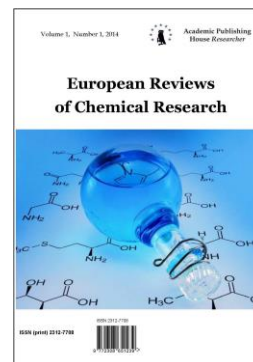


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Published in the Slovak Republic  
European Reviews of Chemical Research  
Has been issued since 2014.  
E-ISSN: 2413-7243  
2018, 5(1): 22-29

DOI: 10.13187/erchr.2018.1.22  
[www.ejournal14.com](http://www.ejournal14.com)



## A Regioselective and Stereoselective Synthesis of 2,5-Dichloro-2,5,9,9-tetramethyl-decahydro-benzocycloheptene via Stepwise addition Reactions between $\alpha$ -himachalene and HCl: Experimental and Theoretical Study

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### Abstract

2,5-Dichloro-2,5,9,9-tetramethyl-decahydro-benzocycloheptene has been prepared using addition reaction of  $\alpha$ -himachalene and HCl. In addition, this reaction have been theoretically studied using DFT methods at the B3LYP/6-31G(d) level of theory. The comparatively low activation energies and Parr functions of the nucleophilic  $\alpha$ -himachalene and 3,7-dichlorohimachalane, as well as electrophilic Parr functions of the electrophilic HCl, expounding the regio- and stereospecific experimentally observed.

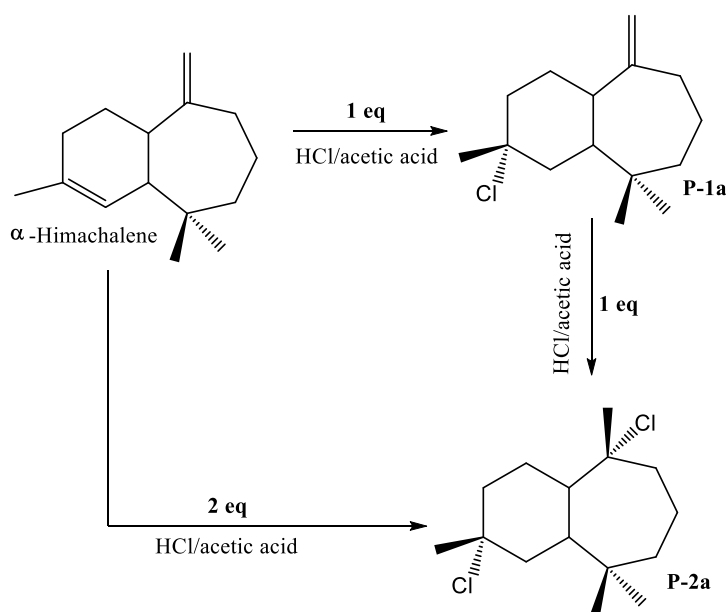
**Keywords:** Addition reaction,  $\alpha$ -himachalene, DFT, Regioselective, Stereoselective.

### 1. Introduction

Essential oils have many biological activities. In herbal medicine, they are used for their antiseptic properties against infectious diseases of bacterial origin, for example against endocanalar bacteria or at the level of the vaginal microflora (Arnal-Schnebelen et al., 2004) and of fungal origin against dermatophytes (Kurkin, 2003). However, they also have cytotoxic properties (Sivropoulou et al., 1996) which bring them closer to antiseptics and disinfectants as broad spectrum antimicrobial agents. In the phytosanitary and agro-food fields, essential oils or their active compounds could also be used as protection agents against phytopathogenic fungi (Zambonelli et al., 2004) and microorganisms invading foodstuffs (Mangena et al., 1999).

To improve the chemical and biological properties, we have studied the action of gaseous hydrochloric acid on the sesquiterpene  $\alpha$ -himachalene isomer gives regioselectively and stereoselectively a dichloride named 3,7-dichlorohimachalane **P-2a** in the crystallized solid form (Figure 1).

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**Fig. 1.** Continuation synthesis procedure of 3,7-dichlorohimachalane

Experimental techniques and theoretical methods have been complementing each other yielding an accelerated progress in the understanding of materials at atomistic dimensions. We will concentrate in this work; our aim is to explicate the mechanism, regioselectivity and stereoselectivity experimentally obtained.

## 2. Experimental

### General procedure for the preparation of products

$\alpha$ -himachalène, (1 g, 4.9 mmol), dissolved in 10 ml of acetic acid, was treated with a stream of hydrochloric acid gas until a solid product appeared. The mixture was allowed to stand at 273 K for 12 h and then at room temperature for 2 h. After filtering under reduced pressure, the compound (3,7-dichlorohimachalane) was obtained in a yield of 85%. After evaporation of hexane, the appropriate crystals are obtained.

### (1S,3R,6S,7R)-3,7-Dichloro-trans-himachalane

(C<sub>15</sub>H<sub>26</sub>Cl<sub>2</sub>)P<sub>f</sub> = 118-120 °C (Solide blanc) (hexane), 80%RMN <sup>1</sup>H (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 0.87, 1.04 (H14, H15, s, s); 1.58, 1.6 (H12, H13, s,s) RMN <sup>13</sup>C(75 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 20.60 33.19 (C14, C15); 34.44, 35.76 (C12, C13); 71.15 (C3); 75.98 (C7); 46.26 (C6); 51.55 (C1); 36.34(C11).

## 3. Computational methods

The geometric parameters for the reactants, TSs, and products of the reactions studied were fully optimized using the density functional theory (DFT) method (Nacereddine et al, 2015). The calculations were performed at B3LYP (Becke, 1993) level with the 6-31G (d) basis set (Rassolov et al., 2009). All calculations reported in this paper were performed on the Gaussian 09 (Frisch et al., 2009), using Berny's algorithm (Schlegel, 1982). Atomic electronic populations and reactivity indices were calculated using natural population (NPA). The global electrophilicity index (Parr et al., 1999)  $\omega$ , was given by the following expression  $\omega = \frac{\mu^2}{2\eta}$ , in terms of the electronic chemical potential  $\mu$  and the chemical hardness  $\eta$ . Both quantities could be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO,  $\epsilon_H$  and  $\epsilon_L$  as  $\mu = \frac{\epsilon_H + \epsilon_L}{2}$  and  $\eta = \epsilon_H - \epsilon_L$ , respectively. The empirical nucleophilicity index N (Domingo et al., 2009) based on the HOMO energies obtained within the Kohn-Sham (Kohn et al., 1965), and defined as  $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$ . the nucleophilicity was referred to tetracyanoethylene (TCE). Electrophilic  $P_k^+$  and nucleophilic  $P_k^-$  Par functions were obtained through analysis of the Mulliken atomic spin density (ASD) of the radical anion and radical cation of the reagents. (El Haib

et al., 2018; Zeroual et al., 2017; Zoubir et al., 2017; El Idrissi et al., 2017; Ourhriss et al., 2017; El Idrissi et al., 2017; Zeroual et al., 2015; Barhoumi et al., 2015; Ryachi et al., 2015).

Geometry optimization calculations were carried out to obtain the global minima for the reactants and products, and to locate the saddle point for the TS. Stationary points were characterized by frequency calculations. All reactants and products had positive Hessian matrices. All TSs had only one negative eigen value in their diagonalized Hessian matrices, and their associated eigenvectors were confirmed to correspond to motion along the reaction coordinate under consideration. TSs were located using the (QST2) algorithm. Intrinsic reaction coordinate (IRC) calculations were carried out for all events to verify that the localized TSs connected with the corresponding minimum stationary points associated with reactants and products (Fukui, 1970).

#### 4. Discussion

This section was divided into three parts: (1) an analysis of the reactivity indices of the reagents. (2) Next, an analysis of the reactivity local indices of the reagents. (3) Finally kinetic study.

##### 4.1. Comparative analysis of the conceptual DFT indices of the reagents

The global indices, namely, the electronic chemical potential,  $\mu$ , chemical hardness,  $\eta$ , electrophilicity,  $w$ , and nucleophilicity,  $N$ , of the reagents involved in these addition reactions are given in Table 1.

**Table 1** DFT/B3LYP/6-31(d) chemical hardness, electronic chemical potential, electrophilicity and nucleophilicity in eV, of the  $\alpha$ -himachalene, 3,7-dichlorohimachalene and HCl acid

Molecule	$\eta$	$\mu$	$w$	$N$
$\alpha$ -himachalene	6.64	-2.74	0.56	3.45
6-chloro- $\alpha$ -himachalene	6.99	-3.07	0.67	2.95
HCl	9.39	-4.32	0.99	0.50

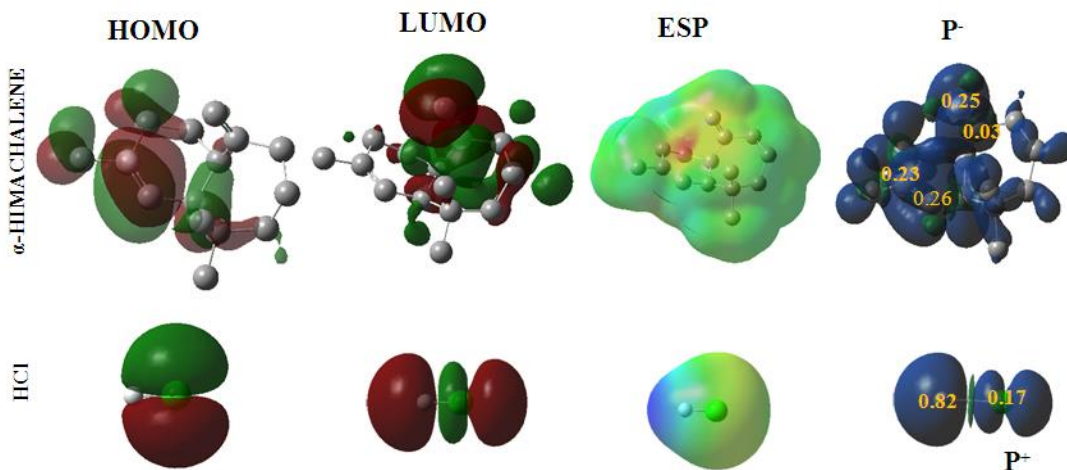
The electronic chemical potential of  $\alpha$ -himachalene and 3,7-dichlorohimachalene, -2.74 and -3.07 eV respectively are slightly higher than that of HCl -4.32 eV. Thus, the  $\alpha$ -himachalene and 3,7-dichlorohimachalene will have a tendency to exchange electron density with the HCl along these addition reactions, suggesting non-polar reactions.

$\alpha$ -himachalene and 3,7-dichlorohimachalene, presents an electrophilicity  $w$  index of 0.56, 0.67 eV and a nucleophilicity  $N$  index of 3.45, 2.95 eV respectively, being classified as a moderate electrophile and as a strong nucleophile according to the electrophilicity<sup>54</sup> and nucleophilicity<sup>55</sup> scales. Note that HCl presents an electrophilicity  $w$  index of 0.99 eV and a nucleophilicity  $N$  index of 0.50 eV, HCl will participating in these reactions as electrophilic derivative.

##### 4.1. An analysis of the reactivity local indices of the reagents

By approaching a non-symmetric electrophilic/nucleophilic pair along a polar or ionic process, the most favourable reactive channel is that associated with the initial two-center interaction between the most electrophilic center of the electrophile and the most nucleophilic center of the nucleophile. Recently, Domingo proposed the nucleophilic  $P_k^-$  and electrophilic  $P_k^+$  Parr functions, derived from the changes of spin electron-density.

Accordingly, the HOMO, LUMO, Electrostatic potential maps, nucleophilic  $P_k^-$  and electrophilic  $P_k^+$  Parr functions centers of the reagents involved in this addition reaction (see Fig. 2).

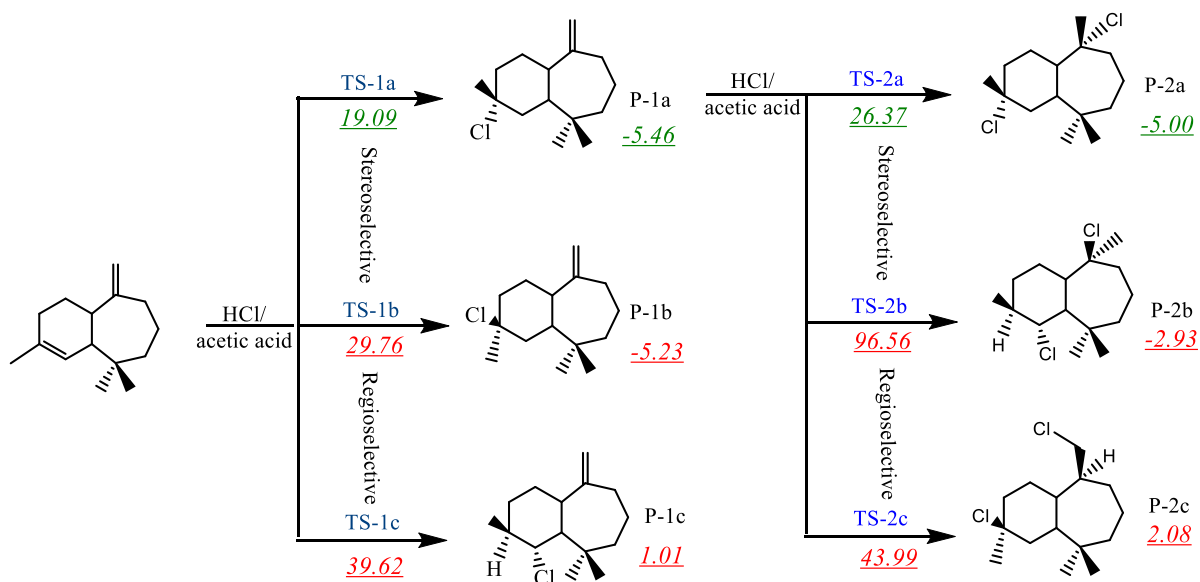


**Fig. 1.** the HOMO, LUMO, Electrostatic potential maps, nucleophilic  $P_k^-$  and electrophilic  $P_k^+$  Parr functions

Therefore, it is predictable that the most favourable electrophile–nucleophile interaction along the nucleophilic attack of  $\alpha$ -himachalene on HCl acid in a polar process will take place between the most nucleophilic center of  $\alpha$ -himachalene, the C2 carbon atom, and the most electrophilic center of HCl, the H hydrogen atom. We also note that the HOMO orbital of  $\alpha$ -himachalene is totally localized on the C2 = C3 double bond, which shows that the attack of one mole of chloridhyric acid is regioselectively on this double bond. This prediction is in complete agreement with the experimental observations.

#### 4.3. Study of the reaction paths associated with the addition reaction of $\alpha$ -himachalene with HCl

Due to the non-symmetry of the two reagents, the addition reaction of  $\alpha$ -himachalene and 3,7-dichlorohimachalane with HCl can take place along four isomeric channels: one pair of stereoisomeric channels and one pair of regioisomeric ones (figure 3). In this part we want to study the stereoselectivity observed experimentally.

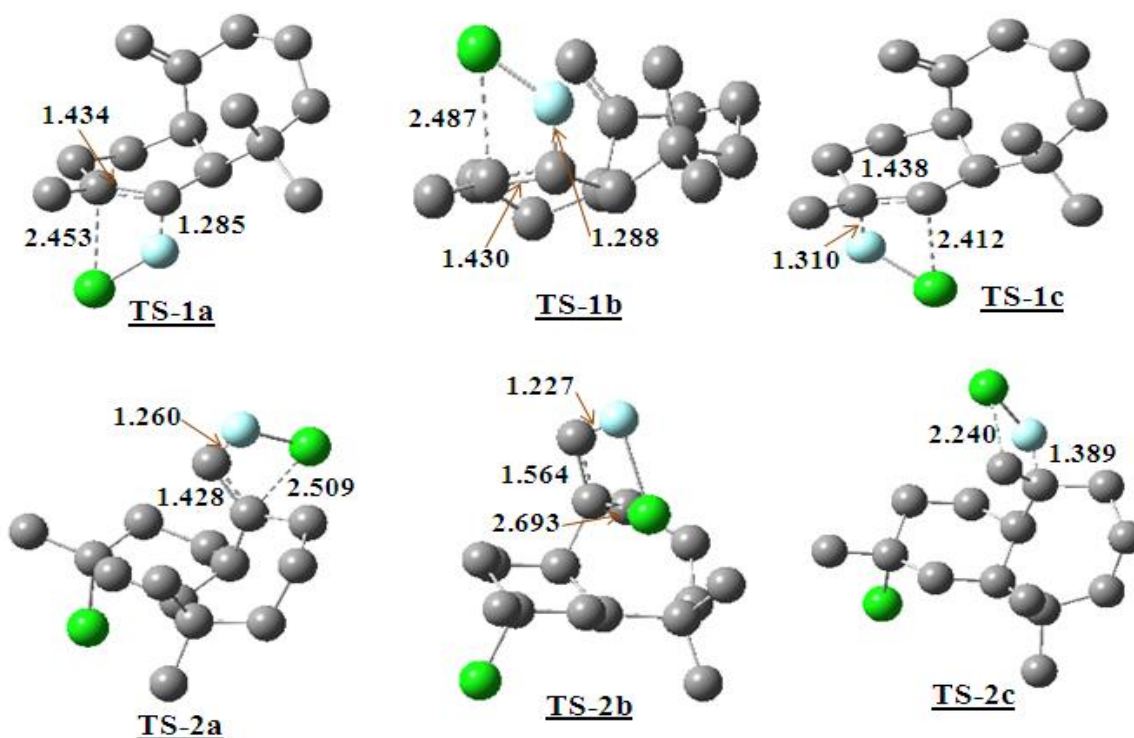


**Fig. 3.** The competitive reactive channels associated with the addition reaction of  $\alpha$ -himachalene and 3,7-dichlorohimachalane with HCl. B3LYP/6-31G(d) relative energies, are given in kcal mol<sup>-1</sup>.

The activation energies associated with the competitive channels are 19.09 (TS1a), 29.76 (TS1b), 39.62 (TS1c), 26.37 (TS2a), 96.56 (TS2b) and 43.99 (TS2c) kcal mol<sup>-1</sup>. Some appealing conclusions can be drawn from these relative energies: (i) the activation energy associated with the addition reaction of  $\alpha$ -himachalene with HCl via TS1a is 19.09 kcal mol<sup>-1</sup> lower in energy than TS1b (29.76) and TS1c (39.62), (ii) the activation energy associated with the addition reaction of 3,7-dichlorohimachalene with HCl via TS2a is 26.37 kcal mol<sup>-1</sup> lower in energy than TS2b (96.56) and TS2c (43.99) indicating that the formation of the product P1a and P1a are kinetically very favored.

(ii) These addition reactions are exergonic by 5.23 and 2.93 kcal mol<sup>-1</sup> (P1b and P2b). Note that the most favourable reactive channel associated with the addition reaction involving the P1a and P2a are exergonic by only 5.46 and 5.00 kcal mol<sup>-1</sup>, the formation of the product P1c and P2c is endothermic by 1.01 and 2.08 kcal mol<sup>-1</sup>, consequently, the products P1a and P2a do not only kinetically favored but also the thermodynamically in good agreement with experimental observations.

Optimized TSs involved in the addition reactions between of  $\alpha$ -himachalene and 3,7-dichlorohimachalene with HCl, including some selected distances, are given in Figure 4.

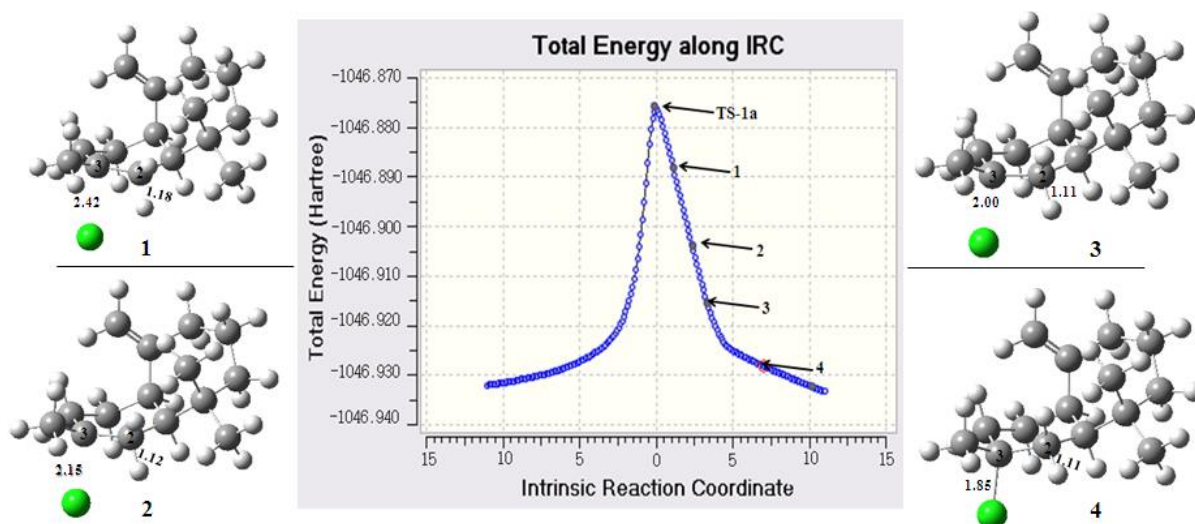


**Fig. 4.** B3LYP/6-31G(d) optimized geometries of the TSs involved in the addition reactions between  $\alpha$ -himachalene and 3,7-dichlorohimachalene with HCl. Distances are given in Angstroms.

At the TSs associated with the addition reaction between  $\alpha$ -himachalene and HCl, the distances between the atoms involved in the formation of the C–Cl and C–H single bonds are: 2.453 Å (C3–Cl) and 1.285 Å (H–C2) at TS1a, 1.288 Å (H–C2) and 2.487 Å (C3–Cl) at TS1b and 1.310 Å (H–C3) and 2.412 Å (C2–Cl) at TS1c.

At the TSs associated with the addition reaction between 3,7-dichlorohimachalene and HCl, the distances between the atoms involved in the formation of the C–Cl and C–H single bonds are: 2.509 Å (C7–Cl) and 1.260 Å (H–C13) at TS2a, 1.227 Å (H–C2) and 2.693 Å (C7–Cl) at TS2b and 1.389 Å (H–C73) and 2.240 Å (C13–Cl) at TS2c. Consequently, the products P1a and P2a are favored.

To better understand the reaction mechanism of this addition reaction, we chose some points on IRC for the analyst's figure 5.



**Fig. 5.** The IRC profile of the favorable TS-1a together with the position of the selected points of the addition reaction between  $\alpha$ -himachalene and HCl

At P1, which is the first point after TS-1a, where the inter-atomic distances between C2-H and C3-Cl are 1.18 Å and 2.42 Å respectively, in this product, the double bond is not disappeared and the simple bonds not formed yet, in the product P2 the lengths of bonds C2-H and C3-Cl are 1.12 Å and 2.15 Å, and firstly the single bond C2-H was formed. In the product P3 the chlorine atom approaches the C3 carbon atom and the bond between the two atoms is not formed, in product P4 the C3-Cl bond is formed on the  $\alpha$ -side, therefore the molecular mechanism of HCl addition on  $\alpha$ -himachalene is non-concerted.

## 5. Conclusion

2,5-Dichloro-2,5,9,9-tetramethyl-decahydro-benzocycloheptene has been synthesized using addition Reactions between  $\alpha$ -himachalene and HCl, our experimental results shows that this reaction is regio- and stereospecific. To understand the mechanism and regio- and stereospecificity, this reaction have been theoretically studied using DFT methods at the B3LYP/6-31G(d) level of theory. The reactive channels corresponded to the regioselective and stereoselective approach modes have been explored and characterized. We can summarize the results of the present study in the following points:

The relatively low activation energies found for both addition reaction are explain by the high nucleophilic nature of both  $\alpha$ -himachalene and 3,7-dichlorohimachalane, and the moderate electrophilic nature of HCl, giving a good explanation of the experimental conditions of these addition reaction.

Analysis of the computed nucleophilic Parr functions of the nucleophilic ethylenes  $\alpha$ -himachalene and 3,7-dichlorohimachalane, as well as electrophilic Parr functions of the electrophilic HCl justifying the regioselectivity and stereoselectivity obtained experimentally.

## References

- Arnal-Schnebelen et al., 2004 – Arnal-Schnebelen B. Hadji-Minaglou F., Peroteau J-F., Ribeyre F., Billerbeck V.G. (2004). Essential oils in infectious gynaecological disease: a statistical study of 658 cases, *International Journal of Aromatherapy*, 14: 192-197.
- Becke, 1993 – Becke A.D. (1993). A new mixing of Hartree-Fock and local density-functional theories, *J. Chem. Phys.*, 98; 1372-137.
- Domingo et al., 2008 – Domingo L. R., Chamorro E., Pérez P. (2008). Understanding the Reactivity of Captodative Ethylenes in Polar Cycloaddition Reactions. A Theoretical Study, *J. Org. Chem.* 73, 4615-4624.
- El Haib et al., 2018 – El Haib A., Elajlaoui R., El Idrissi M., Moumou M., Abouricha S., Zeroual A., Benharref A., El Hajbi A. (2018) “The mechanism, the chemoselectivity and the

regioselectivity of the 1-Benzyl-4-ethynyl-1H-[1,2,3]triazole and 1-Azidomethyl-4-tert-butylbenzene in [3+2] cycloaddition reactions: a DFT study", *Mor. J. Chem.* 6, (1), 14-21.

[El Idrissi et al., 2016](#) – El Idrissi, M., El Haib, A., Zoubir, M., Hammal, R., Zeroual, A., El Hajbi, A. (2016). Understanding the regioselectivity of the Baeyer-Villiger reaction of bicyclo[4.2.0]octan-7-one and bicyclo[3.2.0]heptan-6-one: A DFT Study, *Journal of Computational Methods in Molecular Design*, 6: 75-79.

[El Idrissi et al., 2017](#) – El idrissi M., El Ajlaoui R., Zoubir M., Abouricha S., Moumou M., Ourhriss N., Zeroual A., Benharref A., El Hajbi A. 2017. Theoretical study of the chemo- and regioselectivity toward [3+2] cycloaddition reaction between mesitronitrile oxides and 2-fluorene-9-ylidene-malononitrile, *Journal of Materials and Environmental Sciences*, 8 (10), 3564-3569.

[Fukui, 1970](#) – Fukui K. (1970). Formulation of the reaction coordinate, *J. Phys. Chem.* 74, 4161–4163.

[Kurkin, 2003](#) – Kurkin V.A. (2003) phenylpropanoids from medicinal plants: distribution, classification, structural analysis, and biological activity, *Chemistry of Natural Compounds*, 39: 123–153.

[Mangena et al., 1999](#) – Mangena T., Muyima N.Y.O. (1999). Comparative evaluation of the antimicrobial activities of essential oils of *Artemisia afra*, *Pteronia incana* and *Rosmarinus officinalis* on selected bacteria and yeast strains, *Lett. Appl. Microbiol.* 28: 291-296.

[Nacereddine et al., 2015](#) – Nacereddine A.K., Sobhi C., Djerourou A., Ríos-Gutiérrez M., Domingo L. R. (2015) Non-classical CH O hydrogen-bond determining the regio- and stereoselectivity in the [3 + 2] cycloaddition reaction of (Z)-C-phenyl-N-methylnitrone with dimethyl 2-benzylidenecyclopropane-1,1-dicarboxylate. A topological electron-density study, *RSC Adv.* 5; 99299–99311.

[Ourhriss et al., 2017](#) – Ourhriss, N., Zeroual, A., Ait Elhad, M., Mazoir, N., Abourriche, A., Gadhi, C. A., Benharref, A., El Hajbi, A. (2017). Synthesis of 1-isopropyl-4,7-dimethyl-3-nitronaphthalene: An experimental and theoretical study of regiospecific nitration, *Journal of Materials and Environmental Sciences*, 8 (4): 1385-1390.

[Parr et al 2009](#) – Parr, R. G., Szentpaly, L. V., Liu, S. (1999). Electrophilicity Index, *J Am ChemSoc*, 121: 1922-1924.

[Rassolov et al 2001](#) – Rassolov V. A., Ratner M. A., Pople J. A., Redfern P. C., and Curtiss L. A. (2001). 6-31G\* Basis Set for Third-Row Atoms, *J. Comp. Chem.*, 22: 976-84.

[Schlegel, 1982](#) – Schlegel H.B. (1982). Optimization of Equilibrium Geometries and Transition. Structures, *J. Comput. Chem.*, 2, 214-218.

[Sivropoulou et al., 1996](#)– Sivropoulou A., Papanikolaou E., Nikolaou C., Kokkini S., Lanaras T., Arsenakis M. (1996) Antimicrobial and Cytotoxic Activities of Origanum Essential Oils, *J. Agric. Food Chem.* 44: 1202-1205.

[Zambonelli et al., 2004](#)– Zambonelli A., D'Aurelio A.Z., Severi A., Benvenuti E., Maggi L., Bianchi A., (2004). Chemical Composition and Fungicidal Activity of Commercial Essential Oils of *Thymus vulgaris* L., *J. Essent. Oil Res.*, 16: 69-47.

[Zeroual et al., 2015](#) – Zeroual, A., Benharref, A., El Hajbi, A. (2015). 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), *J Mol Model*, 21: 1610-2940.

[Zeroual et al., 2015](#)– Zeroual, A., El Haib, A., Benharref, A., El Hajbi A. (2015). A combined experimental and theoretical study of highly chemoselectivity acetylation of diterpene, *Journal of Computational Methods in Molecular Design*, 5: 58-62.

[Zeroual et al., 2015](#) – Zeroual, A., Zoubir, M., Hammal, R., Benharref, A., El Hajbi, A. (2015). Understanding the regioselectivity and reactivity of Friedel–Crafts benzylation using Parr functions, *Mor. J. Chem*, 3: 356-360.

[Zeroual et al., 2017](#) – Zeroual A., El Idrissi M., El Ajlaoui R., Ourhriss N., Abouricha S., Mazoir N., Benharref A., El Hajbi A. (2017). MEDT Study of the Mechanism and Regioselectivity of Diazocompounds and Alkenes in [3+2] Cycloaddition Reaction, *European Journal of Molecular Biotechnology*, 5(1), 43-49.

[Zeroual et al., 2017](#) – Zeroual A., El Idrissi M., Zoubir M., El Ajlaoui R., Abouricha S., El Hajbi A. (2017). Theoretical Study of the Mechanism and Regioselectivity of Prop-2-Yn-1-Ol with

Azide in [3+2] Cycloaddition Reactions, *Open Access Journal of Translational Medicine & Research*, 1(1), 1-5.

Zeroual et al., 2017 – Zeroual A., Zoubir M., El Idrissi M., El ajlaoui R., El Haib A., Abouricha S., Mazoir N., El Hajbi A. (2017). Theoretical Analysis of Reactivity and Regioselectivity in [1+2] Cycloaddition Reaction of Some Monoterpenes with Dichlorocarbene, *Global Journal of Science Frontier Research: B Chemistry*, 17 (1) Version 1.0.

Zhang et al., 2015 – Zhang B., White J. M., David J. (2015). Regioselective synthesis of fullerene multiadducts via tether-directed 1,3-dipolar cycloaddition, *Org. Biomol. Chem.* 13, 10505-10510.

Zoubir et al., 2016 – Zoubir M., Zeroual A., Benharref A., El Hajbi A. (2016). Understanding the Holleman Rule in the Electrophilic Substitution Reaction Using Parr Functions, *Journal of Computational Methods in Molecular Design*, 6 (4), 1-4.

Zoubir et al., 2017 – Zoubir M., Zeroual A., El Idrissi M., Bkiri F., Benharref A., Mazoir N., El Hajbi A. (2017). Experimental and theoretical analysis of the reactivity and regioselectivity in esterification reactions of diterpenes (totaradiol, totaratriol, hinikione and totarolone), *Mediterranean Journal of Chemistry*, 6(4), 98-107.

Zoubir et al., 2017 – Zoubir M., Zeroual A., El Idrissi M., El Haib A., Moumou M., Hammal R., Mazoir N., Benharref A., El Hajbi A. (2017). Understanding the Chemoselectivity and Stereoselectivity in Michael Addition Reactions of  $\beta$ -Hydroxypartenolides and Amines such as Pyrrolidine, Morpholine, Piperidine and 1-Methylpiperazine: a DFT Study, *Journal of Materials and Environmental Sciences*, 8 (3), 990-996.

Zoubir et al., 2017 – Zoubir M., El Idrissi M., El Ajlaoui R., El Haib A., Abouricha S., Zeroual A., Benharref A., El Hajbi A. (2017). Theoretical Investigation of the Chemo and the Regioselectivity of the Reaction Oxidation of Bicyclo[3.2.0]Hept-2-En-6-One by Hydrogen Peroxid, *European Reviews of Chemical Research*, 4(1), 28-33.