Theoretical Investigation of the Chemo and the Regioselectivity of the Reaction Oxidation of Bicyclo[3.2.0]Hept-2-En-6-One by Hydrogen Peroxide

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Abstract

The mechanism, the chemoselectivity and regioselectivities of the oxidation reaction of bicyclo[3.2.0]hept-2-en-6-one and hydrogen peroxide, have been studied using B3LYP DFT methods together with the standard 6-31(d) basis set. The potential energy surface (PES) was analyzed by considering the chemo and regio-isomeric Pathways, we found that this reaction was chemo and regioselective and regioisomer P_1 is kinetically and thermodynamically favored in good agreement with experimental Result, in addition the analysis of the potential electrostatic and Parr functions confirming this result.

Keywords: regioselective, PES, chemoselective, the potential electrostatic.

1. Introduction

The Baeyer-Villiger (B.V) oxidation is one the most important reaction in therapeutic and organic chemistry based on oxidation of ketones to esters by peracids like as m-CPBA (Zaki et al., 2015), this reaction has high synthetic value and has been used in various synthesis and hemi-synthesis. In particular is a useful for synthesis optically and active lactones because this reaction was highly stereo and regioselective (Marco et al., 2014). In recent years, an attempt was made to change the traditional peroxyacids with green and environmentally friendly peroxide like hydrogen peroxide H_2O_2 or O_2 (House et al., 1972; Krow, 1993; Ten Brink et al., 2004; Zhou et al., 2014; Renz, Meunier, 1999).

C. Mazzini et al. experimentally studied the B-V reaction between bicyclo[3.2.0]hept-2-en-6-one and hydrogen peroxide (Mazzini et al., 1996), finding that this reaction is chemio and regioselective yielding the corresponding lactone P1 (3,3a,6,6a-tetrahydro-cyclopenta[b]furan-2-one) as the major chemio and regioisomere (see Scheme 1).

Herein, a DFT study of B-V reaction between bicyclo[3.2.0]hept-2-en-6-one and hydrogen peroxide yielding 3,3a,6,6a-tetrahydro-cyclopenta[b]furan-2-one, experimentally studied by C. Mazzini et al. our aim is to perform a theoretical study of the reaction mechanism of this reaction yielding the final product P1, as well as to explain the chemo- and regioselectivity experimentally found.
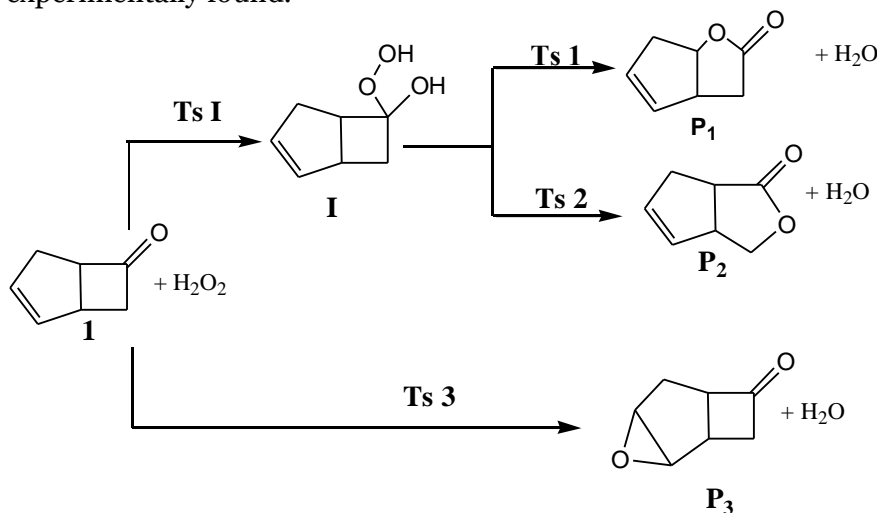
Scheme 1. Competitive chemo and regio-isomeric pathways associated with the reaction of bicyclo[3.2.0]hept-2-en-6-one by hydrogen peroxide.

2. **Materials and methods**

All the calculations were carried out using Gaussian 09 program. Exploration of the potential energy surface (PES) associates with B-V reaction between bicycle[3.2.0]hept-2-en-6-one and hydrogen peroxide was carried out using the B3LYP functional (Zhao et al., 2004) together with the 6-31(d) basis set (Hehre et al., 1986). The optimizations were carried out using Berny analytical gradient optimization method (Schlegel, 1982). The stationary points were characterized by frequency calculations to verify that the transition states (TSs) had one imagery frequency. The IRC paths (Fukui, 1970) were traced to verify the energy profiles connecting to the two associated minima.

The global electrophilicity index (Parr et al., 1999) 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, such as $\mu = (\varepsilon_H - \varepsilon_L)/2$ and $\eta = (\varepsilon_{L-H})$ (Parr et al., 1983). The empirical nucleophilicity index N (Jaramillo et al., 2008), based on the HOMO energies obtained within the Kohn-Sham, and defined as $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$. Electrophylic P_k^+ and nucleophilic P_k^- Parr functions (Zeroual et al., 2015; 2015; Domingo et al., 2015; Zoubir et al., 2017; Ourhriss et al., 2017), were obtained from the analysis of the Mulliken atomic spin density (ASD) of the radical anion and radial cation of the reagents. The local electrophilicity and local nucleophilicity indices were evaluated using the following expressions: $w_k = wP_k^+, N_k = NP_k^-$.

The electrostatic potential is a real property, a physical observable. It can be obtained computationally (Stewart, 1979). While it has been used to interpreting and predicting the regioselectivity (Murray et al., 2011). Regions where V(r) >0 can be expected to be attracted favorably, at least initially, to negative portions of other molecules, while V(r) < 0 predicts attractive interactions with positive portions.

3. **Results and discussion**

The present study has been divided into two sections: i) first, the Baeyer-Villiger reaction between bicyclo[3.2.0]hept-2-en-6-one and hydrogen peroxide is theoretically investigated. The energetic aspects, geometrical parameters of the TSs, ii) Parr functions maps and their electrostatic potential maps are analyzed.

3.1. Kinetic study of the oxidation reaction of bicyclo[3.2.0]hept-2-en-6-one by hydrogen peroxide.

The values of the Gibbs free energies and the relative of the stationary points involved in the B-V reaction between bicyclo[3.2.0]hept-2-en-6-one and hydrogen peroxide are summarized in Table 1. The Gibbs free energy profile of the B-V reaction between bicyclo[3.2.0]hept-2-en-6-one and hydrogen peroxide is given in Figure 1.

Table 1. DFT/6-31G(d) Gibbs free energies (G, in a.u.), and the relative a (ΔG in kcal mol−1), for the stationary points involved in the B-V reaction between bicyclo[3.2.0]hept-2-en-6-one and hydrogen peroxide.

| System	G	ΔG
$1 + H_2O_2$	-498.159264	-------
TS I	-498.059572	62.55
TS 3	-498.0532548	66.52
I	-498.150476	5.51
P 3 + H_2O	-498.229288	-43.94
TS 1	-498.069572	56.28
TS 2	-498.058301	63.35
P 1 + H_2O	-498.293184	-84.03
P 2 + H_2O	-498.289508	-81.72

• **Competition between epoxydation and B V (chemo-selectivite)**
The activation energies associated with epoxydation and B V are 66.52 (TS 3), and 62.55 (TS I) kcal mol−1, these energy results indicate that the formation of intermediate I is kinetically favored. Consequently, due to the strong chemoselectevity character of this reaction and the formation of the product P1 is thermodynamically favored than product P3.
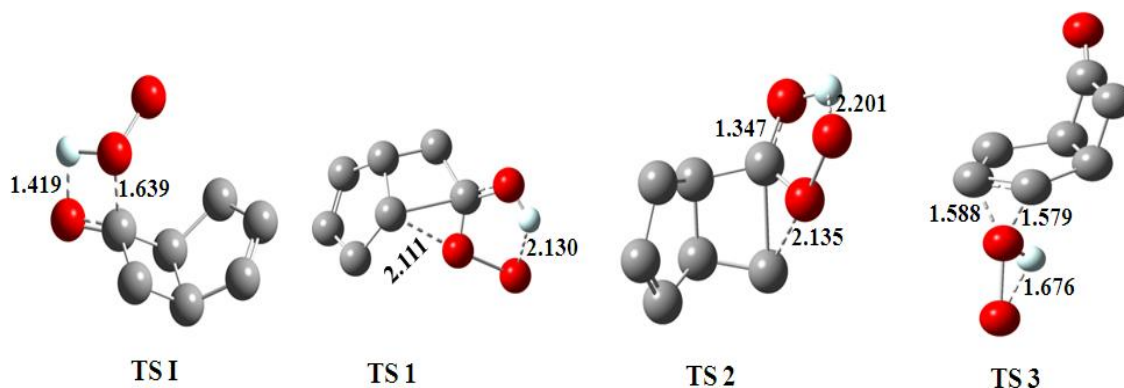• **Understanding the regioselectivity of the B V reaction between bicyclo[3.2.0]hept-2-en-6-one and hydrogen peroxide**.
The activation Gibbs free energy corresponding to the formation the products P1 and P2 are 56.28 (TS 1), and 63.35(TS 2) kcal mol−1favouring kinetically the formation of P1 as the single lactones, in good agreement with the experimental observations. Note that while formation of the products P1 and P2 are exothermic by 84.03 and 81.72 kcal mol−1 respectively; consequently, the product P1 is kinetically and thermodynamically favored.
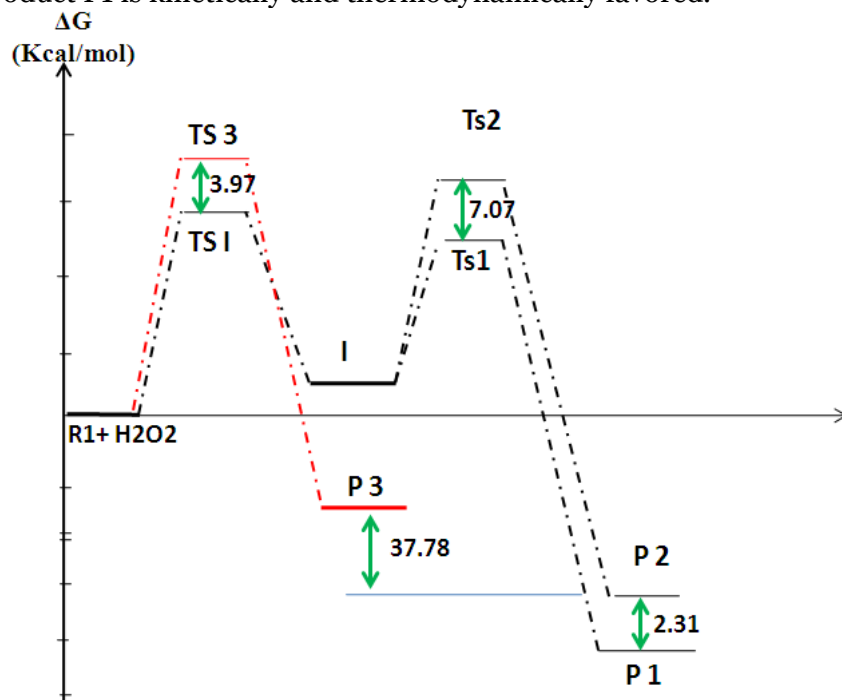
Fig. 1. Gibbs free energy profile (ΔG, in kcal mol−1) of the reaction between the ketone 1 and hydrogen peroxide.

The geometries of the TSs involved in the reaction between bicyclo[3.2.0]hept-2-en-6-one and hydrogen peroxide are given in Figure 2. The lengths of the O-H forming bonds at the TSs TS-3 and TS-I, are 1.676 A and 1.419 A respectively, the lengths of the O-C forming bonds at the TSs TS-1 and TS-2, are 2.111 A and 2.135 A respectively. These geometric parameters suggest an asynchronous bond formation process along the most favorable P1 regioisomeric channel.

Fig. 2. DFT/6-31G(d) optimized structures of the TSs of the bicyclo[3.2.0]hept-2-en-6-one and hydrogen peroxide. Lengths are given in Angstroms.

3.2. Understanding the chemoselectivity of this reaction using electrostatic potential V(r) and Parr functions.

The global DFT indices, namely the electronic chemical potential μ, chemical hadness η, electrophilicity w and nucleophilicity N, are given in table 2.

Table 2. B3LYP/6-31G(d) electronic chemical potential, chemical hardness , electrophilicity and nucleophilicity in eV, of the ketone R-1 and hydrogenperoxid

	μ	η	N	ω
H_2O_2	-3.06	7.27	2.82	0.64
R-1	-3.54	5.96	3.00	1.05

We can observed from Table 1 that the electronic chemical potential of hydrogen peroxide H_2O_2 -3.06 is higher than that of ketone R-1 -3.054 eV, indicating that the global electron density transfer (GEDT) will flux from H_2O_2 framework towords ketone R-1.

We are looked from Table 1 that th electrophilicity and nucleophilicity of the ketone R-1 are higher than electrophilicity and nucleophilicity of H_2O_2 the fact that the most favourable reactive channel is that involving the initial two-centers interaction between the most electrophilic centre and most nucleophilic centre of the reagents.

The nucleophilic P_k^- Parr function, the electrophilic P_k^+ Parr function and the electrostatic potential of the reagents were analyzed in order to characterize the most electrophilic and nucleophilc centers of the species involoved in this reaction, and, thus, to explain the chemoselectivity experimentally observed (Fig. 3).
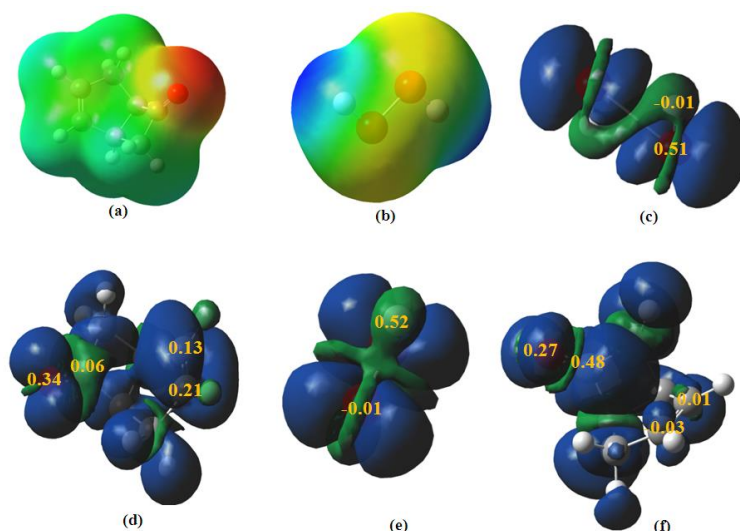
Fig. 3. (a) and (b) electrostatic potential, (c) and (f) the electrophilic Parr function maps, (d) and (e) the nucleophilic Parr function maps of the reagents R1 and H_2O_2, respectively

Analysis of the electrostatic potential maps of reagents indicating that the oxygen atom of the ketone is the most nucleophilic center of this ketone presenting red color and the hydrogen atom of hydrogenperoxid is the most electrophilic center presenting blue color. So the best interaction take place between oxygen atom of the ketone and hydrogen atom of peroxide H_2O_2. On the other hand the The nucleophilic P_k^- Parr function, the electrophilic P_k^+ Parr function of the ketone R-1 indicate that the oxygen atom is the most nucleophilic center $P_k^- = 0.34$ and C7 atom is most electrophilic center $P_k^+ = 0.48$ and for the hydrogen peroxide the nucleophilic P_k^- Parr function, the electrophilic P_k^+ Parr function indicate that the oxygen of this specie is the most nucleophilic center $P_k^- = 0.51$ and hydrogen atom is the electrophilic center $P_k^+ = 0.56$.

Consequently, in this oxidation reaction of the ketone R-1 by hydrogenperoxide H_2O_2, the most favourable electrophile-nucleophile interaction will take place between oxygen of the ketone with hydrogen of hydrogen peroxide and between C7 atom of the ketone and oxygen of peroxide. In clear agreement with the total chemoselectivity experimentally observed.

4. Conclusion

The high chemo and regioselectivity of ketone R-1 towards the lactones P_1 by the B V reaction, has been studied using DFT methods at the B3LYP/6-31(d). Analysis of the relative Gibbs free energies, Parr functions and the electrostatic potential indicates that while the formation of the products P_1 is favorable.

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