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## Articles and Statements

### Synthesis, spectroscopic NMR and theoretical (HF and DFT) investigation of 3,5,5,9-tetramethyl-2-nitro-6,7,8,9-tetrahydro-5H-benzocycloheptene and 2,5,9,9-tetramethyl-1,3-dinitro-6,7,8,9-tetrahydro-5H-benzocycloheptene

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#### Abstract

3,5,5,9-tetramethyl-2-nitro-6,7,8,9-tetrahydro-5H-benzocycloheptene and 2,5,9,9-tetramethyl-1,3-dinitro-6,7,8,9-tetrahydro-5H-benzocycloheptene has been synthesized using nitration reaction of ar-himachalene. Also, optimized geometry of the title compound are evaluated using HF and DFT/B3LYP with 6-31(d) basis set 6-31G(d) methods. Moreover, the <sup>13</sup>C NMR chemical shift values of the molecule (2,5,9,9-tetramethyl-1,3-dinitro-6,7,8,9-tetrahydro-5H-benzocycloheptene) are calculated using HF and DFT/B3LYP/6-31G(d) and compared with experimental results. The global of the reactivity indices and Parr functions of the reagents were calculated by HF and DFT to identify the actives regions of these molecules, we found that these reactions are regiospecific.

**Keywords:** Nitration reaction, ar-himachalene, density functional theory (DFT) and Hartree Fock (HF).

#### 1. Introduction

The bicyclic sesquiterpenes  $\alpha$ - and  $\beta$ -himachalene are the main constituents of the essential oil of Atlas cedar (*Cedrus atlantica*) (Joseph et al, 1968; Plattier et al, 1974). The reactivity of these sesquiterpenes and their derivatives has been studied extensively by our team in order to prepare new products with biological properties (Lassaba et al, 1998; Chekroun et al, 2000; El Jamili et al, 2002; Dakir et al, 2004). Indeed, these compounds have been tested, using the food poisoning technique, for their potential antifungal activity against the phytopathogen *Botrytis cinerea* (Daoubi et al, 2004). Thus, the catalytic dehydrogenation of the mixture of  $\alpha$ - and  $\beta$ -himachalene

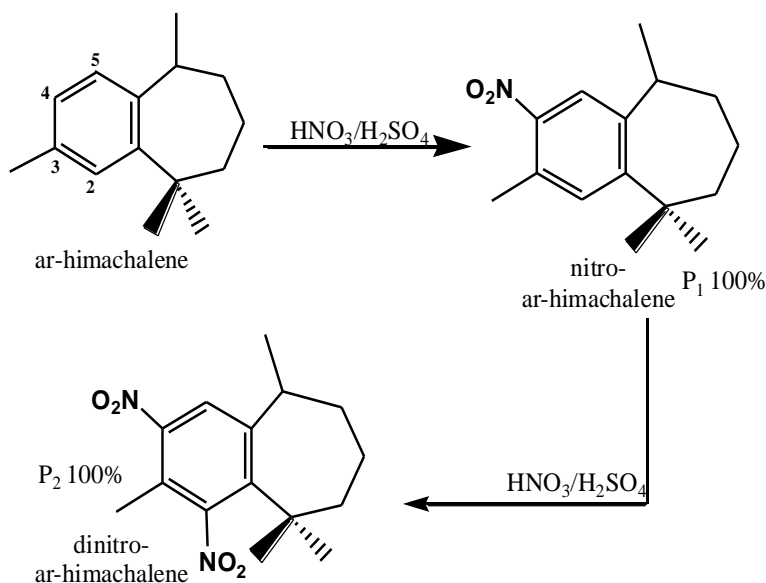
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by 5% of palladium in the charbone (10%), at 150 ° C., we obtained aryl-himachalene with a good yield, (Daunis et al, 1981). Treatment of aryl-himachalene with 1 equivalent and then with 2 equivalents of nitric acid in the presence of sulfuric acid, leads for 4 hours at room temperature, to compounds 1 and 2 (Scheme 1).

In latest years, computational chemistry has become a principal instrument for chemists and a well-accepted instrument for experimental chemistry.

Herein, in order to understand the molecular mechanism and the regioselectivity of the nitration reaction ar-himachalene (scheme 1), a theoretical characterization of the molecular mechanism of this nitration reaction is carried out within the Computational methods. We examine analyses of the reactivity indices of the reagents, Parr functions of ar-himachalene using Hartree Fock (HF) and density functional theory (DFT) methods with 6-31G(d) basis set. Our aim is to explicate the regioselectivity experimentally obtained.



**Scheme 1** the nitration reaction of ar-himachalene, 2-nitroar-himachalene.

## 2. Experimental

### General procedure for the preparation of products

In a reactor of 250 ml volume equipped with a magnetic stirrer and a dropping funnel, were introduced 60 ml of dichloromethane, 3 ml of nitric acid and 5 ml of concentrated sulfuric acid. After cooling, (30 mmol) of ar-himachalene, dissolved in 30 ml of dichloromethane was added dropwise through the dropping funnel. The reaction mixture was stirred for 4 h, then quenched with 50 ml of water ice and extracted with dichloromethane. The organic layers were combined, washed five times with 40 ml with water and dried over sodium sulfate and then concentrated under vacuum. Chromatography on a silica gel column of the residue with hexane–ethyl acetate (96/4) as eluent of the residue gave the title compounds (66%; 20 mmol).

**3,5,5,9-Tetramethyl-2-nitro-6,7,8,9-tetrahydro-5H-benzocycloheptene**, yellow oil,  $^1\text{H NMR } \delta$ : 1,2 (3H, m, CH<sub>3</sub>), 1.24 (2H, m, CH<sub>2</sub>), 1.25- 1,35 (6H, s, CH<sub>3</sub>), 1.46

(3H, d, J 6.9, CHCH<sub>3</sub>), 1.70 - 1.85 (4H, m, CHH), 2.45 (3H, s, CH<sub>3</sub>), 3,2 (1H, m, CHCH<sub>3</sub>), 2,48 (2H, s, ArCH<sub>2</sub>), 7.71 (1H, s, ArH), 7,75 (1H, s, ArH);  $^{13}\text{C NMR } \delta$ : 20.79, 21.09, 24.18, 30, 34.14, 34.78, 36.42, 40.29, 40.97, 122.21, 130.93, 131.48, 143.86, 147.25, 154.03. EIMS, m/z 247.1 (M<sup>+</sup>, 100), 232.1 (68.5), 230.1 (28), 144.1 (18), 41.1 (19). HRMS, 247.0288.

**2,5,9,9-Tetramethyl-1,3-dinitro-6,7,8,9-tetrahydro-5H-benzocycloheptene**, yellow oil,  $^1\text{H NMR } \delta$ : 1,2 (3H, m, CH<sub>3</sub>), 1.24 (2H, m, CH<sub>2</sub>), 1.25 - 1,35 (6H, s, CH<sub>3</sub>), 1.46 (3H, d, J 6.9, CHCH<sub>3</sub>), 1.70 - 1.85 (4H, m, CHH), 2.45 (3H, s, CH<sub>3</sub>), 3,2 (1H, m, CHCH<sub>3</sub>), 2,48 (2H, s, ArCH<sub>2</sub>), 7,8 (1H, s, ArH);  $^{13}\text{C NMR } \delta$ : 14.34, 20.4, 22.9, 30.34, 31.63, 34.48, 35.49, 42.51, 44.61, 122.43, 123.62, 132, 143.22, 146.38, 149. EIMS, m/z 292.1 (M<sup>+</sup>, 100), 248.1 (86), 232.1 (61.5), 230.1 (32), 144 (21), 41.1 (19). HRMS, 292.1090.

### 3. Computational methods

The equilibrium geometries have been optimized at the B3LYP/6-31G (d) calculation level on Gaussian 09 (Frisch et al, 2009), using Berny's algorithm (Schlegel, 1982). Atomic electronic populations and reactivity indices were calculated using natural population (NPA). The global electrophilicity index (Parr et al, 1999)  $\omega$ , was given by the following expression  $\omega = \frac{\mu^2}{2\eta}$ , in terms of the electronic chemical potential  $\mu$  and the chemical hardness  $\eta$ . Both quantities could be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO,  $\varepsilon_H$  and  $\varepsilon_L$  as  $\mu = \frac{\varepsilon_H + \varepsilon_L}{2}$  and  $\eta = \varepsilon_H - \varepsilon_L$ , respectively. The empirical nucleophilicity index N (Domingo et al, 2009) based on the HOMO energies obtained within the Kohn-Sham (Kohn et al., 1965), and defined as  $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$ . the nucleophilicity was referred to tetracyanoethylene (TCE). Electrophilic  $P_k^+$  and nucleophilic  $P_k^-$  Par functions were obtained through analysis of the Mulliken atomic spin density (ASD) of the radical anion and radical cation of the reagents. (El Haib et al, 2018; Zeroual et al, 2017; Zoubir et al, 2017; El Idrissi et al, 2017; Ourhiss et al, 2017; El Idrissi et al, 2017; Zeroual et al, 2015; Barhoumi et al, 2015; Ryachi et al, 2015).

### 4. Discussion

This section was divided into three parts: (1) experimental result, (2) next, an analysis of the reactivity indices of the reagents. (3) After that, predicting the regioselectivite for carrying out the aromatic nitration reaction of ar-himachalene, (3) finally, the <sup>1</sup>H and <sup>13</sup>C NMR chemical shift values of the molecule are calculated and compared with experimental results.

#### 4.1. Comparative analysis of the conceptual DFT indices of the reagents

The global HF and DFT indices, namely, HOMO, LUMO, chemical hadness  $\eta$ , the electronic chemical potential  $\mu$  electrophilicity  $w$  and nucleophilicity  $N$ , are given in table 1.

**Table 1.** HF and DFT at B3LYP/6-31G(d) HOMO, LUMO, chemical hardness, electronic chemical potential, electrophilicity and nucleophilicity in eV, of the ar-himachalene, 2-nitroar-himachalene (3,5,5,9-Tetramethyl-2-nitro-6,7,8,9-tetrahydro-5H-benzocycloheptene) and nitric acid.

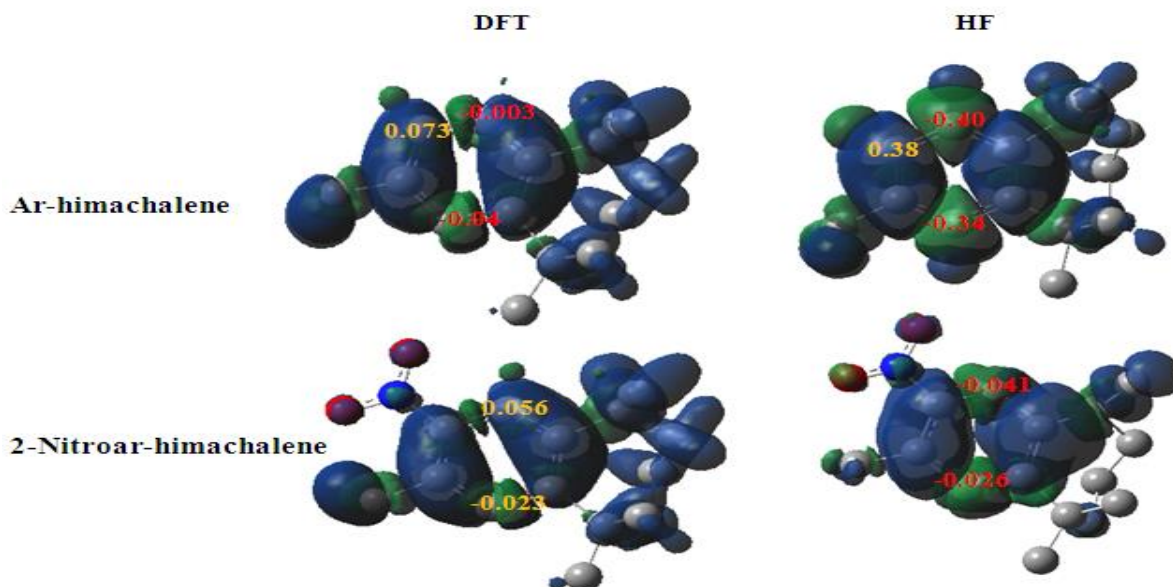
	method	HOMO	LUMO	$\eta$	$\mu$	w	N
Ar-himachalene	DFT	-5.953	0.153	6.106	-2.899	0.688	3.578
	HF	-8.138	3.923	12.061	-2.107	0.184	4.369
2-nitroar-himachalene	DFT	-6.702	-2.093	4.608	-4.397	2.098	2.829
	HF	-8.974	1.617	10.592	-3.678	0.638	3.533
Nitric acid	DFT	-8,179	-2,179	5,999	-5,179	2,235	1,352
	HF	-13,32	2,793	16,114	-5,263	0,859	-0,812

HOMO (TCE) (DFT=-9.532 and HF=-12.508)

Given the values offered in Table 1, the higher electronic chemical potential of ar-himachalene and 2-nitroar-himachalene find by DFT and HF methods, -2.899, -4.397 and -2.107, -3.678 eV respectively, than that of nitric acid, -5,179 (DFT), -5,263 (HF) eV, indicates along the interaction between these compounds the GEDT, as a determine of reaction polarity, have to take place from former toward latter which, respectively, act as nucleophile and electrophile ar-himachalene and 2-nitroar-himachalene has a low global electrophilicity  $w$  index, (0.688, 2.098) and (0.184, 0.638eV), and a elevated nucleophilicity  $N$  index, (3.578, 2.829) and (4.369, 3.533eV), being classified as weak electrophile and a strong nucleophile within the electrophilicity and nucleophilicity scales, respectively. On the other hand, nitric acid exhibits an elevated global electrophilicity  $w$  index, 2,235, 0,859eV, and a weak nucleophilicity  $N$  index, 1,352, -0,812eV, being classified as a strong electrophile but a low nucleophile.

#### 4.2. The nucleophilic $P_k^-$ Parr functions of the ar-himachalene and 2-nitroar-himachalene.

As the non-symmetric reagents, the initial two-center interaction between the most electrophilic center of the electrophile and the most nucleophilic center of the nucleophile. The nucleophilic  $P_k^-$  Parr functions, as powerful tools in the study of the local reactivity in polar processes. Therefore, the nucleophilic Parr functions of the ar-himachalene, and 2-nitroar-himachalene were examined in order to differentiate the most electrophilic and nucleophilic centers of the species involved in these nitration reactions and, thus, to explicate the regioselectivity experimentally observed (Fig. 1).



**Fig. 1.** 3D representation of the nucleophilic  $P_k^-$  Parr functions maps of the ar-himachalene and 2-nitroar-himachalene obtained by HF and DFT.

We can observe from figure 1 that the  $C_4$  carbon of the ar-himachalene molecule has a greater nucleophilic  $P_k^-$  Parr functions value of  $P_4^- = 0.073$  obtained by DFT calculation than the other atoms  $P_2^- = -0.04$  and  $P_5^- = -0.003$ , on the other hand the nucleophilic  $P_k^-$  Parr functions obtained by HF method indicate clearly that ar-himachalene have only one nucleophilic center  $C_4$  carbon,  $P_4^- = 0.38$ . We conclude that the best interaction will be between the carbon atom  $C_4$  of ar-himachalene and the nitro group in good agreement with experience. We can observe that the nucleophilic  $P_k^-$  Parr functions of the  $C_2$  carbon of the 2-nitroar-himachalene obtained by DFT ( $P_2^- = -0.023$ ) small than the  $C_5$  carbon ( $P_5^- = 0.056$ ), in opposite the result obtained by HF method indicate ( $P_2^- = -0.023$ ) high than the  $C_5$  carbon ( $P_5^- = -0.041$ ), indicating that the best interaction between the carbon  $C_2$  of 2-nitroar-himachalene and the nitro group, in total conformity with the experimental observations.

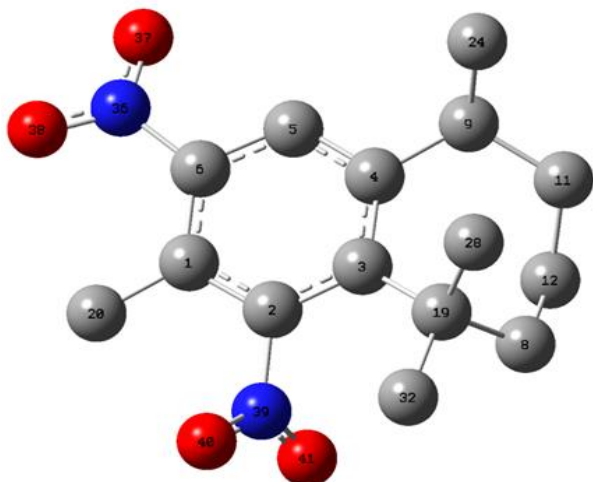
#### 4.2. NMR chemical shift analysis

Nuclear magnetic resonance is a discriminating local investigate that can give perfect information about near atomic environments. To perform this study, we employed DFT and HF combined with the GIAO method (Wolinski et al., 1990; Cheeseman et al., 1996), to calculate the isotropic electronic tensors  $\sigma_{iso}$ . The calculation of the isotropic chemical shifts  $\delta_{iso}$ , are referred to the tetramethylsilane (TMS) and obtained by the relation:

$$\delta_{iso} = -[\sigma_{iso} - \sigma_{ref}]$$

In the present analyze, the theoretical  $^{13}\text{C}$  NMR chemical shift values of title compound 2,5,9,9-tetramethyl-1,3-dinitro-6,7,8,9-tetrahydro-5H-benzocycloheptene were calculated by HF and DFT/B3LYP methods with 6-31G(d) basis set using GIAO method in the gas phase (Atoms

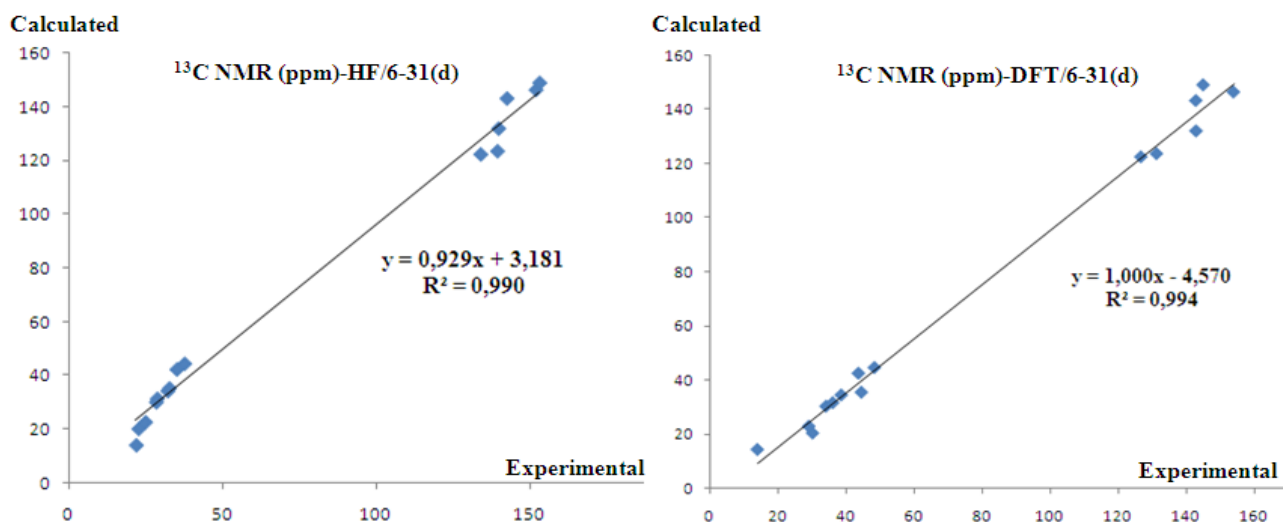
labeling is according to Figure 2). Then calculated  $^{13}\text{C}$  NMR chemical shifts were compared to the experimental values (Tables 3) and the correlation graphics of theoretical chemical shift values of  $^{13}\text{C}$  NMR are illustrated in figure 3.



**Fig. 2.** The theoretical geometric structures of the 2,5,9,9-tetramethyl-1,3-dinitro-6,7,8,9-tetrahydro-5H-benzocycloheptene

**Table 3.** Theoretical and experimental  $^{13}\text{C}$  isotropic chemical shifts for the title compound 2,5,9,9-tetramethyl-1,3-dinitro-6,7,8,9-tetrahydro-5H-benzocycloheptene (Atoms labeling is according to Figure 2).

Carbon number	HF	DFT	Experimental chemical shifts
<b>C20</b>	21.85	13.88	14.34
<b>C12</b>	22.62	30.12	20.40
<b>C24</b>	24.84	29.01	22.9
<b>C32</b>	28.38	34.08	30.34
<b>C11</b>	28.65	36.07	31.63
<b>C28</b>	32.11	38.57	34.48
<b>C19</b>	32.63	44.50	35.49
<b>C8</b>	35.08	43.61	42.51
<b>C9</b>	37.57	48.34	44.61
<b>C1</b>	134.08	126.78	122.43
<b>C5</b>	139.54	131.35	123.62
<b>C4</b>	139.91	143.00	132.00
<b>C6</b>	142.62	142.94	143.22
<b>C2</b>	152.10	154.01	146.38
<b>C3</b>	153.31	145.06	149.00



**Fig. 3.** Correlation graphics of theoretical chemical shift values of  $^{13}\text{C}$  NMR of the title compound 2,5,9,9-tetramethyl-1,3-dinitro-6,7,8,9-tetrahydro-5H-benzocycloheptene

$^{13}\text{C}$  NMR chemical shifts are reported in ppm relative to TMS. According to the results, there can be seen a good agreement between experimental and calculated values. In addition we examined the relation between experimental and theoretical chemical shift values by comparing the experimental and computed results and obtained linear function formula for Figures 2. According to the outcome, the experimental values are in good conformity with the theoretical values by B3LYP/6-31(d) level as compared to HF/6-31(d) level.

## 5. Conclusion

In conclusion, 3,5,5,9-tetramethyl-2-nitro-6,7,8,9-tetrahydro-5H-benzocycloheptene and 2,5,9,9-tetramethyl-1,3-dinitro-6,7,8,9-tetrahydro-5H-benzocycloheptene has been synthesized using nitration reaction of ar-himachalene, which are extensive importance as potential strong biologically active compounds or pharmaceuticals. In the present study also, the global of the reactivity indices and Parr functions of the reagents have been examined using the DFT/B3LYP and HF methods with 6-31(d) basis set, to understand the high regioselectivity observed in experience. In addition, from the theoretical and experimental  $^{13}\text{C}$  NMR chemical shift values, it can be observed experimental values are in good agreement with the theoretical values by DFT/B3LYP/6-31(d) level compared with HF/6-31(d) level.

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