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A theoretical study of regio and stereoselectivity nitration of thymol and carvacrol using DFT approach

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Abstract

This work is a detailed theoretical study of the nitration aromatic substitution reactions of thymol and carvacrol. In this process, a mixture of nitric and sulfuric acids is used to produce the nitronium agent NO_2^+. The computational calculations were performed at the Gaussian 09 using the DFT approaches. The first task of the computing study was to determine the optimized geometry of these compounds using the Becke three-parameter hybrid exchange functional and the Lee-Yang-Parr correlation functional (B3LYP) with the 6-311+G (d, p) basis set. Geometry optimization calculations have been carried out to find the global and local minima for reactants and intermediates, respectively, and to locate the saddle points for the transition states. The vibration frequencies have been calculated in order to check the character of the stationary points obtained after the geometry optimization. It is expected only positive frequencies for reactants, intermediates and products, but only one negative imaginary frequency for transition states. The analysis of the nucleophilic f_k^- Fukui Function and P_k^- Parr functions allows characterising the C_4 carbon atom as the most nucleophilic center of thymol and carvacrol, in clear agreement with the regioselectivity obtained. Calculation of activation energies, analysis of the potential energy surface and the Gibbs free energy indicates that this reaction takes place through a two-step mechanism.

Keywords: *Conceptual DFT; frontier molecular orbital theory; reactivity index; Transition state theory.*

1.Introduction

The nitration reaction is particularly an electrophilic aromatic substitution (EAS) in which a hydrogen atom of the aromatic ring is substituted by a nitro group (-NO_2), to functionalize an aromatic derivative. The formation of the nitronium ion NO_2^+ pass by the protonation of HNO_3 using a strong acid H_2SO_4 along the reaction pathway of $HNO_3 + H_2SO_4 \Leftrightarrow H_2NO_3 + HSO_4^-$ and $H_2NO_3^+ \Leftrightarrow H_2O + NO_2^+$.

The aromatic nitro compounds are of huge industrial importance in synthesis of pharmaceutical drugs [1], polymers and perfumes [2]. However, the early research into aromatic nitration was fuelled exclusively by their use as intermediates in the synthesis of alkaloid compounds [2]. In this work, we investigated the detailed theoretical mechanism and selectivity of thymol and carvacrol nitration by the use the nitrating agent NO_2^+. It acts as an important tool for medicinal chemist to create and develop a newer compound possessing the thymol (iso-propyl-metacresol) and carvacrol (iso-propyl-orthocresol) [3] moiety that could be better pharmacophore in term of efficiency for drug discovery. The regio and stereoselectivity are studied using the theoretical calculations based on several quantum chemistry approaches.

1. Theoretical and Computational Methods

2.1. Global reactivity indices

The quantum theories of reactivity allow, currently, not only to develop the reaction mechanisms and the energy profiles, but also to justify and predict the stereoselectivity and experimental regioselectivity. Several theories have been used for the study of the chemical reactivity. Among them the conceptual density functional theory (DFT) considered as a valuable tool for understanding the chemical reactivity and site selectivity of molecular systems and according to which the electron density is sufficient to determine uniquely all the ground state properties of atoms and molecules. We used chemical potential, global hardness, global softness, electronegativity and electrophilicity in order to predict chemical reactivity of the compounds studied. In this paper, we presented the formal definitions of all these descriptors and working equations concerning their use, and we reviewed in some detail various applications of both global and local reactivity descriptors in the context of chemical reactivity and site selectivity. For an atomic or molecular system, consisting of N electrons with total energy E and external potential v(r), the currently accepted definition of electronegativity χand chemical potential μ [4] is given by the following energy derivative.

$$\mu = -\chi = \left(\frac{\partial E}{\partial N}\right)_{v(r)} \qquad (1)$$

The chemical hardness (η) [4] introduced by Parr and Pearson, is the second derivative of energy

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(r)} \qquad (2)$$

These two values μ and η can be calculated also from the energies of the HOMO (highest occupied molecular orbital) and LUMO (the lowest unoccupied molecular orbital) frontier molecular orbitals using Eq. 3 and 4 [5].

$$\mu = \frac{(E_{HOMO} + E_{LUMO})}{2} \qquad (3)$$

$$\eta = (E_{HOMO} - E_{LUMO}) \qquad (4)$$

In order to demonstrate the nucleophilic/electrophilic nature of the reactants, we also calculated the global electrophilicity index ω[6] and the nucleophilicity index *N*[7]. Both ω and *N* are defined as

$$\omega = \frac{\mu^2}{2\eta} \qquad (5)$$

$$N = E_{HOMO(Nu)} - E_{LUMO(TCE)} \quad (6)$$

The nucleophilicity index (Nu) is referred to tetracyanoethylene (TCE) as this allows us to conveniently handle a nucleophilicity scale of positive values [8].

Besides, the maximum number of electrons that an electrophile [6] can acquire is given by the expression

$$\Delta N_{max} = -\frac{\mu}{\eta} \quad (7)$$

2.2. Local reactivity indices

Most chemical reaction in general involve a change in electron density. The Fukui function (FF) [9,10] indicates this change in electron density ρ(r) of a molecule at a given position when the number of electrons has been changed. The function itself can be quantified mathematically as follows:

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N_{electro}}\right)_{v(r)} = \left(\frac{\partial \mu}{\partial v(r)}\right)_N \quad (8)$$

The condensed FF is calculated using the procedure proposed by Yang and Mortier [11], based on a finite difference method.

$$f_k^+ = \rho_k(N+1) - \rho_k(N) \quad \text{for nucleophilic attack} \quad (9)$$

$$f_k^- = \rho_k(N) - \rho_k(N-1) \quad \text{for elecrtophilic attack} \quad (10)$$

$$f_k^0 = \frac{1}{2}(\rho_k(N+1) - \rho_k(N-1)) \quad \text{for radical attack} \quad (11)$$

Where $\rho_k(N)$; $\rho_k(N\text{-}1)$ and $\rho_k(N+1)$ are the gross electronic populations of the site k in neutral, cationic, and anionic systems, respectively. The local electrophilicity and nucleophilicity indices [12] were calculated as $\omega_k = \omega . P_k^+$, $N_k = N . P_k^-$ respectively, where Electrophylic and nucleophilic Parr functions P_k^+ and P_k^- are obtained by analysing the Mulliken spin density of the anion and the cation [13,14].

2.3. Computational details

The quantum chemistry calculations reported here were carried out using the DFT B3LYP [15,16] exchange-correlation functional method, together with the standard 6-311+G (d,p) basis set [17]. The optimizations were carried out using the Berny analytical gradient optimization method [18]. DFT B3LYP /6-311+G (d,p) was also used to study the transition states and to characterize the stationary points to verify that each transition state had one and only one imaginary frequency. The electronic populations used for the calculation of local reactivity indices were computed using natural population analysis (NPA). All calculations were performed using the Gaussian 09W suite of programs [13,19].

2. Results and Discussion

3.1. *Analysis of the reactivity indices of the reactants in the base state*

3.1.1. Prediction of the regioselectivity

In order to analyze the nucleophilic/electrophilic nature of the reactants, we used DFT B3LYP/6-311+G (d, p) to calculate the global indices shown in Table 1; the electronic chemical potential μ, chemical hardness η, global electrophilicity ω, nucleophilicity N and softness S of thymol, carvacrol and nitronium ion.

Table 1. Electronic chemical potential μ, chemical hardness η, electrophilicity ω, nucleophilicity N and softness S calculated using DFT B3LYP / 6-311+G (d,p) (eV)

System	μ	η	w	N	S	Δ*N*max
Nitronium ion	-10.9695	6.0178	9.9980	-4.8371	0.0830	1.8228
Thymol	-3.3513	5.7182	0.9820	2.9309	0.0874	0.5860
Carvacrol	-3.3217	5.7726	0.9556	2.9333	0.0866	0.5754

Table 1 shows that the electronic chemical potential μ of thymol and carvacrol is greater than that of NO_2^+. whereas the global electrophilicity index ω of NO_2^+ is greater than that of thymol and carvacrol. These results show that these two isomers behave as nucleophiles, while NO_2^+ cation behaves as an electrophile, which implies that charge transfer takes place from thymol and carvacrol to NO_2^+. The prediction of the character electrophilic/nucleophilic is well confirmed also by frontier *molecular orbital theory*. The energy gap between HOMO and LUMO of reagents shows that the most favored interaction will take place between HOMO of thymol and the LUMO of the NO_2^+ cation. The same thing is true for the carvacrol (figure1). These results have confirmed the nucleophilicity of thymol, carvacrol and the electrophilic of nitronium ion.

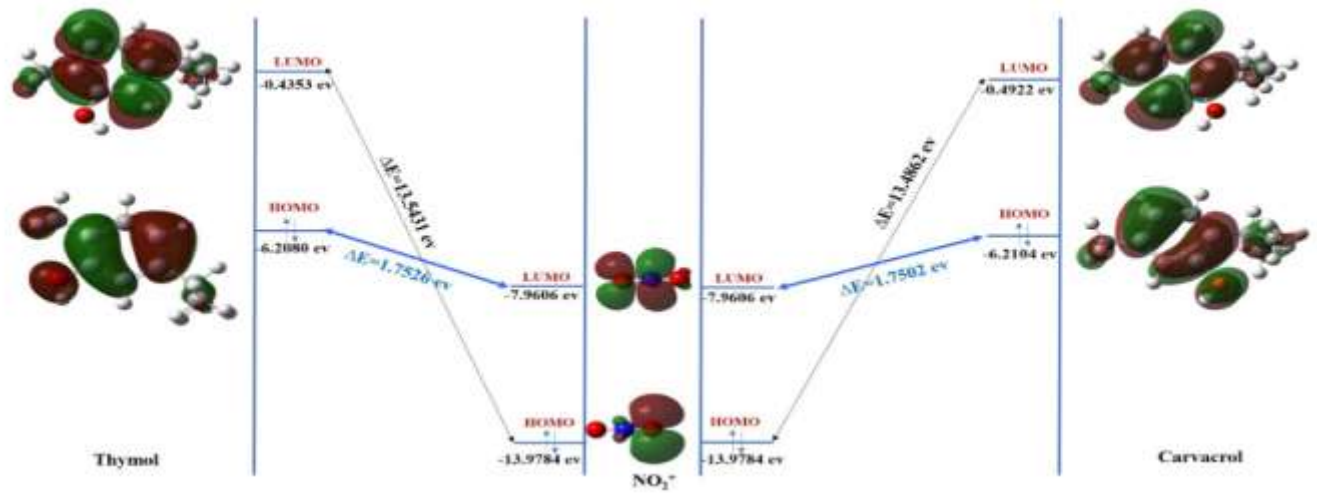
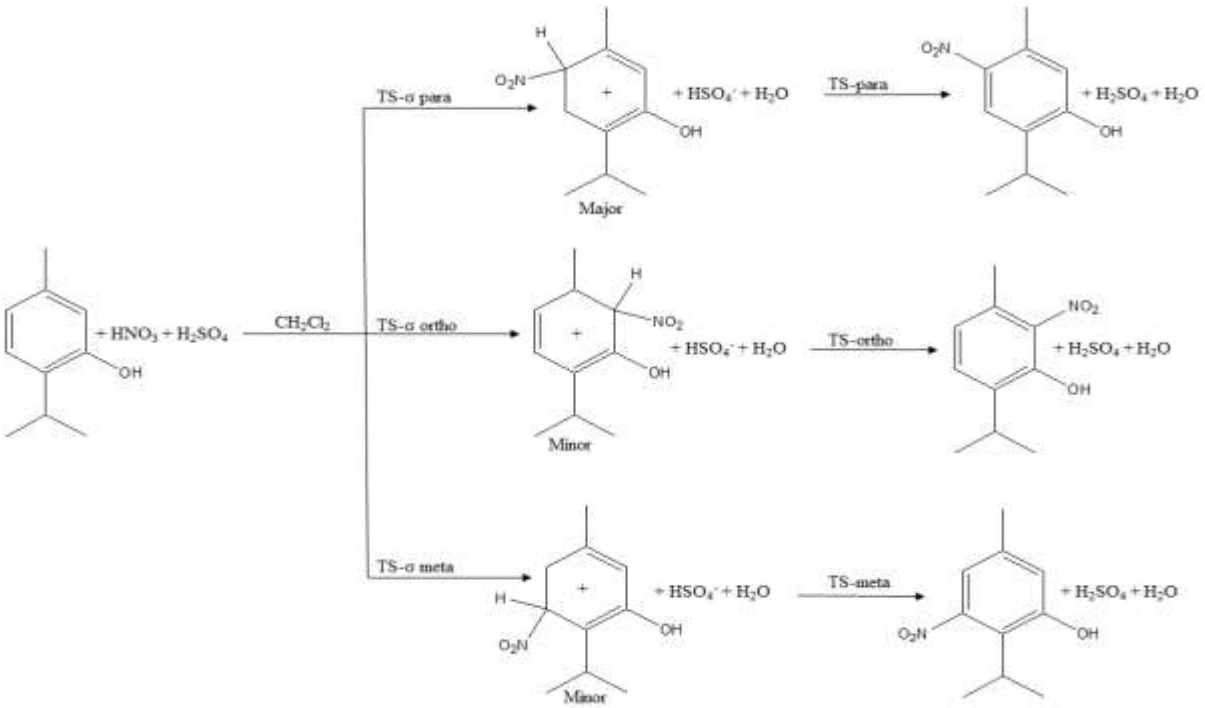


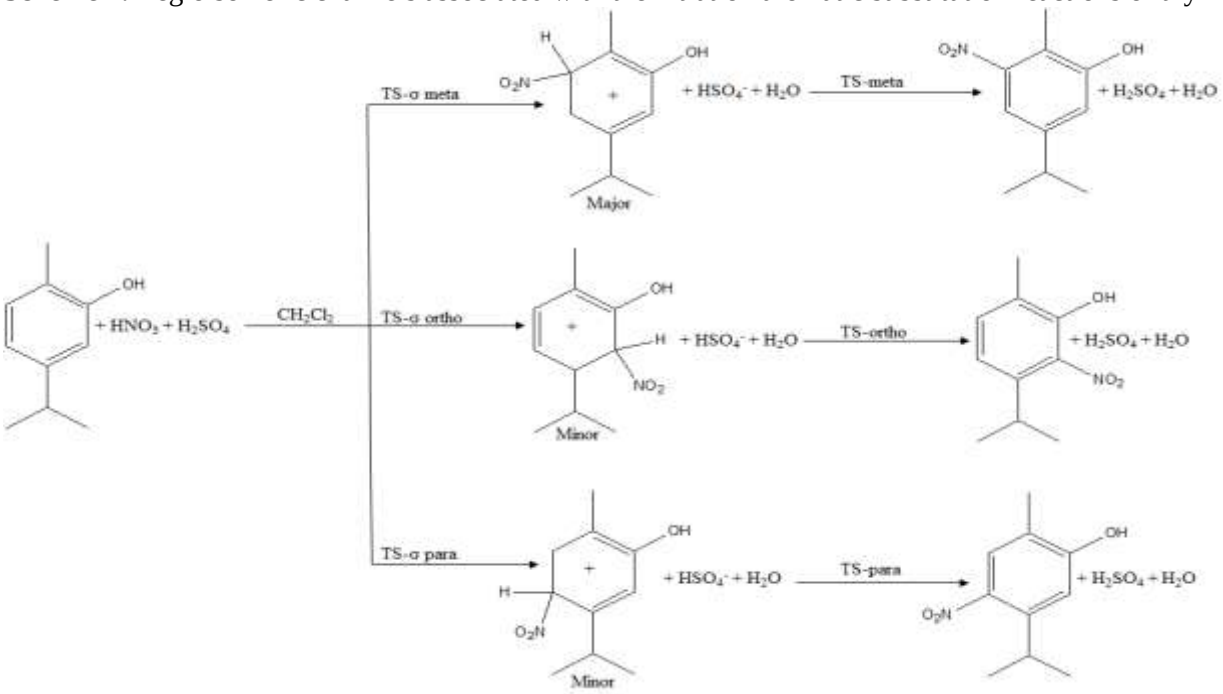
Figure 1. Energy gap between HOMO and LUMO in the reaction of thymol and carvacrol with NO_2^+ (eV)

3.1.2. Using electrophilicity and nucleophilicity indices to predict the region and stereoselectivity of the nitration reactions

Electrophilic attack of thymol and carvacrol by the NO_2^+ cation will probably be on three sites for the two isomers (C_3, C_4 or C_6 carbon) (scheme 1 and 2). We determined Fukui function and Parr function in order to predict the most likely electrophile/nucleophile interaction throughout the reaction pathway. The most favorable reactive channel was that involving the initial two- center interactions between the most electrophilic P_k^+ and nucleophilic P_k^- Parr functions center 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 $f_k^-$and $P_k^-$of thymol and carvacrol indicates that the C_4 carbon atom is the most nucleophilic center of these molecules:$f_{C4}^- = 0.2089$,P_{C4}^-= 0.3594 and$f_{C4}^- = 0.2079$,P_{C4}^-= 0.3638 for thymol and carvacrol respectively (Figure 2).



Scheme 1. Regioisomeric channels associated with the nitration aromatic substitution reactions of thymol



Scheme 2. Regioisomeric channels associated with the nitration aromatic substitution reactions of carvacrol

On the other hand, we calculated the local philicity indices ω_k, $N_k$and S_k in order to predict the most favourable initial electrophile/nucleophile interaction in this nitration reaction. The most favored interaction is that which is associated with the highest local electrophilicity index ω_k of the electrophile and the highest local nucleophilicity index N_k of the nucleophile. The indices values summarized in table 2 show that the most favored interaction will take place between the para center of aromatic compounds (possessing the highest value of N_k). Consequently, all these descriptors enable us to distinguish clearly between nucleophilic and electrophilic attacks at a particular site. The most favourable initial nucleophile/electrophile interaction along the nitration reaction of the two isomers will occur between the most

nucleophilic center of thymol and carvacrol (the C_4 carbon) and the most electrophilic center of NO_2^+ ion (the N atom).

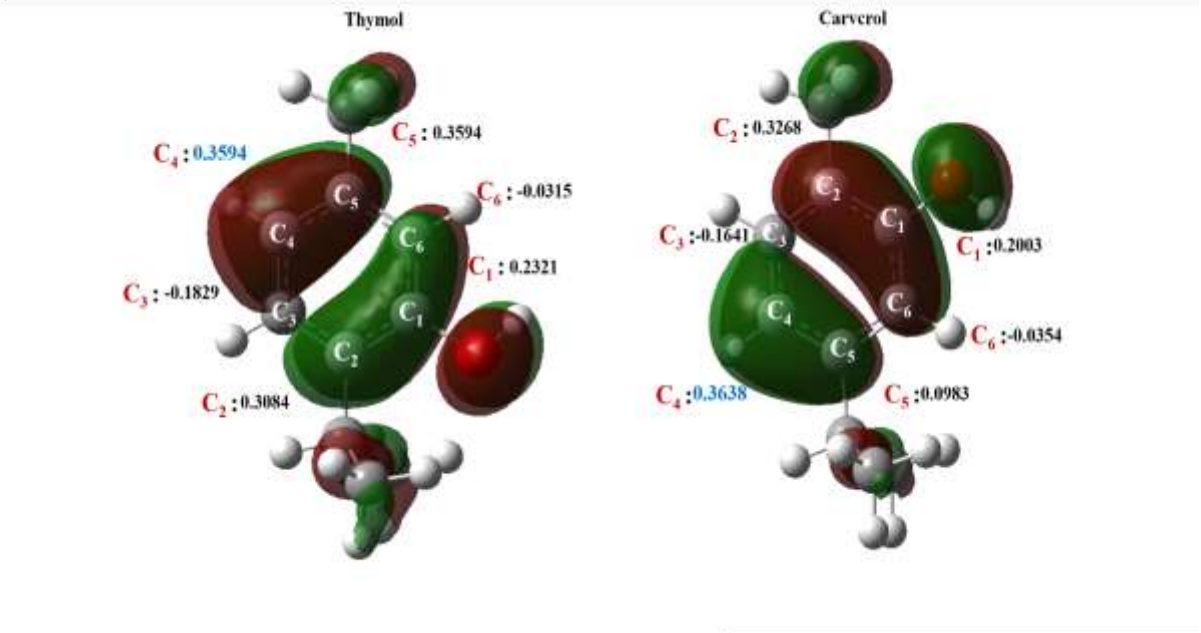


Figure 2. The nucleophilicP_k^- Parr functions of thymol and carvacrol

Table 2. Local reactivity properties of reagents calculated using DFT B3LYP/6-311+G (d,p) for NPA derived charges.

System	Site	f_k^+	f_k^-	ω_k^+	ω_k^-	N_k	S_k^+	S_k^-	Δf_k	$\Delta\omega_k$	ΔS_k
Thymol	C_3	0.2289	-0.0178	0.2248	-0.0175	-0.0701	0.0200	-0.0015	0.2467	0.2423	0.0215
	C_4	0.0085	0.2089	0.0084	0.2052	0.8214	0.0007	0.0182	-0.2004	-0.1968	-0.0175
	C_6	0.2809	0.0246	0.2759	0.0242	0.0968	0.0245	0.0021	0.2563	0.2517	0.0224
Carvacrol	C_3	0.2543	-0.0160	0.2431	-0.0153	-0.0471	0.0220	-0.0013	0.2704	0.2584	0.0234
	C_4	0.0088	0.2079	0.0085	0.1987	0.6099	0.0007	0.0180	-0.1990	-0.1902	-0.0172
	C_6	0.2371	0.0233	0.2266	0.0223	0.0684	0.0205	0.0020	0.2138	0.2043	0.0185
Nitronium ion	N	0.3592	0.4926	3.5916	4.9257	-2.3830	0.0298	0.0409	-0.1334	-1.3340	-0.0110
	O	0.2815	0.0146	2.8146	0.1462	-0.0707	0.0233	0.0012	0.2668	2.6683	0.0221

3.2. *Energy profile and geometry analyses of the thymol and carvacrol nitration*

In order to show that the nitration preferentially attacked on the C4 position. we calculated the energies of the reactants, the intermediates, the products and the transition state energies. Figure 6 summarizes the total and the relative energies for the EAS reaction of thymol and carvacrol respectively. The theoretical study of thymol and carvacrol nitration and transition states allows locating and characterising two TSs (TS-σ para and TS para) when the attack effects on C4 atom, two TSs (TS-σ ortho and TS ortho) when it is on C6 atom and two TSs (TS-σ meta and TS meta) when it is on C3 atom. Thus, indicating that it takes place through a two-step mechanism. The activation energies associated with the tree competitive channels of thymol are 25.81 (TS-σ para), 36.48 (TS para), 25.91 (TS-σ ortho), 43.92 (TS ortho), 30.96 (TS-σ meta) and 37.33 (TS meta) kcal.mol^{-1}. This nitration reaction is completely regioselective as TS-σ para is 0.1 kcal.mol^{-1} lower in energy than TS-σ ortho, 5.15 kcal.mol^{-1} lower in energy than TS-σ meta and as TS para is 7.44, 0.87 kcal.mol^{-1} lower in energy than TS ortho and TS meta respectively. The

activation energies of carvacrol are 26.27 (TS-σ para), 35.16 (TS para), 26.31 (TS-σ ortho), 47.70 (TS ortho) and 30.97 (TS-σ meta), 45.19 (TS meta) kcal.mol^{-1} and the energy levels corresponding to the attack on C4 carbon (para position) is more stable than the others. Consequently, the nitration to the two isomers is kinetically favored on the para site (C4 carbon) (Figure 3).

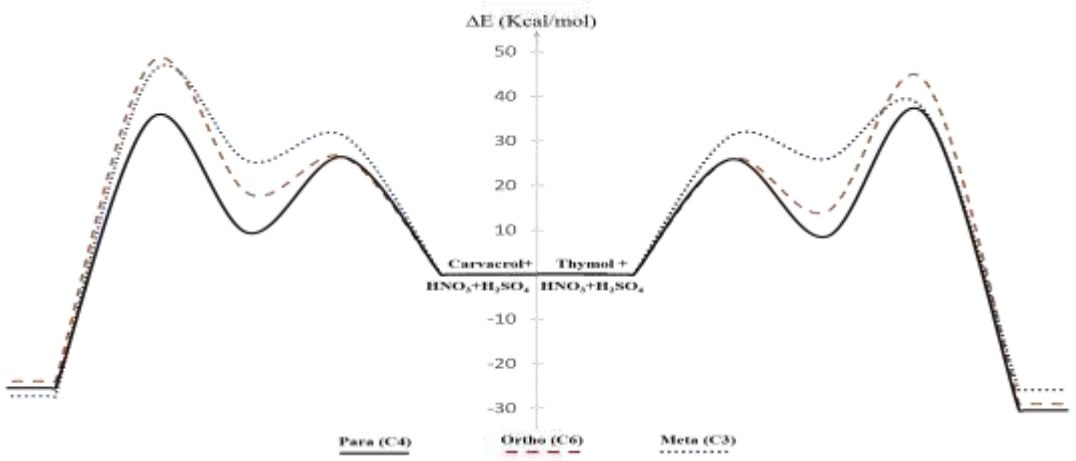


Figure 3. B3LYP/6-311+G (d.p) relative energy profile of thymol and carvacrol nitration byNO_2^+

The activation energies of σ-complexes are 8.49, 14.06 and 25.86 for σ para, σ ortho and σ meta respectively for thymol and 9.29, 18.16 and 25.39 for σ para, σ ortho and σ meta respectively for carvacrol, they showed that the formation of σ para, isomer was kinetically preferred. Values of relative enthalpies, entropies and Gibbs free energies of the stationary points involved in the thymol and carvacrol nitration are summarised in table 3. The products P1 para obtained for a stoichiometric quantity of isomers (thymol or carvacrol) with nitronium ion are strongly exergonic, by -28.064 and -24.112 kcal/mol respectively and exothermic by -30.733 and -26.409 kcal/mol respectively. Consequently, these energy results indicate that the major products P1 para obtained for a stoichiometric quantity is formed by kinetic control. The geometries of the TSs involved in the nitration of thymol and carvacrol with nitroniumcation on para position are given in Figure 4. The lengths of approach distances of the TS- σ para, intermediates and TS para are 3.66, 1.55 and 1.38 Å respectively for the thymol and 3.65, 1.55 and 1.39 Å respectively for the carvacrol

Table 3.B3LYP/6-311+G (d.p) relative enthalpies. entropies and Gibbs free energies. computed at room temperature and 1 atm. for the stationary points involved in the nitration of thymol and carvacrol

System		H (u.a)	ΔH (Kcal/mol)	G (u.a)	ΔG (Kcal/mol)
HNO_3		-280.942347	-	-280.972544	-
H_2SO_4		-700.294621	-	-700.32968	-
HSO_4^-		-699.870946	-	-699.905299	-
H_2O		-76.428509	-	-76.449939	-
Thymol	**Thymol**	-464.636699	-	-464.687705	-
	TS-σ para	-669.535420	24.342367	-669.57874	35.109812
	TS-σ ortho	-669.535323	24.403236	-669.591169	27.310490
	TS-σ meta	-669.527432	29.354917	-669.584477	31.509787
	σ para	-669.560865	8.375375	-669.618341	10.259788
	σ ortho	-669.551970	13.957077	-669.607484	17.072664
	σ meta	-669.533993	25.237824	-669.590803	27.540158
	TS para	-669.520540	33.679716	-669.576302	36.639681
	TS ortho	-669.509497	40.609309	-669.564817	43.846633
	TS meta	-669.519010	40.609309	-669.575403	37.203812
	P1 para	-669.199514	-30.733557	-669.255033	-28.064129
	P2 ortho	-669.197401	-29.407628	-669.251997	-26.159009
	P3 meta	-669.192208	-26.148969	-669.248779	-24.139682
Carvacrol	**Carvacrol**	-464.639434	-	-464.689327	-
	TS-σ para	-669.530599	29.083833	-669.587478	30.644450
	TS-σ ortho	-669.537576	24.705696	-669.593449	26.897588
	TS-σ meta	-669.530984	28.842242	-669.588085	30.263552
	σ para	-669.562183	9.264558	-669.619149	10.770581
	σ ortho	-669.548074	-17.830195	-669.603920	20.326931
	σ meta	-669.538056	24.404491	-669.595218	25.787523
	TS para	-669.525569	32.240209	-669.581675	34.285891
	TS ortho	-669.505879	44.595881	-669.560693	47.452306
	TS meta	-669.509634	42.239581	-669.566159	44.022336
	P1 para	-669.195358	-26.409386	-669.250357	-24.112071
	P2 ortho	-669.191938	-24.263302	-669.246485	-21.682353
	P3 meta	-669.197212	-27.572789	-669.254012	-26.405620

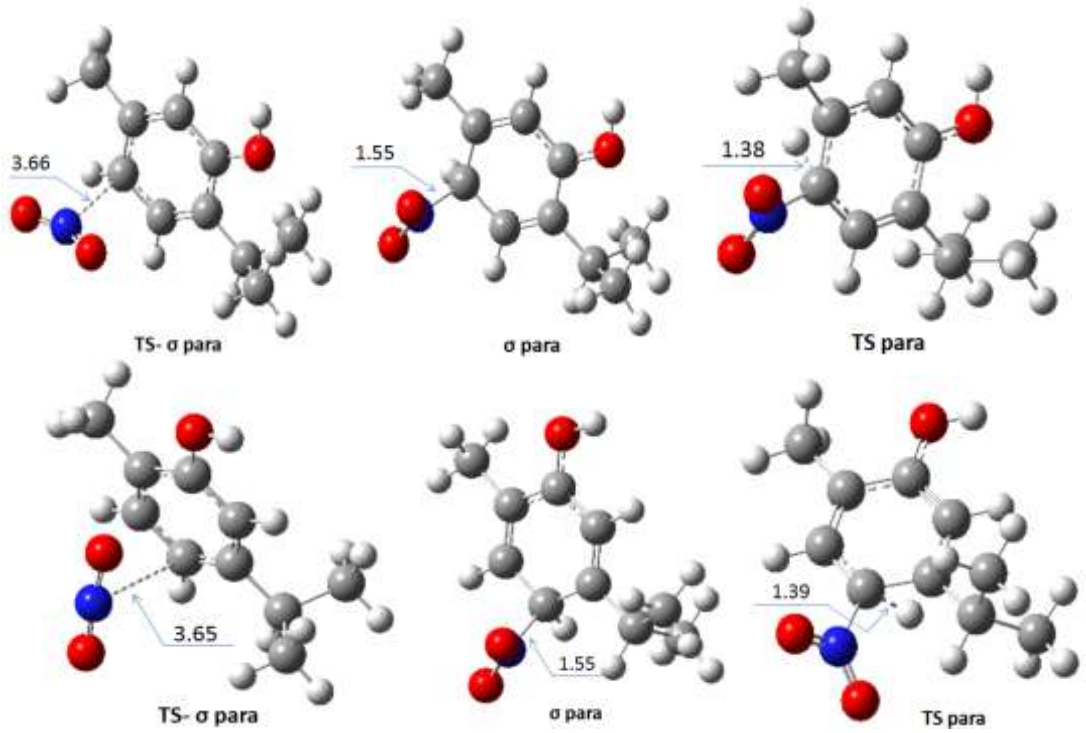


Figure 4. B3LYP/6-311+G (d.p) optimized geometries of the TSs involved in the nitration aromatic substitution reactions of thymol and carvacrol. Distances are given in Angstroms.

4. Conclusion

The mechanisms of thymol and carvacrol nitration have been theoretically investigated by using DFT methods at the B3LYP/6-311+G (d,p) computational level. The obtained results are supported by the combination of the analysis of the reactivity indices at the ground state of the reagents, derived from the conceptual DFT. The analysis of the nucleophilicf_k^- Fukui Function and P_k^- Parr functions allows characterising the C4 carbon atom as the most nucleophilic center of thymol and carvacrol, in clear agreement with the regioselectivity found. Calculation of activation energies, analysis of the potential energy surface and the Gibbs free energy G indicates that it takes place through a two-step mechanism. The para nitration of these isomers is thermodynamically and kinetically favored.

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