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Understanding of the stereoselective epoxidation on triterpene derivative using transition state theory

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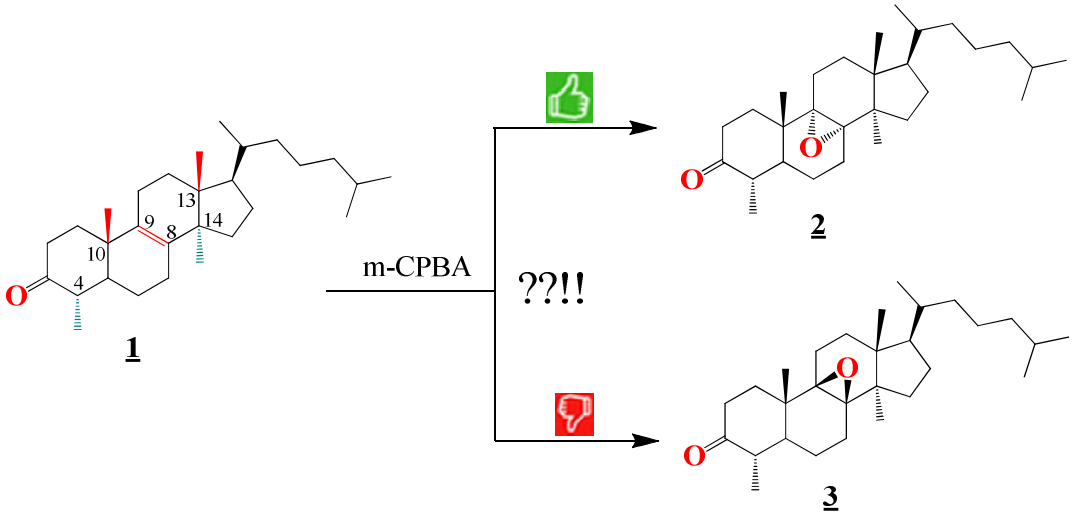
ABSTRACT

A theoretical study of the molecular mechanism and stereoselectivity of the epoxidation reaction of 4α,14α-dimethyl-5α-cholest-8-en-3-one using m-CPBA have been carried out at the B3LYP/6-31(d,p) level of theory. The calculation of activation and reaction energies indicated that the attack α side on the double bond of 4α,14α-dimethyl-5α-cholest-8-en-3-one was favored both kinetically and thermodynamically and was in agreement with the experimental data.

Keywords: triterpene, epoxidation, stereoselectivity, B3LYP/6-31(d,p), TST.

INTRODUCTION

Epoxidation reactions of alkenes are the key of chemical transformations in synthetic organic chemistry [1-3]. Epoxides are the raw materials for a wide variety of products [4,5]. Indeed, many efforts were devoted to the development of new active and selective epoxidations. The asymmetric epoxidations of prochiral alkenes provide versatile intermediates for the synthesis of functionalized optically active of organic substances. In order to prepare new oxirane triterpene derivatives, we were interested to the reactivity of the carbonyl compound, hemisynthesized from *Euphorbia officinarum* latex [6-8] using equimolecular quantity of compound 1 and meta-chloroperbenzoic acid (m-CPBA) [9] in the presence of dichloromethane. Thus, the reaction yielded, after heating at reflux during 2h, to oxirane derivatives **2** and **3** with high stereoselectivity (Schema 1). The structure of the obtained products was established by ^{1}H, ^{13}C NMR [10] and confirmed by single-crystal X-ray diffraction [11]. Then, the second aim concerns theoretical studies using DFT methods, trying to obtain some informations about the factors affecting the reactivity and the selectivity of these reactions.



Scheme 1: Epoxidation reaction of triterpene 1

MATERIALS AND METHODS

DFT computations were carried out using the B3LYP functional [12] together with the standard 6-31G(d) basis set. [13] The optimizations were carried out using the Berny analytical gradient optimization method. [14] The stationary points were characterized by frequency computations in order to verify that TSs have the one and only imaginary frequency. The IRC paths [15] were traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism using the second order González–Schlegel integration method. [16]

The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method. [17] All computations were carried out with the Gaussian 09 suite of programs. [18] The global electrophilicity index [19] ω, was given by the following expression, $\omega = (\mu^2/2\eta)$, in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities may be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, eH and eL, as $\mu = (eH - eL)/2$ and $\eta = (eL - eH)$, respectively. [20] Recently, we introduced an empirical (relative) nucleophilicity index N, [21] based on the HOMO energies obtained within the Kohn–Sham scheme, [22] and defined as $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$. The nucleophilicity is referred to tetracyanoethylene (TCE), because it presents the lowest HOMO energy in a large series of molecules already investigated in the context of polar cycloadditions.

RESULTS AND DISCUSSION

3.1. Analysis of the reactivity indices of the reactants.

The static global properties, namely electronic chemical potential μ, chemical hardness η, global electrophilicity index ω and global nucleophilicity index N of triterpenic compound **1** and m-CPBA are the chemical properties which we used to analyze the reactivity at various sites in the reactants (Table1).

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

	μ	η	N	ω
m-CPBA	-4.368	5.412	2.457	1.763
compound **1**	-3.038	4.636	4.173	0.995

We can deduce from table 1 that:

- The electronic chemical potential of starting material **1** is greater than the m-CPBA which implies that electron transfer takes place from **1** to m-CPBA.
- The nucleophilicity index of the compound **1** (4.173 eV) is greater than the m-CPBA (2.457 eV), implying that in this reaction, the product **1** behaves as a nucleophile while the m-CBPA as electrophile.

3.2. Kinetic study of the two modes of attack (Determination of the kinetic parameters).

Relative enthalpies (ΔH), entropies (ΔS), and Gibbs free energies (ΔG) for the species involved in the epoxidation reaction between triterpene **1** and m-CPBA were displayed in Table 2.

Table 2: B3LYP/6-31G(d) relative [a] enthalpies, ΔH in kcal mol^{-1}, entropies, ΔS in cal mol^{-1} K^{-1} and Gibbs free energies, ΔG in kcal mol^{-1}, for the species involved in the epoxidation between triterpene and m-CPBA

	ΔH	ΔS	ΔG
TS1	**94.1**	-27.6	**55.8**
TS2	**216.4**	-63.6	**186.3**
P1	-6.9	-98.7	-28.8
P2	-3.1	-200.8	-2.5

[a] *: relative to triterpene **1** + **m-CPBA***

The activation enthalpies associated with the reactions between triterpene **1** and m-CPBA, yielding triterpene derivatives **2** and **3**, with oxirane bridge, were 94.1 (TS1) and 2116.4 (TS2) kcal mol^{-1}, respectively. These high activation enthalpies indicate that these reactions were very unfavorable. Addition of entropies to the enthalpies raises the activation free energy of TS1 to 55.8 kcal mol^{-1}, and decreases the activation free energy of TS2 to 186.3 kcal mol^{-1}. These changes were due to the favorable activation entropy associated with these retro epoxidation (ΔS = −27.6 and -63.6 cal mol^{-1} K, respectively). In addition, the formation of the product **2** was thermodynamically favorable than **3**. These results agree with experimental reports, where only the product **2** was obtained [11].

Therefore, two TSs: TS1 and TS2, and two products **2** and **3** with oxirane bridge, associated to the C=C, have been located and characterized. The optimized geometries of the TSs were depicted in Figure 1.

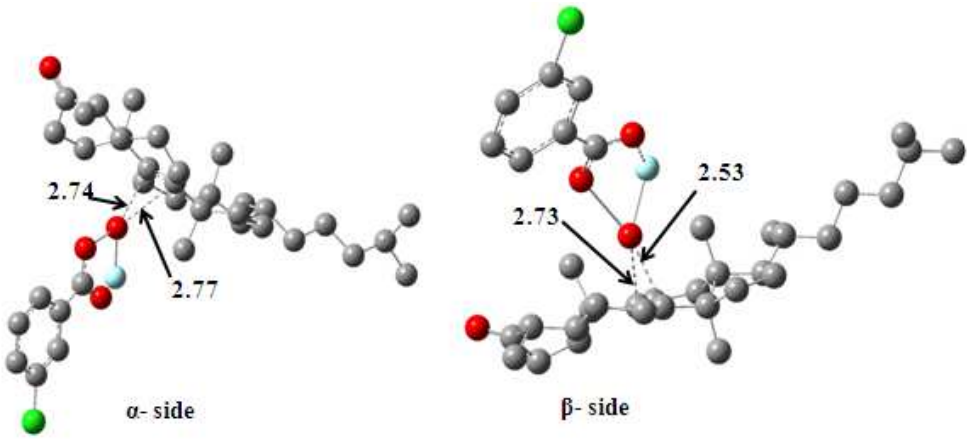


Figure 1: Geometries of the TSs involved in the stereo-isomeric pathways associated between triterpene 1 and m-CPBA. Distances are given in Angstroms

CONCLUSION

Using the DFT method with B3LYP/6-31G*(d,p) to calculate total and relative energies, transition state energies of the epoxidation reaction between 4α,14α-dimethyl-5α-cholest-8-en-3-one and m-CPBA, we have shown that:

- The values of total and relative energies of both reactions were negative, implying that the reactions were exothermic.
- The stereoselectivity and chemoselectivity observed at the α side of the double bond were confirmed by the α and β transition states energy, and the formation of 4α,14α-dimethyl-8α,9α-epoxy-5α-cholestan-3-one: **2** was kinetically and thermodynamically preferred than the 4α,14α-dimethyl-8β,9β-epoxy-5α-cholestan-3-one: **3**.

The product **2**, with the oxirane bridge linking the two C atoms, C8 and C9, and *cis* to the methyl groups attached to atoms C4 and C14, was kinetically favored so as the presence of two methyl groups linked to the C10 and C13 of tritepene derivative **1** hemisynthesized from *Euphorbia officinarum* latex.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper. Also, they declare that this paper or part of it has not been published elsewhere.

CONTRIBUTION OF THE AUTHORS

Abdellah Zeroual: Localisation of transition state, analyzed the data and revised the paper.
Noureddine Mazoir: hemi-synthesized compound **1** and revised the paper.
Ahmed Benharref: initiated the collaborative project

Abdeslam El Hajbi: analyzed the data, revised the draft paper.

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