DFT Study of the Mechanism, Regio- and Stereoselectivity of the Epoxidation Reaction of the Methyl 2-((2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydro Naphthalen-2-yl)acrylate by m-CPBA

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Abstract

The mechanism and regioselectivity of the epoxidation reaction of the methyl 2-((2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)acrylate **1** by m-CPBA, have been theoretically studied at the DFT/ B3LYP/6-31(d) computational level. The possible 1/2/3 regioselective and sterioselective channels were explored and characterized, the energies analysis associated with the different reaction pathways indicates that this epoxidation reaction is highly regioselective, in good conformity with the experimental observations.

Keywords: Molecular Electron Density Theory, stereooselective, regioselective, epoxidation, DFT/ B3LYP/6-31(d).

1. Introduction

Eudesmane products are pervasive in species of plant (Fraga, 2007). Among them, eudesmane acids and esters have attracted considerable interest due to their extensive spectrum of pharmacological properties: as, isocostic acid (Figure 1), (Zaki et al., 2017) Showing significant antifungal, antibacterial properties (Shtacher, Kashman 1970). The eudesmane acid derivatives have antipyretic properties and the hydrocostic acid is toxic to Artemisia Salina and has an anti-appetizing activity against Spodopetra Littoralis (Barbetti et al., 1985).

Eudesmane scaffold

isocostic acid

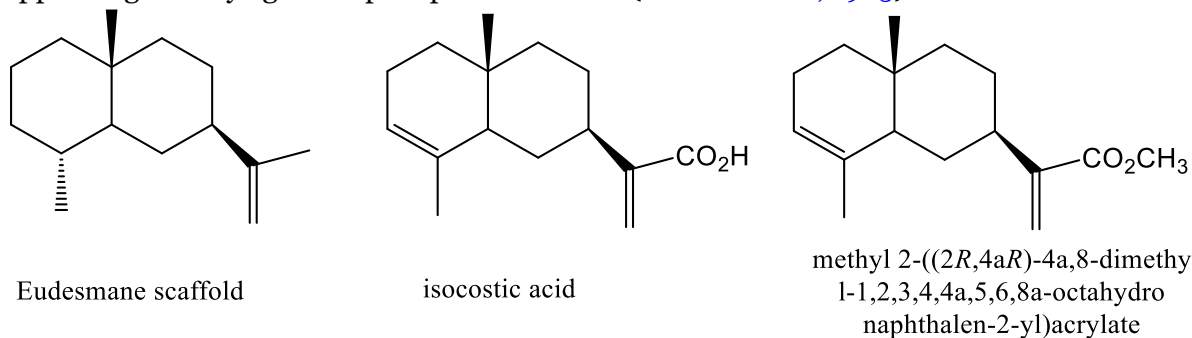methyl 2-((2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydro naphthalen-2-yl)acrylate

Fig. 1. Structures of the eudesmane, isocostic acid and isocostic-methyl ester

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Herein, in order to understand the molecular mechanism, regio- and stereoselectivite of the epoxidation reaction of the methyl 2-((2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)acrylate by m-CPBA (Figure 2), a theoretical characterization of the molecular mechanism of this epoxidation reactions is carried out within the MEDT using DFT methods at the B3LYP/6-31G(d) computational level, this new theory very recently proposed by Domingo to study the reactivity in organic chemistry named Molecular Electron Density Theory (MEDT) (Domingo et al 2016), when the partition of the total density of the TS geometry into two separated structure does not any physical sense within density functional DFT.
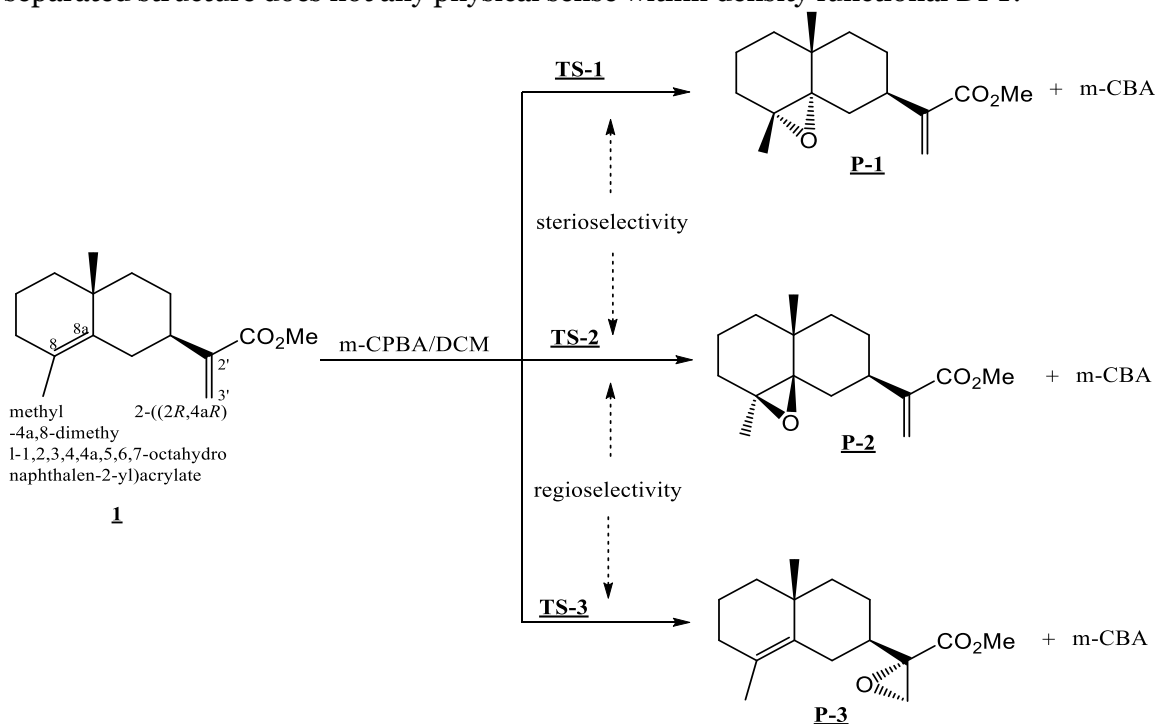

Fig. 2. Competitive regio- and stereoisomeric pathways associated with epoxidation reactions of the methyl 2-((2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)acrylate by m-CPBA

2. Computational methods

DFT computations were carried out using the B3LYP functional (Yanai et al 2004), together with the standard 6-31(d) basis set (Yanai et al 1982). The optimizations have been realized using the Berny analytical gradient optimization method. All computations have been shown with the Gaussian 09 suite of programs (Frisch et al 2009). The global electrophilicity index (Parr et al., 2009) ω, was given by the following expression $\omega = \frac{\mu^2}{2\eta}$, in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities could be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L as $\mu = \frac{\varepsilon_H + \varepsilon_L}{2}$ and $\eta = \varepsilon_H - \varepsilon_L$, respectively. The empirical nucleophilicity index N (Domingo et al 2008; Domingo, Pérez 2011), based on the HOMO energies obtained within the Kohn-Sham (Kohn, Sham 1965), and defined as $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$. the nucleophilicity was referred to tetracyanoethylene (TCE). This choise allowed us to handle conveniently a nucleophilicity scale of positive values. Electrophylic 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. The local electrophilicity and the local nucleophilicity indices were evaluated using the following expressions $\omega_k = \omega P_k^+$ and $N_k = N P_k^-$ (Ourhriss et al., 2018; El Haib et al., 2018; Ourhriss et al., 2017; El Idrissi et al., 2017; Zeroual et al., 2017; Zoubir et al., 2017; Zeroual et al., 2017; Zeroual et al., 2017; El Idrissi et al., 2017; Zoubir et al., 2016; Zeroual et al., 2016; El Idrissi et al., 2016; Zeroual et al., 2015; Barhoumi et al., 2015; Ryachi et al., 2015; Zeroual

et al., 2014; El Idrissi et al., 2013). The stationary points were characterized by frequency computations in order to verify that TSs have one and only one imaginary frequency. Intrinsic reaction coordinate (IRC) (Fukui, 1970) pathways were traced to verify the connectivity between minima and associated TSs.

3. Results and discussion

This theoretical study has been divided into three parts: (1) first, an analysis of the DFT reactivity indices of the reagents involved in these oxidation reaction; (2) then, a PES study of the reactions involved in this oxidation reactions are characterized and discussed; (3) finally, an analysis of the transition state structures are evaluated.

3.1. DFT analysis based on the global and local reactivity indexes

In order to understand the mechanism of the oxidation reaction studied, we used DFT B3LYP/6-31G (d) to calculate the global indices shown in Table 1 the electronic chemical potential μ, chemical hardness η, global electrophilicity ω and nucleophilicity N of the methyl 2-((2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)acrylate **1** and m-CPBA

Table 1. Electronic chemical potential μ, chemical hardness η, electrophilicity ω and nucleophilicity N calculated using DFT B3LYP/6-31G (d) (eV)

System	μ	η	w	N
1	-3.26	5.11	1.04	3.71
m-CPBA	-4.35	5.29	1.79	2.52

The electronic chemical potential of the ester **1**, μ = −3.26 eV, is higher than that of the m-CPBA, μ = −4.35 eV, thereby indicating that along a polar reaction the global electron density transfer (GEDT) will go from ester **1** towards the m-CPBA.

The ester **1** presents an electrophilicy ω index of 1.04 eV and a nucleophilicity N index of 3.71 eV, being classified as strong nucleophile and ω index of the m-CPBA, 1.79 eV and a nucleophilicity N index of 2.52 eV. Consequently, the m-CPBA is classified as a strong electrophile, while the ester **1** as a strong nucleophile.

Recently, the electrophilic and nucleophilic Parr functions have been proposed to analyse the local reactivity in polar processes involving reactions between a nucleophile/electrophile pair. Accordingly, the nucleophilic Parr functions, the density of the HOMO and LUMO orbitals for 1a and **1** are represented in Figure 3.
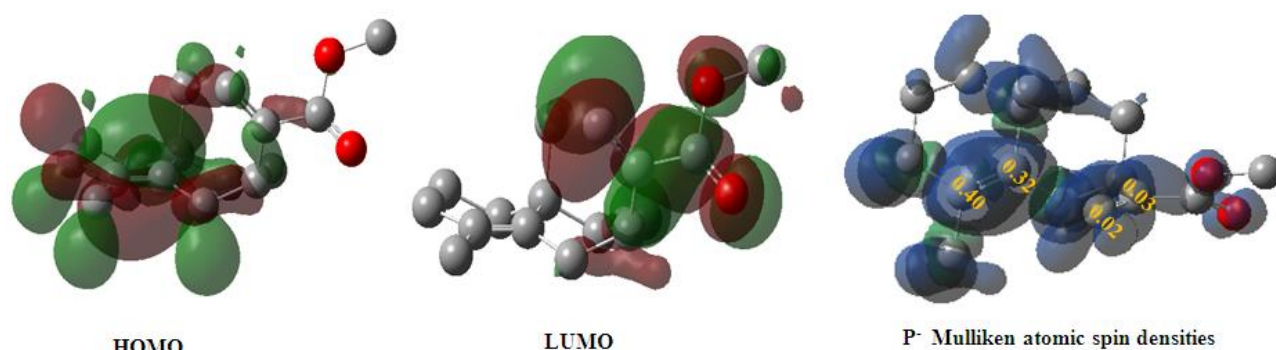

Fig. 3. Maps of the HOMO, LUMO orbital and nucleophilic Parr functions for 1

From Figure 3, we find that:

The HOMO orbital of reagent 1 is highly condensed on the C8a = C8 double bond and the LUMO orbital is condensed on the C2 '= C3' double bond, which shows that the nucleophilic power is condensed on the C8a = C8 double bond.

The Parr nucleophilic functions of the C8a (0.32) and C8 (0.40) carbons are greater than the Parr functions of the C2 '(0.03) and C3' (0.02) carbons, which shows that the attack is very favorable at the level of double bond C8a=C8, this result is in good agreement with experience.

To confirm this result we conducted an energy study.

3.2 Energies study

Due to the non-symmetry of both ester **1**, epoxidation reaction of the ester (1) py m-CPBA can take place through three competitive reactive channels namely 1, 2 and 3 and to interpret the regio- and stereoselectivity experimentally observed in this epoxidation, the energies and relative energies were calculated and summarized in Table 2, PES of the reaction was calculated by B3LYP/6-31G(d) method. Intrinsic Reaction Coordinate (IRC) calculations were performed to characterize the transition states on the PES (Figure 4).

Table 2. B3LYP/6-31G (d) energies E (in a.u.) and relative energies (ΔE, in kcal/mol) of the reagents, transition states and products.

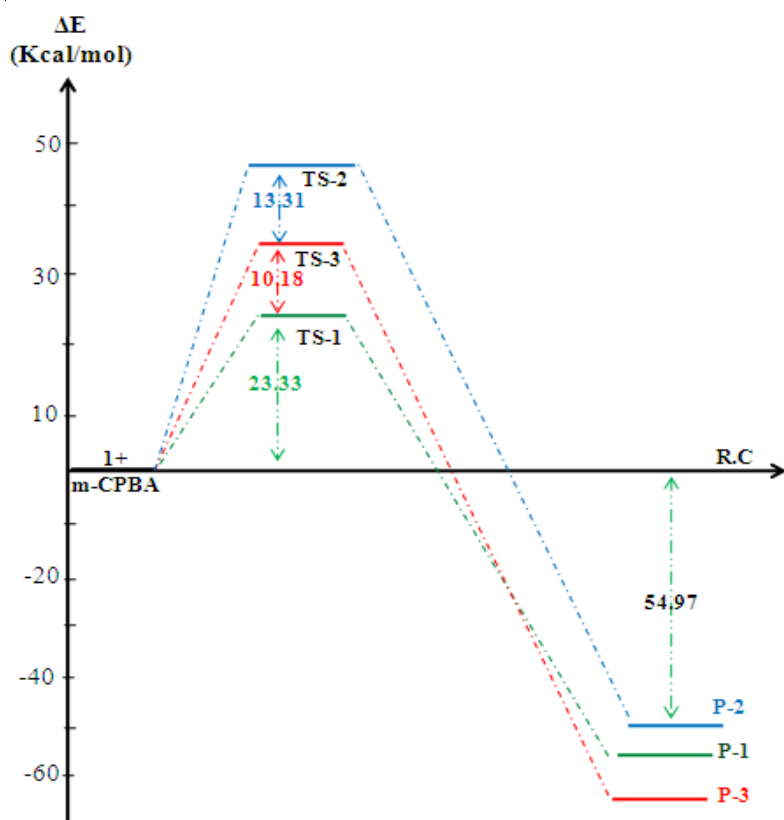| System	E	ΔE
1+m-CPBA	-1730,098803	-------
TS1	-1730,061794	23,22
P 1+m-CBA	-1730,187139	-55,43
TS 2	-1730,024362	46,71
P 2+m-CBA	-1730,196361	-61,21
TS3	-1730,045573	33,40
P 3+m-CBA	-1730,186418	-54,97

Fig. 4. Pathways for epoxidation reaction of the methyl 2-((2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)acrylate **1** and m-CPBA

We can see from Table 2 and Figure 4 that the activation energies of the products associated with the three reactive channels of the reaction between the methyl 2-((2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)acrylate 1 and m-CPBA are 23.22, 46.71 and 33.40 for TS1, TS2 and TS3 respectively, indicating that the formation of product P1 1, was kinetically preferred, the deference between TS1 and TS3 is 10.18 (eV) and TSσ1 and TS2 is 23.49 (eV) which shows that the formation of the complexes P2 and P3 is impossible.

Other hand the formation of the compounds P1, P2 and P3 are exothermic by 55.43, 61.21 and 54.97 indicating that the complex P2 is more stable than P1 and P3, which shows that the formation of the product P1 is kinetically favorable in good agreement with the experimental results.

3.3. Geometries study

The geometries of the TSs involved in the three competitive reaction channels are given in Fig. 3. At the TSs, the lengths of the C8−O and C8a−O forming bonds are 1.482 and 1.495 Å (TS-1) and , the lengths of the C8−O and C8a−O forming bonds are 2.589 and 2.714 Å (TS-2), and the lengths of the C3'−O and C2'−O forming bonds are 2.006 and 2.418 Å (TS-3). Some appealing conclusions can be drawn from these geometrical parameters: (1) the TSs associated with the 1 channels are more asynchronous than those associated with the other one.
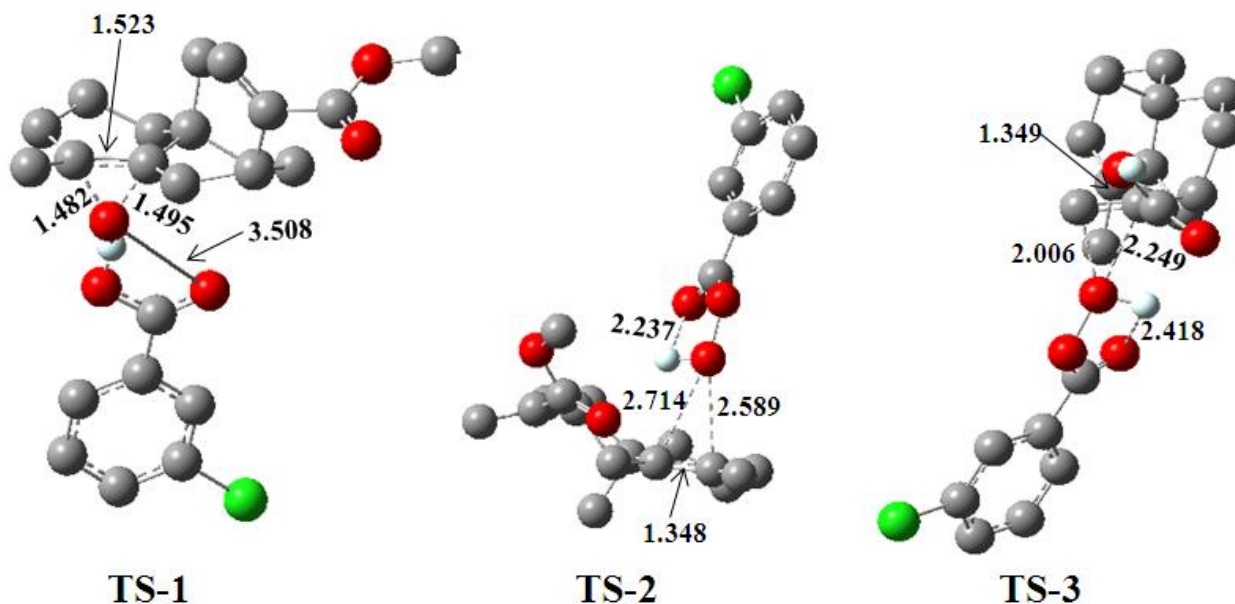

Fig. 3. DFT/6-31G(d) optimized density map and structures of the TSs of the epoxidation reaction of the methyl 2-((2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)acrylate 1 and m-CPBA. Lengths are given in Angstroms.

4. Conclusion

The regioselectivity and the nature of the molecular mechanism of the epoxidation reaction of the methyl 2-((2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)acrylate **1** by m-CPBA have been theoretically studied using DFT methods at the B3LYP/6−31G(d) level of theory. Three reactive channels corresponded to the 1, 2 and 3 regio and stereoselective approach modes have been explored and characterized for the methyl 2-((2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)acrylate 1. We can summarize the results of the present study in the following points:

Analysis of the computed nucleophilic Parr functions of the nucleophilic 2-((2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)acrylate **1** indicates that the double bond $C_8=C^{8a}$ is the most nucleophilic centers, justifying the regioselectivity obtained experimentally

The formation of the compounds P1, P2 and P3 are exothermic by 55.43, 61.21 and 54.97 indicating that the complex P2 is more stable than P1 and P3, which shows that the formation of the product P1 is kinetically favorable in good agreement with the experimental results.

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