

Theoretical investigation of the mechanism, chemo- and stereospecificity in the epoxidation reaction of limonene with meta-chloroperoxybenzoic acid (m-CPBA)

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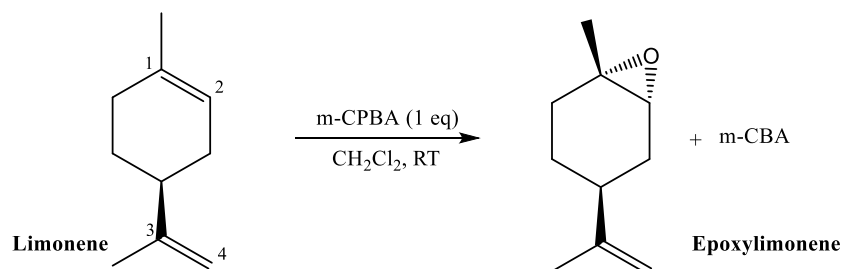
Abstract

The epoxidation of limonene **1** with m-CPBA has been examined within the MEDT at the B3LYP/6-311(d,p) computational level. The chemo- and stereoisomeric reaction paths involving the two C=C double bonds of limonene have been scrutinized. DFT computations account for the high chemospecificity involving the C₁=C₂ double bond and the stereospecificity, in complete conformity with the experimental results. An ELF analysis of the epoxidation shows the formation of the epoxide ring taking place of the two new C-O single bonds is somewhat asynchronous.

Keywords: B3LYP/6-311(d,p); Limonene; DFT; Epoxidation; meta-Chloroperoxybenzoic Acid.

1. Introduction

Epoxides are versatile intermediates in organic synthesis due to their high cyclic tension. This intrinsic tension is at the origin of a particular reactivity (in particular with respect to nucleophilic substitutions) which allows different transformations for the creation of carbon-carbon or carbon-heteroatom bonds. Epoxides are even more interesting components in synthesis since the advent of asymmetric epoxidation methods by Sharpless [1], Jacobsen [2-5] or Shi [6, 7] which make it possible to obtain optically active compounds. On the other hand, a research has recently been carried out on the synthesis of 24(S),25-epoxycholesterol from cholenic acid [8]. Ourisson et al. [9] used epoxidation to facilitate the analytical study of mixtures of tetracyclic triterpenes from Moroccan cactoid euphorbia. Other researchers have studied the total synthesis of triterpene epoxides with interesting pharmacological properties, namely the synthesis of Aragusterol [10]. These exhibit a very strong in vitro inhibition of the proliferation of KB cells and a large anti-tumor activity in vitro against leukemia in mice. Numerous theories have been advanced to explicate the molecular mechanism, reactivity and selectivities (regio, chemo and stereo). In this respect, bonding evolution theory (BET) [11], the conceptual density functional theory (CDFT) [12], and the electron localization function (ELF) method [13], have presented to scrutinize the reaction mechanism [14] within a current model named a molecular electron density theory (MEDT) [15]. Our theoretical studies devoted to the epoxidation of R-carvone with peracid demonstrate the high chemoselectivity involving the exocyclic C=C double bond and the low diastereoselectivity [16]. Herein, a MEDT study in the epoxidation reaction, using equimolar quantity of m-chloroperoxybenzoic acid, toward limonene in order to comprehend the formation of epoxide compound (Scheme 1), the molecular mechanism, plus the regio- and diastereofacial selectivities [17].



Scheme 1. Epoxidation of limonene.

2. Computational methods

DFT computations were executed employing the B3LYP functional [18, 19] jointly with the 6-311G(d,p) basis set [20]. Optimizations were supported out utilizing the Berny analytical gradient optimization technique [21, 22]. The stationary points were described by frequency calculations so as to confirm that TSs have only one imaginary frequency. The intrinsic reactions coordinate [23] (IRC) paths were drawn to pattern the energy profiles joining every TS to the two related minima [24, 25]. Dissolvable impacts of dichloromethane (DCM) were considered by full improvement of the gas stage structures utilizing the polarizable continuum model (PCM) developed by Tomasi's group [26, 29]. Conceptual DFT (CDFT) global reactivity indices [30] and each calculation were carried out with the Gaussian 09 [31]. Topological analyses of the ELF were functioned with the TopMod [32] package using the monodeterminantal wave functions.

3. Results and Discussions

The present search has been apportioned in three sections: (i) first, the CDFT reactivity indices of the reagents are studied; (ii) in the second part, the competitive reaction paths associated with the epoxidation reaction of limonene by

m-CPBA are examined; and finally (iii) in the third part, topological analysis of the ELF and non-covalent interaction study of this epoxidation reactions.

3.1. Analysis of the CDFT indices of the reagents

Many reviews caring to organic reactions have shown that the analysis of the reactivity indices described within CDFT [36] is a powerful tool to understand organic chemical reactivity. Therefore, in order to predict the reactivity of the limonene (**1**) in epoxidation reaction, the global indices assembled in Table 1, i.e. the electronic chemical potential, μ , chemical hardness, η , electrophilicity, ω , and nucleophilicity, N , are studied.

Table 1. B3LYP/6-311G(d,p) electronic chemical potential μ , chemical hardness η , electrophilicity ω , nucleophilicity N , in eV, of limonene (**1**) and m-CPBA (**2**).

System	η	μ	N	ω
limonene	6.85	-2.97	2.97	0.64
m-CPBA	5.38	-4.61	2.06	1.97

The electrophilicity ω indices of the limonene (**1**) and m-CPBA (**2**) are 0.64 and 1.97 eV while the nucleophilicity N indices are 2.97 and 2.06 eV, respectively. From these values, we can classify the limonene as moderate electrophile and the strong nucleophiles, while m-CPBA as a strong electrophile and a moderate nucleophile. In this reaction the limonene will participate as nucleophile and m-CPBA as electrophile. In current times, the electrophilic P_k^+ and nucleophilic P_k^- Parr functions have been suggested to scrutinize the local reactivity relating reactions between a nucleophile/electrophile pair [33-38]. Thus, the nucleophilic P_k^- Parr functions for the limonene **1** are analyzed (Figure1).

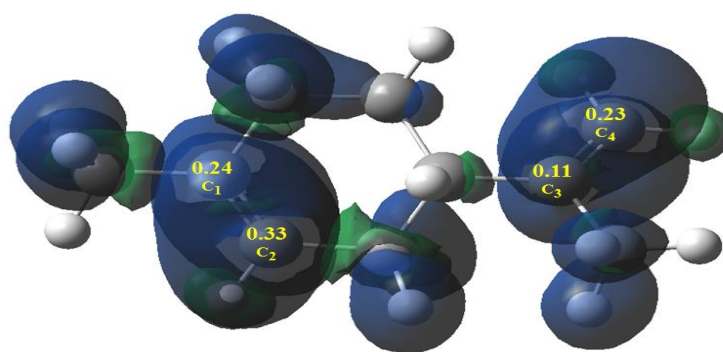
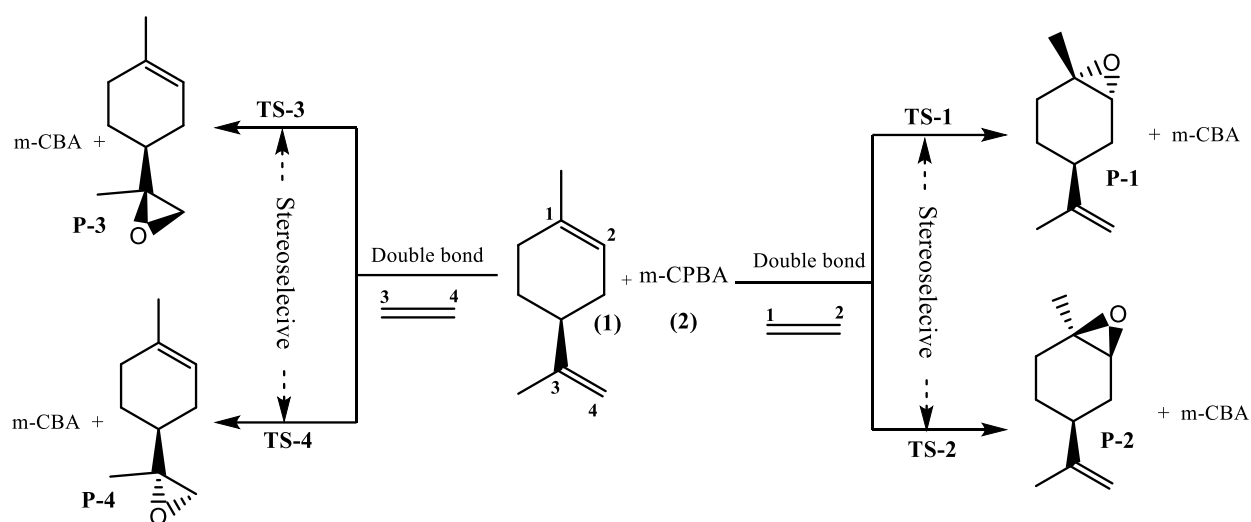


Figure 1. Three-dimensional (3D) representations of the Mulliken atomic spin densities of radical anion together with the nucleophilic P_k^- Parr functions of limonene **1**.

Exploration of the nucleophilic P_k^- Parr functions of limonene **1** shows that the double bonds $C_1=C_2$ (0.24, 0.33) are highest nucleophilic centers than other double bond $C_3=C_4$ (0.11, 0.23), indicating that the electrophilic attack will be carried out on double bond $C_1=C_2$ of compound **1**, in agreement with experience.

3.2. Energetic study in epoxidation reaction of limonene 1 with m-chloroperbenzoic acid.

Owing to asymmetric and the presence of two double $C=C$ bonds in limonene **1**, four competitive reaction paths are feasible for this epoxidation reaction (see Scheme 2). There are related to the regioselective attack of m-CPBA on the $C_1=C_2$ or $C_3=C_4$ double bonds and the diastereoselective attack through the two faces of each double bond.



Scheme 2. The four considered regio- and diastereofacial isomeric reaction paths associated to the epoxidation reaction of limonene **1** by m-CPBA.

An examination for the stationary points along the four reaction paths facilitated the characterization and localization of the reagents **1** and **2**, four TSs, TS-1, TS-2, TS-3 and TS-4, as well as the corresponding epoxides **P-1**, **P-2**, **P-3**, **P-4**, and m-CBA. Therefore, this epoxidation reaction takes place via one-step mechanism. Relative energies are given in Table 1. The energies profiles of the reaction paths associated with the epoxidation reaction of limonene **1** by m-CPBA are presented in Figure 2.

Table 2. B3LYP/6-311G(d,p) total (E, in a.u.) and relative ^a(ΔE, in kcal•mol⁻¹) energies, in gas phase and in DCM, for the species involved in the epoxidation reaction of limonene (**1**) with meta-chloroperoxybenzoic acid (**2**).

	In gas		In DCM	
System	E	ΔE	E	ΔE
Limonene (1)	-390.77985562	-----	-390.78195831	-----
m-CPBA (2)	-955.696087620	-----	-955.705503656	-----
m-CBA	-880.559895354	-----	-880.566561209	-----
1+2	-1346.47594324	-----	-1346.487461966	-----
TS-1	-1346.46785149	5.07	-1346.47444693	8.16
P-1+ m-CBA	-1346.560804369	-53.25	-1346.57165959	-52.83
TS-2	-1346.46862772	4.59	-1346.47826535	5.77
P-2+ m-CBA	-1346.562283755	-59.25	-1346.573502229	-53.99
TS-3	-1346.46169107	8.94	-1346.47143812	10.05
P-3+ m-CBA	-1346.555781532	-50.09	-1346.566287565	-49.46
TS-4	-1346.46583781	6.34	-1346.47566544	7.40
P-4+ m-CBA	-1346.559973466	-52.72	-1346.570872602	-52.34

^a relative to **1+2**

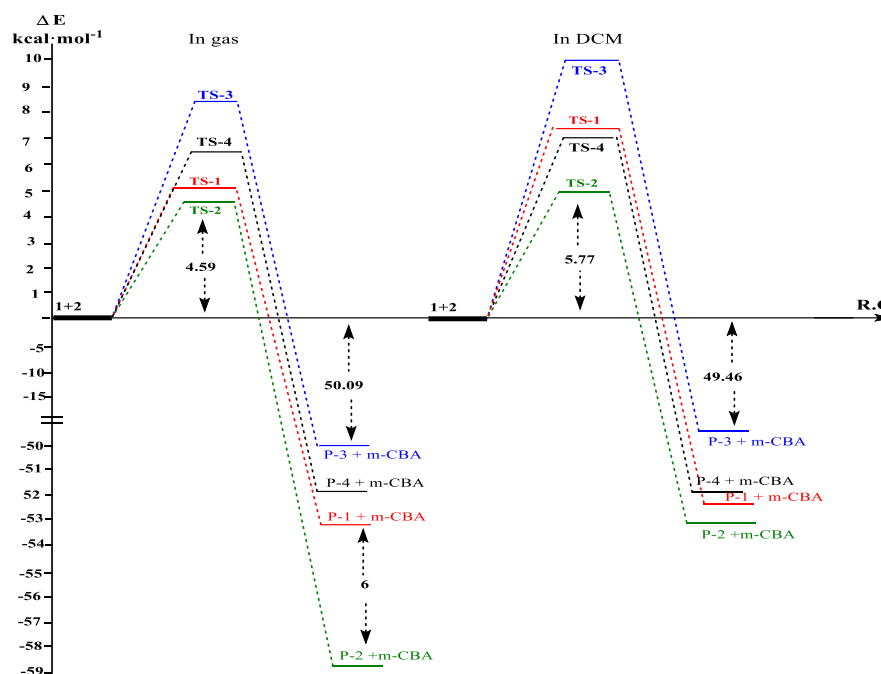


Figure 2. Energies (ΔE) profiles, for the studied reaction paths of the epoxidation reaction of limonene (**1**) with m-CPBA (**2**), in gas and in presence of DCM at 25°C.

According to the relative energy values in the gas phase summarized in Table 2 and the energy profile shown in Figure 2, the activation barriers of channels 1, 2, 3 and 4 associated with reaction 1 are TS-1 (5.07 kcal/ mol), TS-2 (4.59 kcal/ mol), TS-3 (8.94 kcal/ mol) and TS-4 (6.34 kcal/ mol), therefore kinetically, the two reaction paths 1 and 2 are possible. The formation of the two epoxides **P-1** and **P-2** are exothermic. Thermodynamically and kinetically, the epoxide **P-2** is more favored than the epoxide **P-1** by 6 kcal/ mol in coherence with the experimental results. Adding the influence of DCM on the energies of the activation barriers, we note an increase of 3.09 kcal / mol for TS-1, 1.18 kcal/ mol for TS-2, 1.11 kcal/ mol for TS-3 and 1.06 kcal/ mol for TS-4 and a decrease in the stability of epoxides of 1.42 kcal/ mol for **P-1**, 5.26 kcal/ mol for **P-2**, 0.63 kcal/ mol for **P-3** and 0.38 kcal/ mol for **P-4**. Adding the influence of DCM on the energies of the activation barriers, we note an increase of 3.09 kcal/ mol for TS-1, 1.18 kcal/ mol for TS-2, 1.11 kcal/ mol for TS-3 and 1.06 kcal/ mol for TS-4 and a decrease in the stability of epoxides of 1.42 kcal/ mol for **P-1**, 5.26 kcal/ mol for **P-2**, 0.63 kcal/ mol for **P-3** and 0.38 kcal/ mol for **P-4**. We can conclude that the addition of DCM deactivates the reaction kinetically and destabilizes the products thermodynamically without any influence on the chemo- and stereospecificity of the reaction. The gas phase geometries of the TSs involved in the competitive reaction channels are given in Figure 3. The lengths of the bonds forming O_3-C_1 and O_3-C_2 are 2.186 and 2.166 Å (TS-1); 2.159 and 2.148 Å (TS-2), while TS at double bond $C_3=C_4$, the lengths of O_3-C_3 and O_3-C_4 , the bonds forming are 2.344 and 1.993 Å (TS-3) and 2.284 and 2.026 Å (TS-4). Interesting conclusions can be drawn from these geometric parameters: (1) the TS associated with $C_1=C_2$ channels are more asynchronous than those associated with $C_3=C_4$ channels; and (2) to TS associated with $C_1=C_2$ channels, the formation of $O_3 - C_2$ bonds involving the **P-2** epoxide is more advanced than that of O_3-C_1 .

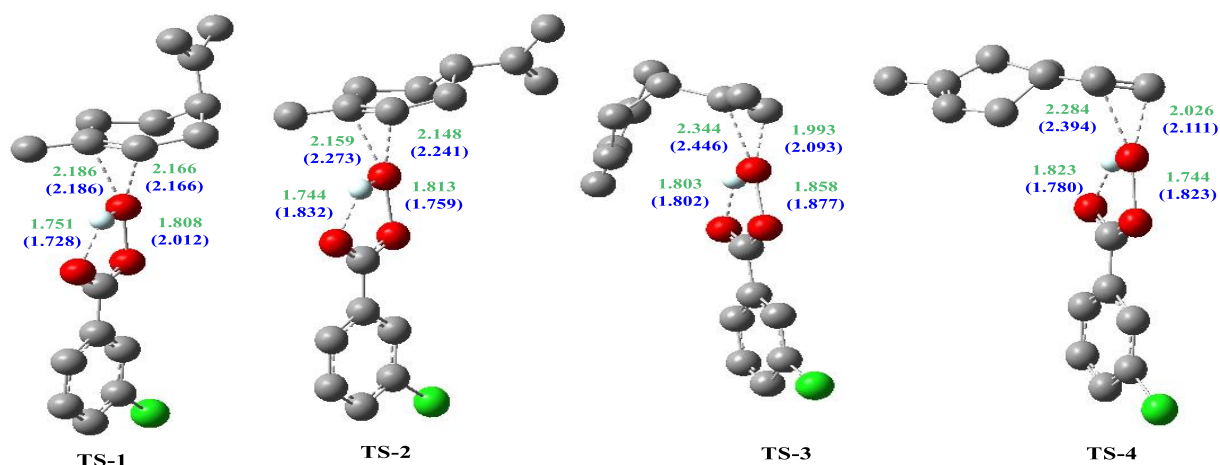


Figure 3. B3LYP/6-311G(d,p) optimized geometries of the regioisomeric TSs involved in the epoxidation reaction of limonene with m-CPBA. Values in DCM are given in parentheses. Distances are given in angstroms, Å.

3.3. ELF topological study of the C–O bond formation along the epoxidation reaction of limonene 1 with meta-Chloroperoxybenzoic acid

In order to explain the formation of C–O bonds along the epoxidation reaction of limonene **1** with m-CPBA, a topological examination of the ELF along the IRC associated with the most favorable reaction path was executed. The IRC structures directly involved in the formation of the new single C–O bonds were chosen by carrying out the topological analysis of the ELF for all the IRC structures having $2.8 > d(\text{O-C}) > 1.5$. ELF valence basin populations of TS-2 and the selected structures of the IRC involved in the formation of the new O–C single bonds are given in table 3 and ELF localization domains of the structures S1, TS-2, S6, and S8 are given in Figure 4.

Table 3. ELF valence basin populations of TS-2 and the selected structures of the IRC involved in the formation of the new O–C single bonds along the in the epoxidation reaction between limonene and m-CPBA.

	S1	S2	S3 (TS-2)	S4	S5	S6	S7	S8
V(C ₁ -C ₂)	1.99	2.02	2.02	2.77	2.27	2.12	2.07	2.00
V'(C ₁ -C ₂)	1.47	1.50	1.50	-----	-----	-----	-----	-----
V(O ₃)	2.37	2.54	2.48	2.58	2.53	1.88	2.94	2.39
V'(O ₃)	2.44	2.09	2.56	2.41	2.61	5.06	3.19	2.73
V(O ₃ -C ₁)	-----	-----	-----	-----	-----	-----	1.02	1.11
V'(O ₃ -C ₂)	-----	-----	-----	-----	-----	-----	-----	1.02
V(O ₃ -O ₄)	0.49	-----	-----	-----	-----	-----	-----	-----
V(O ₄)	2.35	2.37	2.60	2.30	2.86	2.69	2.70	2.68
V'(O ₄)	2.45	2.44	2.68	3.07	2.61	2.79	2.94	2.75
V(C ₅ -O ₄)	1.64	1.74	1.88	2.02	2.14	1.89	1.81	1.80
V(C ₅ -O ₆)	2.34	2.28	2.12	2.08	1.95	2.18	2.24	2.26
V(O ₆)	2.55	2.85	2.52	2.45	2.18	3.86	2.76	2.24
V'(O ₆)	2.79	2.53	2.94	3.09	3.47	1.81	4.42	2.20
V H-O ₆ ()	-----	-----	-----	-----	-----	-----	0.99	-----

Interesting deductions can be described from this ELF topological analysis: i) the activation energy of the reaction of limonene **1** with m-CPBA, relatively low 6.55 kcal • mol⁻¹ for TS-2, can be joined to the division of the O₃-O₄ bond of m-CPBA, it is the formation of an electron density O₃ oxygen of hydrogen peroxide; ii) the creation of the first single O-C bond takes place approximately at distance 1.95 Å, with a preliminary population of 1.22, by sharing part of the electron density without bond of the center C₂; iii) The construction of the second single bond O₃-C₂ takes place approximately at a distance 1.65 Å, with a primary population of 0.83e, donating a certain electron density of oxygen O₃ to carbon C₂; and finally taking into account the IRC values of the structures at which the creation of the two single bonds occurs, that is to say **P-2**, the construction of the bond can be considered asynchronous.

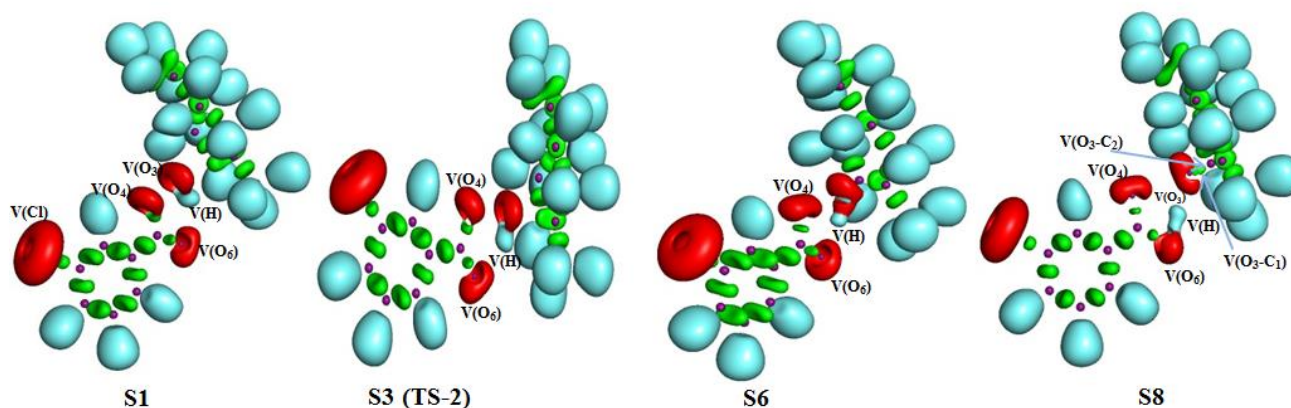


Figure 4. B3LYP/6-31G(d) ELF localisation domains of the structures S1, TS-2, S6, and S8 involved in the formation of the two oxirane ring C-O single bonds along the most favourable reaction path associated with the between limonene and m-CPBA, represented at an isosurface value of ELF = 0.75;

4. Conclusion

The stereospecificity, the chemospecificity and the mechanism of the reaction of limonene with m-CPBA leading to the corresponding epoxide were studied by means of DFT calculation methods at theoretical level B3LYP / 6-311 (d, p). Analysis of the CDFT indices accounts for the reactivity of limonene **1** was classified as a nucleophile. Furthermore, analysis of the nucleophilic P_k^- Parr functions indicated that the carbon atoms of the double bond C₁=C₂ were the most nucleophilic centers. This characteristic explains the regioselectivity and the asynchronicity found in the formation of C-O bonds to the most favourable TS associated with the epoxidation reaction that took place through an a one-step mechanism, in which the formation of the two new C-O single bonds was somewhat asynchronous. Analysis of the energy profiles associated with the epoxidation reaction demonstrated that this reaction exhibited high chemo- and diastereoselectivity

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