation energy 5.35 kcal/mol. This value is 3.77 kcal/mol lower than that associated with product 1. The energy profiles associated with the two competitive CA-2 reactions show that TS4 is located 5.8 kcal/mol below TS3, in agreement with the preferential formation of cycloadduct 4.

The activation enthalpies associated with the four competitive reaction paths of the CA-1 and CA-2 reactions are: 12.32 (TS1), 9.27 (TS2); 7.23 (TS3), and 1.59 kcal/mol (TS4); formation of the corresponding compounds is exothermic by 87.54 (1), 87.86 (2); 46.02 (3) and 46.67 kcal/mol (4), respectively. These energy results account for the total chemo- and stereoselectivity, in complete agreement with the experimental outcomes.

On the other hand, the Gibbs free energy profiles associated with the CA-1 reaction between β-himachalene with ·CH₂ are given in Fig. 3. The activation Gibbs free energy associated with the more favourable regioisomeric reaction path of the formation of cycloadduct 2 being strongly exergonic by 74.51 kcal/mol, via TS2, is 13.89 kcal/mol, although TS2 is 2.15 kcal/mol below TS1. Form CA-2, formation of cycloadduct 4, *via* TS4, presents an activation Gibbs free energy of 14.20 kcal/mol and below by 6.21 kcal/mol of TS3, being exergonic by 34.35 kcal/mol.

Scheme 2: B3LYP/6-311+G(d, p) relative energies, in Kcal/mol, are given in parentheses of β-himachalene with :CH_2 and :CBr_2 cycloaddition.

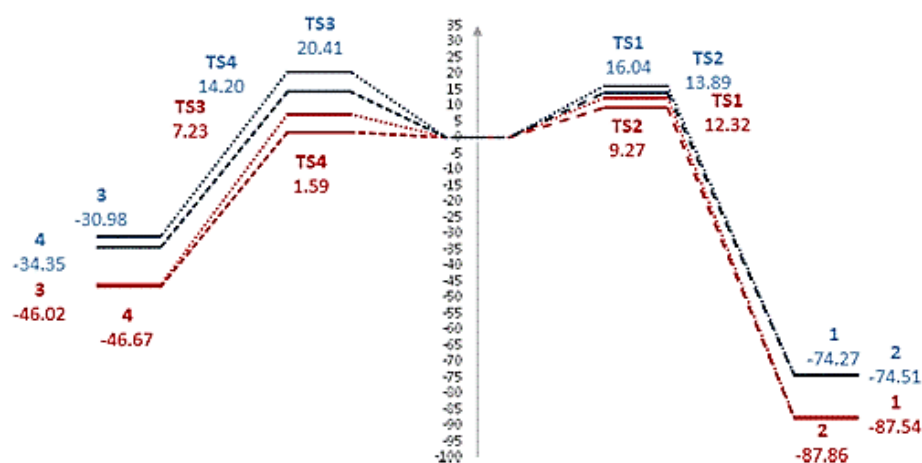*Fig. 3. Enthalpy (ΔH in red) and Gibbs free energy (ΔG in blue) profiles, in kcal/mol, for the β-himachalene with :CH_2 and :CBr_2 reaction paths.*

Thermodynamic analysis indicates that the relative energies, enthalpies, and Gibbs free energy are very negative for all products of these CA reactions. This indicates that these molecules are more stable.

The geometries of the TSs associated with β-himachalene with :CH_2 and :CBr_2 cycloaddition reactions are shown in Fig. 4. The lengths of the two forming bonds at the TSs associated with the reaction paths are between 2.10Å and 2.53Å, indicating that they are associated with slightly asynchronous.

The polar character of these competitive CA reactions was evaluated by analyzing the GEDT at the four TSs located.

The GEDT values computed at the TSs of these CA are higher than 0.2e corresponding to polar processes, CA-1: 0.204e at TS1 and 0.202 TS2, and TSs of CA-2: 0.336e at TS3 and 0.315e at TS4, respectively, in clear agreement with the analysis of the conceptual DFT reactivity indices of the reagents.

CONCLUSIONS

Global reactivity indices analysis using DFT calculations shows that the strong nucleophile character of β-himachalene and the strong electrophile of :CH_2 and :CBr_2, and its participation in polar cycloaddition reactions

TS1
GEDT = 0.204e

TS3
GEDT = 0.336e

TS2
GEDT = 0.202e

TS4
GEDT = 0.315e

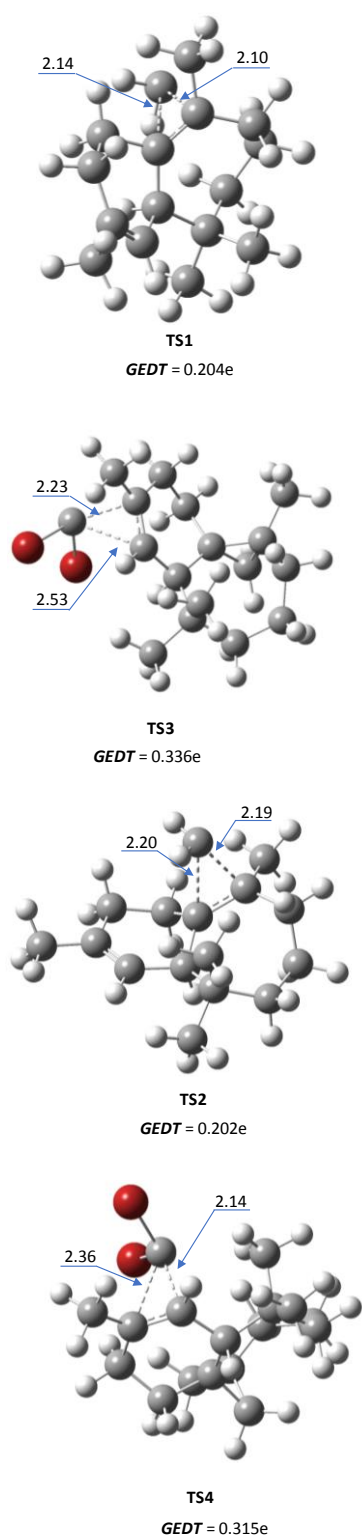***Fig. 4: Geometries and lengths of the forming bonds, in Angstrom, and GEDT values of the TSs involved in the polar cycloaddition of β-himachalene with $:CH_2$ and $:CBr_2$.***

measured by the GEDT. The analysis of the local nucleophilicity indicates that the β-himachalene in the presence of $:CH_2$, in diethyl ether, and $:CBr_2$, in DCM, is completely chemo and stereoselective, in agreement with the experimental results.

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