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A theoretical investigation of the regio- and stereoselectivities of the β-himachalene

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ABSTRACT

In this work we used DFT B3LYP/6-31G*(d) to study the stoichiometric reaction between the β -himachalene and dichlorocarbene. We have shown that β -himachalene behaves as a nucleophile, while dichlorocarbene behaves as an electrophile; and that β -himachalene reacts with an equivalent quantity of dichlorocarbene to produce only one product (referred to here as P_1). P_1 is formed at the only α side of the $C_6=C_7$ double bond of β -himachalene this regioselectivity conformed by Parr and Zeroual functions. This reaction is exothermic, stereoselective, chemospecific, and is controlled by charge transfer. We are studying too the mechanism and the stereoselectivity of epoxydation of the product P_1 by the meta-chloro-per-benzoic acid, the analysis of the surface of potential energy and the IRC calculation shows that this reaction follows a concerted mechanism asynchronous and that the mechanism of this epoxydation is an electrophile attack of the link low polarized Oxygene-Oxygene on the orbital π of the product P_1 . In this mechanism, the proton of the peracide is transferred from its oxygen that will form the epoxide, to give MCBA. The epoxide form is the result of an syn addition on the alkene P_1 this addition is stereospecifique. We find from this study that the origin of this stereoselectivite is due to the difference of the transition state energy, and that the product P_2 is kinetically favored by report to the product P_3 is in good agreement with experiment.

Keywords: β - himachalene, DFT, oxirane, *stereoselectivity*, epoxydation.

INTRODUCTION

M-Chloroperbenzoic acid, (MCPBA) is used for reactions epoxydation on olefinic hydrocarbons, like for the reaction oxidation of Baeyer-Villiger, where a ketone is oxidized out of ester. To prepare the epoxies from the β -himachalene is treated by one equivalent of dichlorocarbene, led chimospéciquement one product noted P₁ *{(1S, 3R, 8S)-2,2-dichloro- 3,7,7,10- tetramethyltricyclo [6.4.0.0^{1,3}]dodec-9-ene}* [1-3]. Its structure was determined by spectral data (NMR, ¹H, ¹³C and mass spectrometry) and stereochemistry was confirmed by X-ray diffraction [4]. (Figure 1) after the product P₁ was treated by one equivalent of meta-chloroperbenzoic acid in dichloromethane as solvent leads to two products P₂ and P₃ (Figure 1). The structures of the products: P₂:{(1S, 3R, 8S, 9S, 2.2 10R)- -dichloro-9-10-epoxy- -tetramethyl-tricyclo[6.4.0. 3,7,7,10 01.3]dodecane} and P₃:{(1S, 3R, 8S, 9R, 10S)- 2.2 -dichloro-9-10-epoxy- 3,7,7,10 -tetrahydro-tricyclo [6.4.0. 01.3] dodecane} were determined by the spectral data (NMR, ¹H, and ¹³C) and the stereochemistry of the product P₃ was confirmed by X-ray diffraction [5, 6].



Fig. 1 Reaction of preparation of product di-chlorine (P1), di-chlorine epoxies (P2, P3)

MATERIALS AND METHODS

Computational Methods

DFT computations were carried out using the B3LYP [7,8] hybrid meta functional, together with the standard 6-31G* basis set [9]. The optimizations were carried out using the Berny analytical gradient optimization method [10,11]. The stationary points were characterized by frequency computations in order to verify that TSs have one and only one imaginary frequency. The IRC paths [12] 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 Gonzlez-Schlegel integration method [13, 14]. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method [15, 16]. All computations were carried out with the Gaussian 09 suite of programs [17]. The global electrophilicity index, ω , is given by the following expression [18], $\omega = \frac{\mu^2}{2\eta}$, 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 orbitals HOMO and LUMO, as $\mu \approx \frac{E_{HOMO} + E_{LUMO}}{2}$ and $\eta \approx E_{LUMO} - E_{HOMO}$, respectively [19, 20]. Recently, we introduced an empirical (relative) nucleophilicity index N [21, 22], based on the HOMO energies obtained within the Kohn-Sham scheme [23], and defined as $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$. Nucleophilicity is referred to tetracyanoethylene (TCE), because it presents the lowest HOMO energy in a long series of molecules already investigated in the context of polar cycloadditions. This choice allows us to conveniently handle a nucleophilicity scale of positive values.

The local electrophilicity indices ω_k [24], and the local nucleophilicity indices N_k [25], at the atomic site k defined in terms of the related condensed Zeroual functions, Z_k^+ and Z_k^- , as

$$\omega_k = \omega_{\cdot} Z_k^+$$
 and $N_k = N_{\cdot} Z_k^-$

Where Z_k^+ and Z_k^- [26] they are the electrophilic and nucleophilic Zeroual functions respectively, obtained through the analysis of the Mulliken atomic spin density of the radical anion, the radical cation and the radical neutrel of the studied molecules.

$$Z_k^- = [D_k(N) - D_k(N-1)] Z_k^+ = [D_k(N+1) - D_k(N)]$$

Where $D_k(N)$, $D_k(N-1)$ and $D_k(N+1)$ are of the Mulliken atomic spin density of the site k in neutral, cationic, and anionic systems, respectively, and we compared with Parr functions [23-36].

RESULTS AND DISCUSSION

3-1- Analysis of the global reactivity indexes for dichlorocarbene and β - himachalene.

The μ , η , ω , N and $\Delta\omega$ values for a dichlorocabene and the β -himachalene used in cycloaddition reaction most of them having a known electrophilic/nucleophilic character are displayed in Table 1. The molecules are given in decreasing order of the *N* value. At the top of this table appears β -himachalene, which is classified as a strong nucleophile (*N*=3.427 eV), while at dichlorocarbene (*N*= 1.762 eV). The chemical hardness of the β -himachalene (6,488 eV) is superior to the chemical hardness of the dichlorocarbene (3,806 eV) and the electronic chemical potential of the β -himachalene (-2,499 eV) is higher to that of the dichlorocarbene (-5,454 eV), what shows that the electron transfer takes place from the β -himachalene to dichlorocarbene and we shows that dichlorocarbene is strongly electrophilic than β -himachalene.

 $Table 1. B3LYP/6-31G* \ electronic \ chemical \ potential \ \mu, \ chemical \ hardness \ \eta, \ global \ electrophilicity \ \omega, \ global \ nucleophilicity \ N \ indices \ nucleophilicity \ N \ nucleophilicity \ nucleophilicity \ N \ nucleophilicity \ nucl$

| and | Δω, in | eV |
|-----|--------|----|
|-----|--------|----|

| | μ | η | ω | Ν | Δω |
|-----------------|--------|-------|-------|-------|-------|
| β-himachalene | -2.499 | 6.488 | 0.696 | 3.427 | 3.211 |
| Dichlorocarbene | -5.454 | 3.806 | 3.806 | 1.762 | |

3-2- Analysis of the local reactivity indexes for dichlorocarbene and β - himachalene.

Polar Diels–Alder (P-DA) reactions involving asymmetrically substituted reagents take place through high asymmetric transition state structures (TSs).[37] Several studies have established that the most favourable regioisomeric reactive channel is that involving the most favourable local electrophilic and nucleophilic interactions. This behaviour is well predicted by the analysis of the local electrophilicity ω_k and the nucleophilicity N_k indices derived from the Zeroual functions. (Figure 2)

Despite the similarity of the electrophilic and nucleophilic local activations given for the Parr and Zeroual functions for the β -himachalene given in Table 2.

Table 2. Electrophilic and nucleophilic Zeroual functions of the β -himachalene (see atom numbering in figure 2)

| | $D_k(N-1)$ | $D_{k}(N+1)$ | $D_k(N)$ | P_k^- | Z_k^- |
|----|------------|--------------|----------|---------|---------|
| C2 | 0.14 | 0.08 | 0.01 | 0.14 | -0.04 |
| C3 | 0.09 | 0.13 | -0.005 | 0.09 | -0.095 |
| C6 | 0.25 | 0.27 | 0.92 | 0.25 | 0.67 |
| C7 | 0.27 | 0.28 | 0.92 | 0.27 | 0.65 |

Table 2 shows that the Zeroual functions agree with the Parr functions as the observed electrophilic/nucleophilic behaviour does correspond to changes in charge distribution, as proposed by the Zeroual functions. The Parr functions yield the same pattern for the electrophilic and nucleophilic local activation as Zeroual functions. Thus, the Zeroual functions correctly suggested that the C6 and C7 carbon is more nucleophilic centre than C2 and C3, in clear agreement with the experimental results. Similar results are obtained with the Parr functions.



Fig. 3Illustration of the favorable interactions using local nucleophilicities (Nk calculated from Zeroual functions)

Our study shows that the double bond C6 = C7 is attacked only by the face α [38].

3-3- Analysis of the global reactivity indexes for M-Chloroperbenzoic acid and P₁.

The electronic chemical potential (μ), chemical hardness (η), the electrophilicity index (ω) and global nucleophilicity index (N). for the product P₁ and M.C.P.B.A gathered in table3

Table 3. The chemical descriptors intramolecular (in eV) for the product P1 and M-Chloroperbenzoic acid (MCPBA)

| | μ (ev) | η (ev) | ω (ev) | N (ev) |
|------------------------|--------|--------|--------|--------|
| Product P ₁ | -3.091 | 6.341 | 0.753 | 3.269 |
| M.C.P.B.A | -4.368 | 5.412 | 1.763 | 2.457 |

Table 3 shows that:

*The index of the electrophilicity of MCPBA (1.763 eV) is higher than that of the product P_1 (0.753 eV). Therefore, in this cycloaddition of MCPBA will behave as electrophilic when the product P_1 will behave as a nucleophile.

* $\Delta \omega = \omega(P_1) - \omega(A.M.C.P.B) > 1$ eV This shows that this reaction has a low polar character. [39, 40]

* The electronic potential chemical of product P_1 (- 3.091ev) is higher than that of the M.C.P.B.A (- 4.368eV), which implies that the transfer of electrons will take place of product P_1 to the M.C.P.B. A.



Fig. 4. Interaction between the orbital borders of the P1 and M.C.P.BA reacting according to a reaction of epoxydation, the images are the representations of the same orbital, from a quantum calculation by DFT/6-31 (d)

We can draw important information from this diagram, we see immediately that:

*The Homo of the product P_1 is very close to the's LUMO of A.M. P. C. B which confirms that the product P_1 is nucleophile and the A.M. C. P. B is electrophile.

* The difference between the HOMO energy of the product P_1 and LUMO of the MCPBA is of order ($\Delta[\epsilon(HO)-\epsilon(BV) (eV)=4.6 \text{ or} = 7.1$) which shows that the reaction is controlled by charge transfer.

3-4- Analysis of the local descriptors.

The site electrophilic attack for electrophilic meta chloroperbenzoic acid is determined from the calculation of Parr and Zeroual functions table 4:

 Table 5. Electrophilic Parr and Zeroual functions of the product P1 and M-Chloroperbenzoic acid, (MCPBA) (see atom numbering in figure 4)

| | \mathbf{P}^+ | \mathbf{Z}^{+} | $\omega_k = \omega \cdot Z^+$ |
|----|----------------|------------------|-------------------------------|
| 01 | 0.166 | 0.149 | 0.262 |
| O2 | 0.148 | 0.116 | 0.204 |
| 0 | -0.009 | -0.135 | -0.238 |

In figure 4, we have been given the values of the local electrophilic power on the sites oxygen's for M.C.P.B.A and the values of the local nucleophilic power on the sites of the product P1.



Fig. 5 Values of the local electrophilic and local nucleophilic of the reagents; (calculated from Zeroual functions)

The oxygen O1 has the highest value of the index of electrophilic local, then the proton of the peracid is transferred from its oxygen that will form the epoxid, toward its oxygen doubly linked, to give the sub-product carboxylic acid MCBA as well that the epoxid form is the result of a **syn** addition on product P1

Kinetic study.

To highlight that the attack of the double bond $C_2 = C_3$ by the alpha side of the product P_1 is preferred, we determined the energy of the reactants, the energy of the products obtained , transition state energy TS α , TS β and deference to transition energy (Table 5).

| Table 6. Total Energies B3LYP/6-31G (d) (E, in a.u) and relative energies Δ E* (kcal / mol) for the stationary points of the equimo | olaı |
|--|------|
| reaction between the product P ₁ and MCPBA | |

| | E (a.u) | ΔE*(Kcal/mol) | $\Delta(TS\beta-TS\alpha)$ (Kcal/mol) |
|-------------------|------------|--|---------------------------------------|
| | | $(\mathbf{E} - \mathbf{E}_{\mathbf{R}})$ | |
| Réactifs energy | -2500.0421 | | |
| E _{TS β} | -2500.015 | 17.005 | |
| E _{TS a} | -2500.026 | 10.102 | 9.903 |
| Product 2 α | -2500.123 | -50.764 | |
| Product 3 β | -2500.130 | -55.157 | |

* We see from this table that the approaches α and β are thermodynamically possible and that these reactions are exothermic.

* Based on the difference Δ (TS β -TS α) = 9.903 we can conclude that the alpha approach is kinetically favored what is good agreement with the experience.



Starting from table 5, we happen to schematize the energy profile of the reaction (figure 3).

Fig. 6 Energy Profile of a reaction of an equivalent of the product P1 and one equivalent of the MCPBA

Figure 5 shows that:

*The TS β (transition state energy of β side) is located 9.903 Kcal/mol below TS α (transition state energy of α side). The activation energies corresponding to the faces attacks of double bond C2 = C3 of the Product P1 are 17,005 (Kcal/mol) for the attack β -side and 10,102 (kcal / mol) for attack α -side.

*The difference between energies of activations of the products P2 and P3 is of a nature 9.903 Kcal/mol what shows that the formation of isomer alpha is kinetically favored than the isomer bita, this result is in accordance with note experimental.

*The formation of the products P2 and P3 is exothermic by -50.764 and -55.157 Kcal/mol respectively.

*The bond lengths of state transitions are represented in figure 3 and are given in A° .

CONCLUSION

Using the DFT method with B3LYP/6-31G*(d) to calculate total and relative energies, transition state energies and interatomic distances of the [1+2] cycloaddition reaction between β -himachalene and dichlorocarbene we have shown that:

• The values of total and relative energies of both reactions are negative, implying that the reactions are exothermic.

• The energy difference between the HOMO of β -himachalene and the LUMO of dichlorocarbene and between the LUMO of β -himachalene and the HOMO of dichlorocarbene is greater than 2 eV, indicating that the reaction mechanism is controlled by charge transfer.

• Although the proposed Zeroual functions give a similar local reactivity as the Parr functions, both are derived from conceptually different reactivity models. The local reactivity given by the Zeroual electrophilic and nucleophilic functions is in agreement with experimental results.

• The calculation of activation energies, the analysis of the SEP and the IRC calculation show that epoxydation of P_1 by MCPBA follows a concerted mechanism asynchronous and that the alpha side of the double bond C2 =C3 is favored; this result is in conformity with the experimental findings.

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