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Theoretical Analysis of Reactivity and Regioselectivity in [1+2] Cycloaddtion Reaction of Some Monoterpenes with Dichlorocarbene

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Theoretical Analysis of Reactivity and Regioselectivity in [1+2] Cycloaddtion Reaction of Some Monoterpenes with Dichlorocarbene

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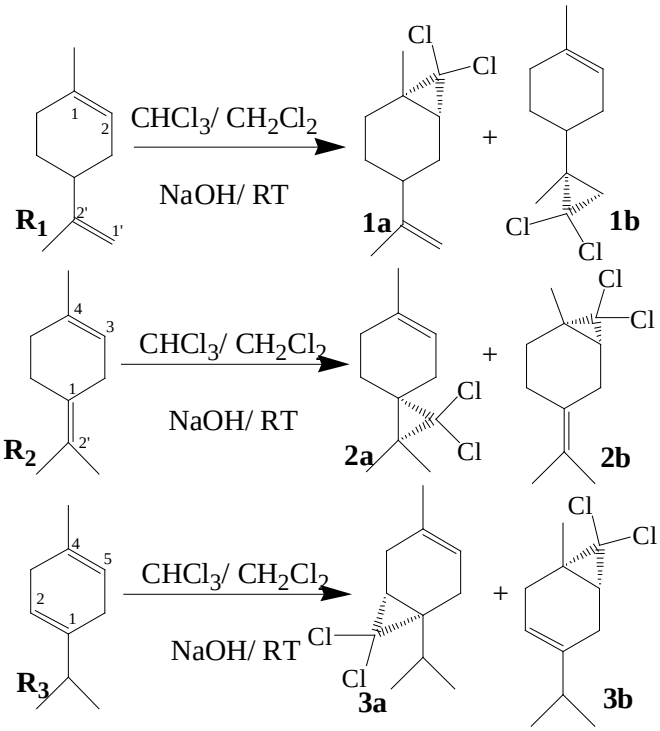
I. Introduction

The monoterpenes are essential ingredients in fine chemical industry and flavor and perfume industry. It is used to flavour many kinds of baked goods, confections, pudding, meats, sausages, sauces, vegetables and beverages [1]. The pharmacological activities of nutmeg mainly exist in its essential oil fraction [2]. Nutmeg oil possesses a wide array of pharmacological actions including analgesic [3], antifungal [4-7], antimicrobial [8-12], anti-inflammatory [13], antibacterial [14-16], antioxidant [17-18], antidepressant [19], as well as hepatoprotective activity [20]. The most important constituents of monoterpenes are α- and β- pinene. We were interested in a classical reactivity of carbenes. The dichlorocarbene reacts with alkenes such as limonene R_1 (4-Isopropenyl-1-methyl-cyclohexene), terpinolene R_2 (4-Isopropylidene-1-methyl-cyclohexene) and γ-terpinene R_3 (1-Isopropyl-4-methyl-cyclohexa-1,4-diene) in dichloromethane, to form the cyclopropane derivative (Scheme 1). The structures of these products have been determined by spectroscopy (^{1}H, ^{13}C and mass spectroscopy). [21]



Scheme 1: [1+2] cycloaddition reaction of limonene 1, terpinolene 2 and γ-terpinene 3 with dichlorocarbene.

Herein, a DFT study of the [1+2] cycloaddition reaction of limonene 1, terpinolene 2 and γ-terpinene 3 with dichlorocarbene yielding: 4-(2-propene)-1-Methyl-7,7-dichloro-bicyclo[4.1.0]heptane, 1,1-Dichloro-2,2,6-trimethyl-spiro[2.5]oct-5-ene and 7,7-Dichloro-4-isopropyl-1-methyl-bicyclo[4.1.0]hept-3-ene,experimentally studied by Hossni Ziyat et al. [21] are presented (see Scheme 1). Our aim is to perform a theoretical study of the reaction mechanism of these cycloaddition reactions yielding the final products: 1a, 2a and 3a, as well as to explain the regioselectivity experimentally observed.

II. Computational Details

All calculations reported in this work were performed in the GAUSSIAN 09, B3LYP/6-31G(d,p) as well as theoretical levels were performed. Optimizations of the stable structures were performed with the Berny

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algorithm, whereas the transition states were calculated using the QST2 procedure followed by the TS method. Stationary points were characterized by frequency calculations. All transition states showed only one negative eigen value in their Hessian matrices. For all reactions, IRC [22] calculations were performed to connect previously computed transition structures with suitable minima. Solvent effects of dichloromethane were taken into account through single point energy calculations using the polarisable continuum model (PCM). [23]

The global electrophilicity index [24] 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 μ = (eH - eL)/2 and η = (eL - eH), respectively. [25] The empirical nucleophilicity index N, [26] based on the HOMO energies obtained within the Kohn–Sham scheme, [27] and defined as $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$. The nucleophilicity was referred to tetracyanoethylene (TCE). Electrophylic P_k^+ and nucleophilic P_k^- Parr functions, [28-34] were obtained through the analysis of the Mulliken atomic spin density (ASD) of the radical anion and radial cation of the reagents. The local electrophilicity and nucleophilicity indices, were evaluated using the following expressions: $\omega_k = \omega . P_k^+$, $N_k = N . P_k^-$

III. Results and Discussion

The present theoretical study is divided into three parts: (i) first, an analysis of DFT reactivity indices at the ground state of the reagents involved in the [1+2] cycloaddition reaction between dichlorocarbene and limonene **1**, terpinolene **2** and γ-terpinene **3** is performed in order to explain the reactivity in these reactions; (ii) in the second part, potential energy surfaces (PESs) are analyzed (iii) in the third part, we proposed new method to calculate the percentages of the products.

a) DFT analysis based on the global and local reactivity indexes

These [1+2] CA reactions were first analyzed using the reactivity indices. The global indices, named electronic chemical potential μ, chemical hardness η, global electrophilicity w and global nucleophilicity N, for the reagents involved in these [1+2] CA reactions are gathered in Table 1.

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

	μ	η	N	ω
limonene **1**	-3.17	5.85	3.42	0.85
terpinolene **2**	-2.46	6.60	3.76	0.45
γ-terpinene **3**	-2.55	6.66	3.63	0.49
Dichlorocarbene **4**	-5.45	3.80	2.17	3.90

The electronic chemical potential of dichlorocarbene, μ= -5.45 eV, is lower than that of limonene **1**, μ= -3.17 eV, terpinolene **2** μ= -2.46 eV and γ-terpinene **3**, μ= -2.55eV, indicating that the global electron density transfer (GEDT) along the corresponding reactions will flux from these the alkenes toward the dichlorocarbene. It also is clear from the table 1 that the dichlorocarbene presents a high electrophilicity w index, w= 3.90 eV, being classified as a strong electrophile and a very low nucleophilicity N index, N= 2.17 eV. On the other hand, limonene **1**, terpinolene **2** and γ-terpinene **3** present very low electrophilicity, w= 0.85 eV, w= 0.45 eV and w= 0.49 eV respectively, and nucleophilicity indices, N= 3.42 eV, N= 3.76 eV and N = 3.63 eV. In spite of the high nucleophilic character of these alkenes (limonene **1**, terpinolene **2** and γ-terpinene), the high electrophilic character of dichlorocarbene allows the participation of these alkynes (limonene **1**, terpinolene **2** and γ-terpinene) in cycloaddition reactions [1+2] as nucleophiles.

The most favourable reactive channel is that involving the initial two-centre interaction between the most electrophilic P_k^+ and nucleophilic P_k^- Parr functions centre of both reagents.

Recently, electrophilic P_k^+ and nucleophilic P_k^- Parr functions have been proposed to analyse the local reactivity in polar processes involving reactions between a nucleophile– electrophile pair.

The analysis of the nucleophilic P_k^- Parr functions of limonene **1**, terpinolene **2** and γ-terpinene **3** (figure 2) shows that the C1 and C2 carbon of limonene **1**, the C1 and C2' carbon of the terpinolene **2** and C1 and C2 carbon of γ-terpinene **3** present the maximum values of P_k^- : 0.22, 0.29, 0.25, 0.27, 0.26 and 0.29 respectively, indicating that these sites are the most nucleophilic centers of these species (see Scheme 1 for atom numbering). Consequently, the regioselectivity observed is predicted correctly by the Parr function.

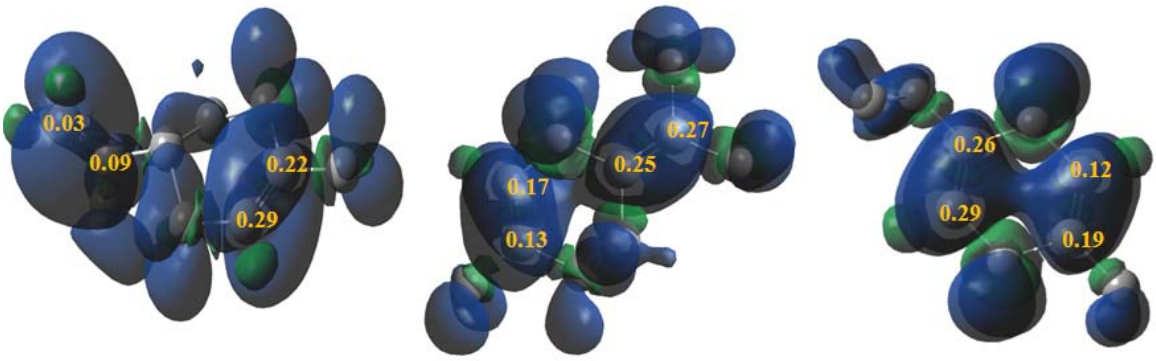


Figure 1: Nucleophilic P_k^- Parr functions of limonene **1**, terpinolene **2** and γ-terpinene **3**

b) Kinetic study

In order to show that the dichlorocarbene preferentially attacks the one double, we calculated the thermodynamic parameters of the reactants, the products and transition states energies, table 2 contains the total and relative enthalpies, entropies, and free energies for the CA [1+2] reaction of the monoterpenes (limonene 1, terpinolene 2 and γ-terpinene 3) and dichlorocarbene.

Table 2: B3LYP/6-31G(d,p) enthalpies H (in a.u.) and relative enthalpies (ΔH, in kcal/mol), entropies S (in cal mol^{-1} K^{-1}) and relative entropies (ΔS, in cal mol^{-1} K^{-1}), free energies G (in a.u.) and relative free energy (ΔG, in kcal/mol) in dichloromethane

System	H	ΔH	G	ΔG	S	ΔS
limonene 1+ CCl_2	-1448.831198	---------	-1448.908944	----------	163.632	----------
TS1a	-1348.849017	-11,181	-1348.908121	**5.165**	124.394	-39,238
TS1b	-1348.833066	-1,172	-1348.892982	**10.016**	126.105	-37,527
1a	-1348.925478	-59,161	-1348.980834	**-45.111**	116.508	-47,124
1b	-1348.905222	-46,450	-1348.957245	**-30.309**	109.492	-54,14
terpinolene 2+ CCl_2	-1448.834525	---------	-1448.913443	----------	166.097	----------
TS2a	-1348.848528	-8,787	-1348.905490	**4.990**	119.885	-46,212
TS2b	-1348.833066	0,915	-1348.892982	**12.839**	126.105	-39,992
2a	-1348.918920	-52,95	-1348.974718	**-38.450**	117.437	-48,66
2b	-1348.914813	-50,381	-1348.967514	**-33.930**	110.919	-55,178
γ-terpinene 3+ CCl_2	-1448.837111	---------	-1448.913249	----------	160.247	----------
TS3a	-1348.843054	-3,729	-1348.900732	**7.854**	121.393	-38,854
TS3b	-1348.834701	1,512	-1348.891202	**13.834**	118.915	-41,332
3a	-1348.913711	-48,0675	-1348.964080	**-31.896**	106.011	-54,236
3b	-1348.906103	-43,293	-1348.959633	**-29.106**	112.663	-47,584

Relative to limonene 1+CCl_2, terpinolene 2+CCl_2 and γ-terpinene 3+CCl_2

As can be observed, while activation free energies are 5.165 (TS1a), 10.016 (TS1b), 4.990 (TS2a), 12.839 (TS2b), 7.854 (TS3a), and 13.834 (TS3b) kcal mol^{-1}, reaction free energies imply that formation of the corresponding formal [1+2] cycloaddition is highly exothermic; -45.111 (1a), -30.309 (1b), -38.450 (2a), -33.930 (2b), -31.896 (3a) and -29.106 (3b) kcal mol^{-1}. These values clearly indicate that the products 1a, 2a and 3a are preferred.

Using the data given in Table 2, we can sketch the energy profile of these reactions (Fig. 2).

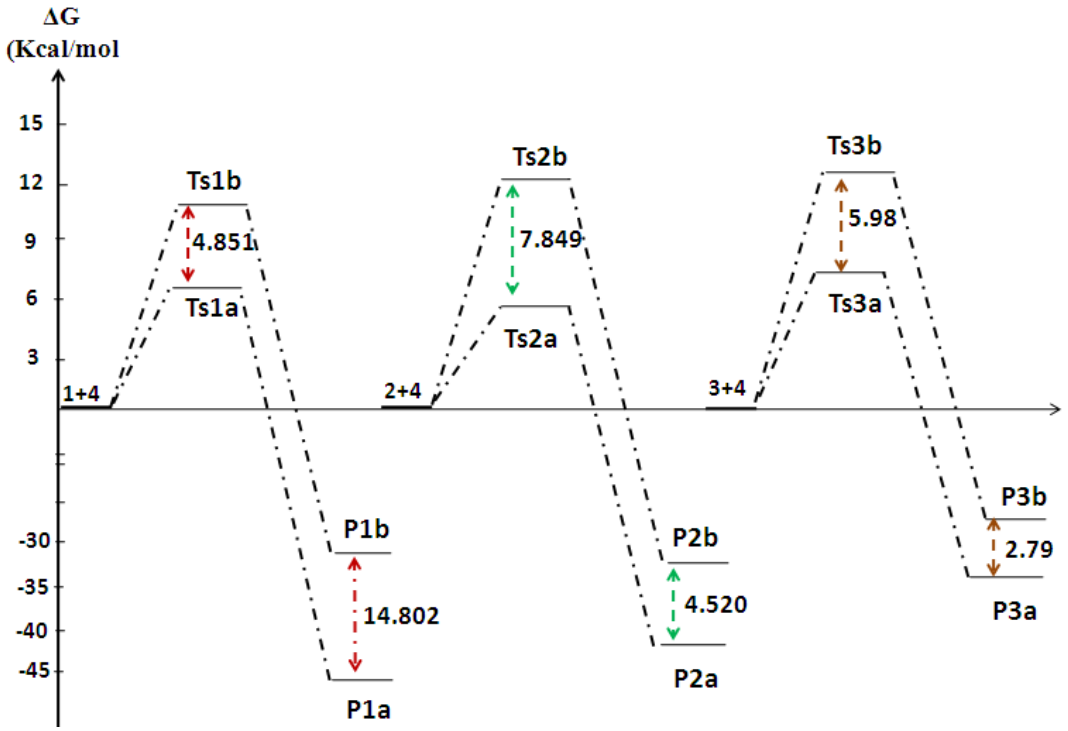
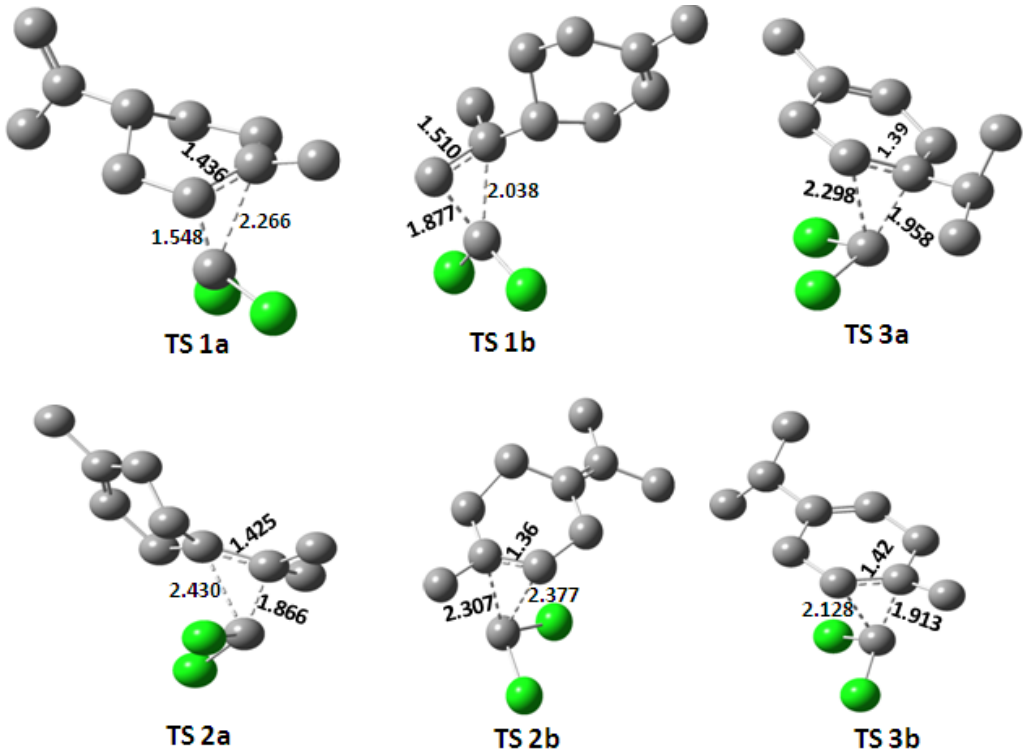


Figure 2: Gibbs free energy profile of [1+2] cycloaddition reaction between dichlorocarbene and alkenes.

We can observed from figure 2 that the deference between activation free energies are 4.851 (Ts1b-Ts1a), 7.849 (Ts2b-Ts2a) and 5.98 (Ts3b-Ts3a), showing that the formation of P1a, P2a and P3a isomers are kinetically preferred. The deference between reaction free energies are 14.802 (1b-1a), 4.520 (2b-2a) and 2.79 (3b-3a), showing that the formation of P1a, P2a and P3a regioisomers are thermodynamically preferred in clears agreement with experimental results.

The optimized geometries of the TSs involved in the studied cycloaddition reaction and the distances of the forming bonds are presented in Figure 3.



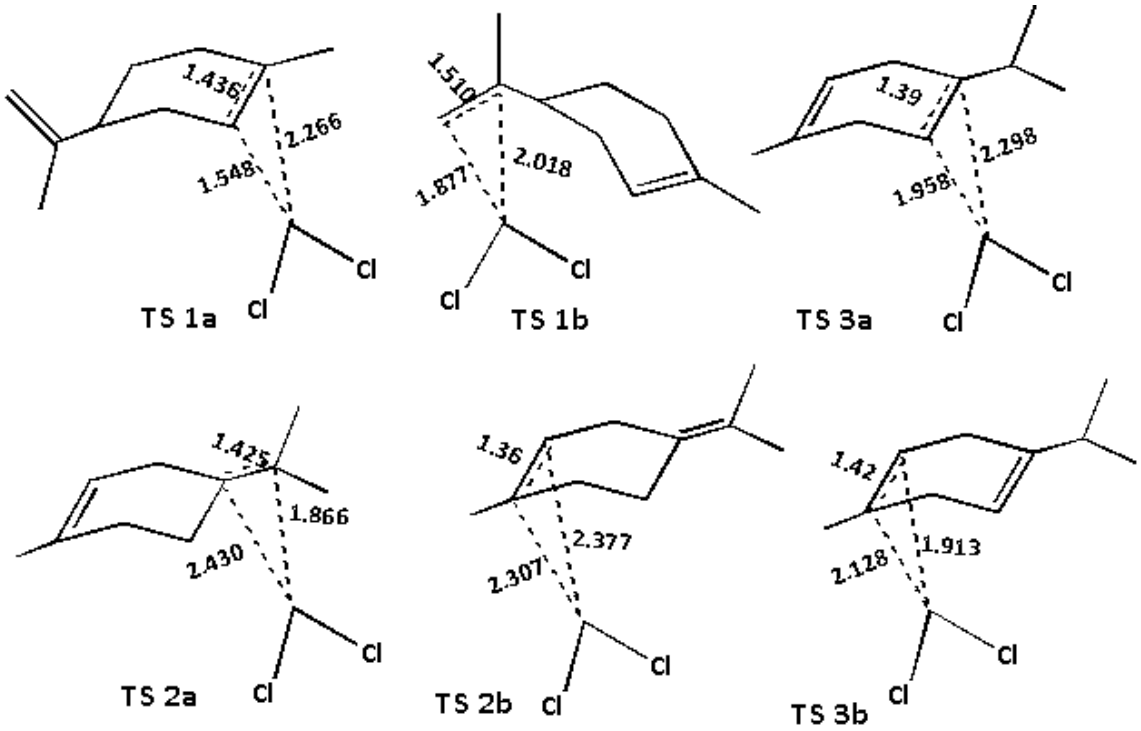


Figure 3: Optimized TS involved in the CA [1+2] reaction of dichlorocarbene–alkene (limonene 1, terpinolene 2 and γ-terpinene 3) the lengths of the newly forming bonds are given in (Å)

c) Calculation of the percentage of the products

According to transition state theory (TST), the second order rate constant (k_{TST}) at a given temperature (T) can be determined using the following equation [35]:

$$K_{TST} = \frac{k_B T}{hC_0} e^{\frac{-\Delta G^{\#}}{RT}} \quad (1)$$

Where k_B, h, C_0, and R denote Boltzmann's constant, Planck's constant, standard concentration (1 mol L^{-1}), and the universal gas constant R = 1,987 cal·K^{-1}·mol^{-1}, respectively.

To calculate the theoretical percentage of the products we use the following equation:

$$\frac{K_{TST}(P1)}{K_{TST}(P2)} = \frac{\frac{k_B T}{hC_0} e^{\frac{-\Delta G^{\#}(P1)}{RT}}}{\frac{k_B T}{hC_0} e^{\frac{-\Delta G^{\#}(P2)}{RT}}}$$

$$= e^{\frac{\Delta G^{\#}(P2)-\Delta G^{\#}(P1)}{RT}} = \frac{\%\, P1}{\%\, P2} = \frac{50+n}{50-n} \qquad with: 0 \le n < 50$$

$$n = \frac{50\left(e^{\frac{\Delta G^{\#}(P2)-\Delta G^{\#}(P1)}{RT}} - 1\right)}{e^{\frac{\Delta G^{\#}(P2)-\Delta G^{\#}(P1)}{RT}} + 1} \quad (2)$$

$$\Delta G^{\#}(P2) - \Delta G^{\#}(P1) = RT Ln\left(\frac{50+n}{50-n}\right) \quad (3)$$

The difference of relative free energy and percentage of the products are reported in table 3.

Table 3: $\Delta G^{\#}(P2) - \Delta G^{\#}(P1)$ Difference of relative free energy (in Kcal/mol) and percentage of the products

n	$\Delta G^{\#}(P2) - \Delta G^{\#}(P1)$	% P1	% P2
0	0	50	50
1	0,0236882	51	49
2	0,04739537	52	48
3	0,07114057	53	47

4	0,09494305	54	46
5	0,11882234	55	45
6	0,14279832	56	44
7	0,1668914	57	43
8	0,19112252	58	42
9	0,21551336	59	41
10	0,24008643	60	40
15	0,36654921	65	35
20	0,50170709	70	30
25	0,6505169	75	25
30	0,82086093	80	20
35	1,02710238	85	15
40	1,3010338	90	10
41	1,3699634	91	9
42	1,44617718	92	8
43	1,53164601	93	7
44	1,6292556	94	6
45	1,74347887	95	5
46	1,8818083	96	4
47	2,05828841	97	3
48	2,30444799	98	2
49	2,72088994	99	1

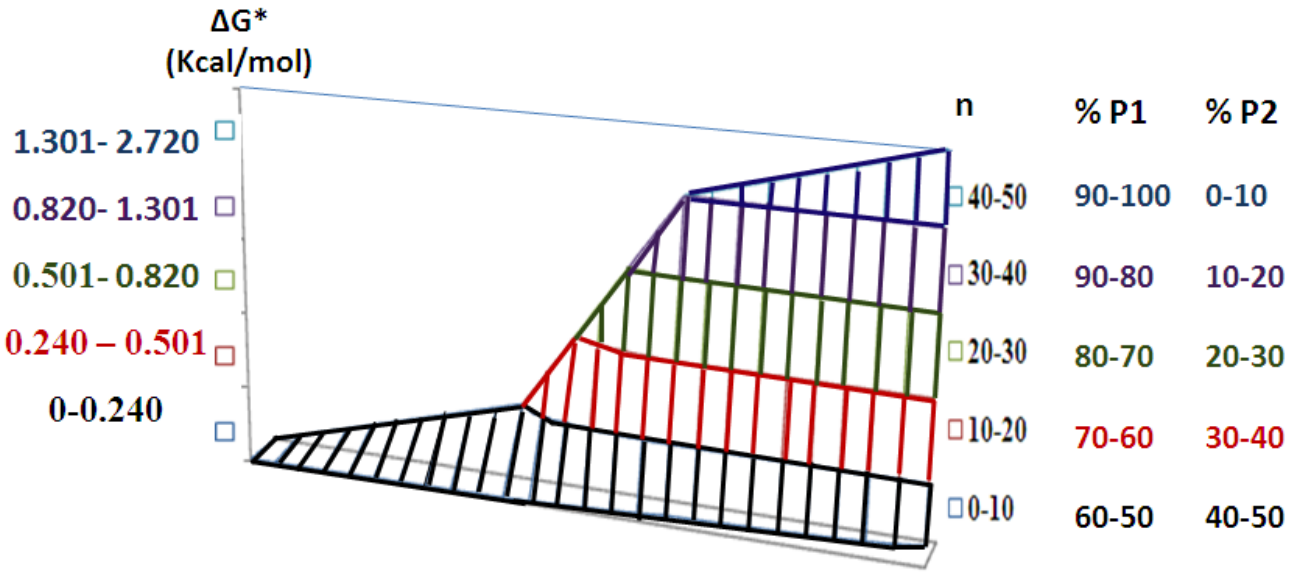


Figure 4: $\Delta G^{\#}(P2) - \Delta G^{\#}(P1)$ Difference of relative free energy (in Kcal/mol) and percentage of the products

We can deduce from figure 4 that:

- When $\Delta G^{\#}(P2) - \Delta G^{\#}(P1) = 0$, n=0, consequently the percentages of the products are equal (%P_1=%P_2= 50%).
- When $\Delta G^{\#}(P2) - \Delta G^{\#}(P1)$ varies between 0 and 0.240 (eV), n varies between 0 and 10, therefore the reaction will be selective (regio, sterio, diasterio and chemio) and the percentages of P_1 varies between] 50 - 60] and the percentages of P_2 varies between] 40 - 50[.
- When $\Delta G^{\#}(P2) - \Delta G^{\#}(P1)$ takes values between 1.301-2.720 (eV), n varies between 40-50, the percentages of the product P1 varies between] 90 - 100[and the percentages of the product P2 varies

between]0-10[, consequently the reaction will be very selective.

- When $\Delta G^{\#}(P2) - \Delta G^{\#}(P1)$ is greater than 2.720 (eV) the reaction will be specific (%P1= 100%)
- In this work we observed that the difference of relative free energy are superior than 2.720 (eV), indicated that these reactions are regio-specific in good agreement with experimental result.

IV. Conclusion

In this paper, we have discussed the molecular mechanism and the regioselectivity of the [1+2] cycloaddition reactions of limonene **1**, terpinolene **2** and γ-terpinene **3.** with dichlorocarbene yielding 1a, 2a and 3a, respectively, experimentally studied by by Hossni Ziyat et al, has been investigated using DFT methods at the DFT/6-31G(d,p) computational level. Analysis of the nucleophilic P_k^- Parr functions allows characterising the carbons atoms of the double multi-substitute as the most nucleophilic centre of the monoterpenes (limonene **1**, terpinolene **2** and γ-terpinene **3**) used in this work, in clear agreement with the regioselectivity found in result. An exploration of the PESs associated with these cycloaddition reactions indicates that these cycloaddition reactions are strongly exothermic, and from the activation free energies we can conclude that these reactions are completely regiospecific.

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