Unravelling the mechanism, chemo- and stereospecifity in the epoxidation reaction of valencene

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Abstract
The epoxidation of valencene by m-CPBA has been investigated within the DFT at the B3LYP/6-311(d,p) computational level. The chemo- and stereoisomeric reaction paths involving the two C=C double bonds of valencene have been analyzed. DFT computations account for the high chemospecifity involving the endo-double bond and the high stereospecifity, in total agreement with the experimental outcome. An ELF examination of epoxidation shows that the establishment of the two new single C-O bonds is a little asynchronous.

Keywords: B3LYP/6-311(d,p); valencene; DFT; Epoxidation; m-CPBA.

1. Introduction
The epoxidation of olefins is a partial oxidation reaction by the insertion of an oxygen atom coming from an oxidizing agent on a double bond, leading to the formation of an epoxide group, cyclic ether composed of 3 atoms [1-3].

In general, the reactivity of alkenes towards the oxidizing agent depends on the number of substitutions around the double bond. The alkenes most substituted by alkyl groups are more reactive since they are considered as electron donors on the double bond and therefore more nucleophilic. [4, 5]
The tetrasubstituted alkenes by alkyl groups are generally 200 times more reactive than the monosubstituted for the epoxidation reaction under the same reaction conditions. However, other criteria may affect the speed of the reaction. For example, the size of the alkyl group which can lead to steric hindrance of the double bond. In addition, cis alkenes are generally more reactive than trans alkenes, since these are generally less congested and have a more accessible double bond. [6]

Epoxides are highly reactive molecules since they are both polar, but also have high tension energy in order to maintain the structure of the oxirane ring whose internal angles are more obtuse than the optimal angle of the tetrahedron which is 109,5° [7]. These two particularities are at the origin of the high reactivity of epoxides which make these compounds key intermediates both in the field of polymers and in pharmaceuticals. [7]

Consequently, they can therefore also react with the components of the reaction medium and thus carry out a secondary reaction which consists in the opening of the oxirane ring by a nucleophilic attack leading to the formation of diols, of ether glycols or to the formation of ester glycols, shown in Scheme 2. [8-10]

Various theories have been advanced to elucidate 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 show the high chemoselectivity involving the exocyclic C=C double bond and the low diastereoselectivity [16].

Herein, a DFT study in the epoxidation reaction of valencene using m-chloroperoxybenzoic acid, so as to understand the formation of epoxide compound (Scheme 3), plus the chemio- and diastereofacial selectivities [17].
2. Computational methods

DFT calculation were executed using the B3LYP functional [18, 19] mutually 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 (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 monodeterminant wave functions.

3. Results and discussion

3.1. Analysis of the CDFT indices of the reagents

Many researches 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. So, in order to predict the reactivity of the valencene (1) in epoxidation reaction, the global indices assembled in Table 1, the electronic chemical potential, $\mu$, chemical hardness, $\eta$, electrophilicity, $\omega$, and nucleophilicity, $N$, are analyzed.

Table 1. B3LYP/6-311G(d,p) electronic chemical potential $\mu$, chemical hardness $\eta$, electrophilicity $\omega$, nucleophilicity $N$, in eV, of limonene (1) and m-CPBA (2).

<table>
<thead>
<tr>
<th>System</th>
<th>$\eta$</th>
<th>$\mu$</th>
<th>$N$</th>
<th>$\omega$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valencene (1)</td>
<td>6.46</td>
<td>-2.83</td>
<td>3.29</td>
<td>0.62</td>
</tr>
<tr>
<td>m-CPBA (2)</td>
<td>5.38</td>
<td>-4.61</td>
<td>2.06</td>
<td>1.97</td>
</tr>
</tbody>
</table>

The electrophilicity $\omega$ indices of the Valencene (1) and m-CPBA (2) are 0.62 and 1.97 eV while the nucleophilicity $N$ indices are 3.29 and 2.06 eV, respectively. From these values, we can classify the Valencene as moderate electrophile and the strong nucleophiles, while m-CPBA as a strong electrophile and a moderate nucleophile. In this reaction the Valencene will participates as nucleophile and m-CPBA as electrophile.
In present times, the electrophilic $P_+^*$ and nucleophilic $P_-^*$ Parr functions have been suggested to analyze the local reactivity relating reactions between a nucleophile/electrophile pair [33-38]. Thus, the nucleophilic $P_-^*$ Parr functions for the Valencene 1 are evaluated (Figure 1).

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

Exploration of the nucleophilic $P_-^*$ Parr functions of Valencene 1 shows that the double bonds C1=C2 (0.30, 0.31) are highest nucleophilic centers than other double bond C3=C4 (0.06, 0.13), demonstrating that the electrophilic attack will be carried out on double bond C1=C2 of Valencene 1, in conformity with experience.

3.2. Energetic examination in epoxidation reaction of Valencene 1.
Due to asymmetric and the existence of two double C=C bonds in Valencene 1, four competitive reaction paths are possible for this epoxidation reaction (see Scheme 4). There are associated to the regioselective attack of m-CPBA on the C1=C2 or C3=C4 double bonds and the diastereoselective attack through the two faces of each double bond.

Scheme 4. The four considered regio- and diastereofacial isomeric reaction paths associated to the epoxidation reaction of valencene 1 by m-CPBA.
An examination for the stationary points along the four reaction paths facilitated the description and localization of the reagents 1 and 2, four TSs, TS-1, TS-2, TS-3 and TS-4, plus the analogous epoxides P-1, P-2, P-3, P-4, and m-CBA. As a result, this epoxidation reaction takes place via one-step mechanism. Relative free energies are given in Table 1. The free energies profiles of the reaction paths associated with the epoxidation reaction of valencene 1 by m-CPBA are offered in Figure 2.

Table 2. B3LYP/6-311G(d,p) relative a(ΔG, in kcal•mol⁻¹) free energies, in gas phase and in DCM, for the species elaborate in the epoxidation reaction of valencene (1) with m-CPBA (2).

<table>
<thead>
<tr>
<th>System</th>
<th>ΔG In gas</th>
<th>ΔG In DCM</th>
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<tbody>
<tr>
<td>1+2</td>
<td>-----</td>
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</tr>
<tr>
<td>TS-1</td>
<td>08.80</td>
<td>09.98</td>
</tr>
<tr>
<td>P-1+ m-CBA</td>
<td>-55.04</td>
<td>-49.78</td>
</tr>
<tr>
<td>TS-2</td>
<td>09.28</td>
<td>12.37</td>
</tr>
<tr>
<td>P-2+ m-CBA</td>
<td>-49.04</td>
<td>-48.62</td>
</tr>
<tr>
<td>TS-3</td>
<td>13.15</td>
<td>14.26</td>
</tr>
<tr>
<td>P-3+ m-CBA</td>
<td>-45.88</td>
<td>-45.25</td>
</tr>
<tr>
<td>TS-4</td>
<td>10.55</td>
<td>11.61</td>
</tr>
<tr>
<td>P-4+ m-CBA</td>
<td>-48.51</td>
<td>-48.13</td>
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</table>

a relative to 1+2

According to the relative values of free energy in the gas phase developed in Table 2 and the free energy profile shown in Figure 2, the activation barriers of channels 1, 2, 3 and 4 associated with this reaction are TS -1 (8.80 kcal / mol), TS-2 (9.28 kcal / mol), TS-3 (13.15 kcal / mol) and TS-4 (10.55 kcal / mol), therefore kinetically, both reaction paths 1 and 2 are possible. The formation of the four epoxides P-1, P-2, P-3 and P-4 are exothermic by 55.04, 49.04, 45.88 and 48.51 respectively. Thermodynamically and kinetically, the epoxide P-1 is more favored than the other epoxides in coherence with the experimental results.

Count the effect of DCM on the free energies of the activation barriers, we observe an augment 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 diminish 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.
Figure 2. Energies (ΔG) profiles, for the studied reaction paths of the epoxidation reaction of valencene (1) with m-CPBA (2), in gas and in presence of DCM at 25°C.

We can conclude that the addition of DCM disable 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 O3–C1 and O3–C2 are 2.186 and 2.166 Å (TS-1); 2.159 and 2.148 Å (TS-2), while TS at double bond C3=C4, the lengths of O3–C3 and O3–C4, 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 C1=C2 channels are more asynchronous than those associated with C3=C4 channels; and (2) to TS associated with C1=C2 channels, the formation of O3 – C2 bonds involving the P-1 epoxide is more advanced than that of O3–C1.
Figure 3. B3LYP/6-311G(d,p) optimized geometries of the regioisomeric TSs involved in the epoxidation reaction of valencene (1) with m-CPBA. Values in DCM are given in parentheses. Distances are given in angstroms, Å.

3.2. ELF topological study of the C–O bond formation along the epoxidation reaction of valencene (1) with meta-Chloroperoxybenzoic acid

In order to explain the formation of C–O bonds along the epoxidation reaction of valencene (1) with m-CPBA, a topological examination of the ELF along the IRC associated with the most favourable 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 2.7 > d (O-C) > 1.6; ELF valence basin populations of TS-1 and the selected structures of the IRC involved in the formation of the new O-C single bonds are given in table 3.

Table 3. ELF valence basin populations of TS-1 and the selected structures of the IRC involved in the formation of the new O-C single bonds along the in the epoxidation of valencene (1) by m-CPBA.

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III (TS-1)</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
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<tr>
<td>(</td>
<td>\text{C}_1\text{-C}_2</td>
<td>1.93</td>
<td>2.01</td>
<td>2.00</td>
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<td>1.44</td>
<td>1.47</td>
<td>1.50</td>
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<td>(\text{O}_3</td>
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<td>2.51</td>
<td>2.45</td>
<td>2.54</td>
<td>2.54</td>
<td>2.51</td>
<td>2.91</td>
</tr>
<tr>
<td>(</td>
<td>\text{O}_3</td>
<td>2.4²</td>
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<td>2.54</td>
<td>2.41</td>
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<td>1.01</td>
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<td>(</td>
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<tr>
<td>(\text{O}_3\text{-O}_4</td>
<td>0.47</td>
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<td>(\text{O}_4</td>
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<td>2.34</td>
<td>2.57</td>
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<td>2.66</td>
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<td>2.42</td>
<td>2.41</td>
<td>2.65</td>
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<td>2.91</td>
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<tr>
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<td>\text{C}_2\text{-O}_4</td>
<td>1.62</td>
<td>1.70</td>
<td>1.85</td>
<td>2.01</td>
<td>2.11</td>
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<tr>
<td>(\text{C}_3\text{-O}_4</td>
<td>2.33</td>
<td>2.26</td>
<td>2.11</td>
<td>2.03</td>
<td>1.92</td>
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<td>2.23</td>
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<tr>
<td>(\text{O}_6</td>
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<td>2.84</td>
<td>2.51</td>
<td>2.42</td>
<td>2.14</td>
<td>2.72</td>
<td>2.22</td>
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<tr>
<td>(</td>
<td>\text{O}_6</td>
<td>2.76</td>
<td>2.50</td>
<td>2.91</td>
<td>3.05</td>
<td>3.43</td>
<td>4.41</td>
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<td>(\text{H-O}_6</td>
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<td>0.98</td>
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</table>
Interesting deductions can be described from this ELF topological analysis: i) the activation energy of the reaction of valencene (1) with m-CPBA, relatively low 08.80 kcal • mol⁻¹ for TS-1, 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-1, the construction of the bond can be considered asynchronous.

4. Conclusion
The mechanism, the chemospecificity and the stereospecificity of the epoxidation reaction of valencene (1) by 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 valencene (1) was classified as a nucleophile. Furthermore, analysis of the nucleophilic $P^-_x$ Parr functions indicated that the carbon atoms of the endocyclic 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 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

References