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Understanding the Reaction Mechanism of The Regio Selective Acylation of Isocadalene In Dichloromethane: A DFT Study.

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ABSTRACT

A theoretical study of the mechanism and selectivity of isocadalene acylation is performed at the DFT B3LYP/6-311G(d,p) computational level. The interaction between isocadalene and acyl chlorides with aluminum trichloride, AlCl₃, a Lewis acid catalyst appears to involve a two-stage mechanism. The optimizations of the stable structures were performed with the Bery algorithm, whereas the transition states were calculated using the QST2 procedure followed by the TS method. The stationary points were characterized by frequency calculations in order to verify that the transition states had one and only one imaginary frequency. These results are in good agreement with experimental outcomes.

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

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INTRODUCTION

This work is the part of our ongoing program concerning the valorisation of essential oil of the Atlas Cedar *cedrus atlantica* [1- 3]. It is one of the raw materials in perfume industry. This oil has been the object of various important studies which focused on the isolation, identification, and reactivity of its constituents [4 - 6].

The aromatic acylation is particularly an electrophilic aromatic substitution (EAS) in which a hydrogen atom of the aromatic ring is substituted by a acyl cation to form acylated products. The aromatic acyl compounds are of huge industrial importance in synthesis of pharmaceutical drugs [7, 8], polymers and perfumes [9], In our study we looked at the action of a stoichiometric quantity of acyl chlorides with aluminum trichloride, $AlCl_3$, a Lewis acid catalyst on isocadalene (figure 1), and analysed the regioselectivity of these reactions.

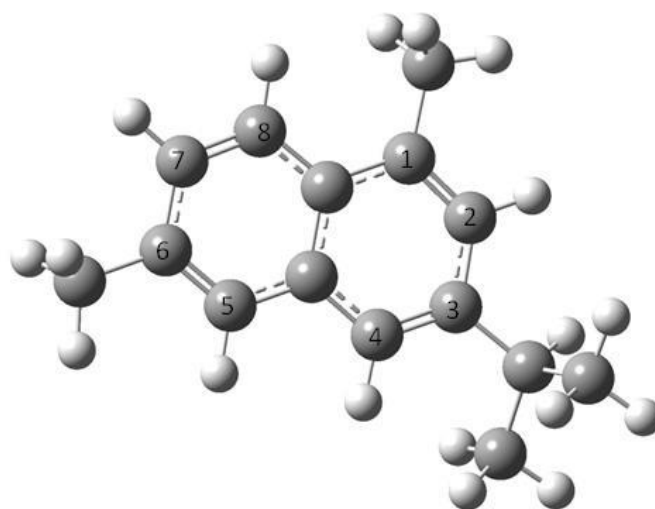


Fig 1: The optimized equilibrium structure of isocadalene (1).

The understanding of chemical reactivity and site selectivity of the molecular systems has been effectively handled by the conceptual density functional theory (DFT) [10]. Chemical potential, global hardness, global softness, electronegativity and electrophilicity are global reactivity descriptors, highly successful in predicting global chemical reactivity trends. Fukui function (FF) [11] and Parr function are extensively applied to probe the local reactivity and site selectivity. The formal definitions of all these descriptors and working equations for their computation have been described. Various applications of both global and local reactivity descriptors in the context of chemical reactivity and site selectivity have been reviewed in detail [12].

Theory and computational details

In order to demonstrate the nucleophilic/electrophilic nature of the reactants, we calculated the electronic chemical potential μ and the global hardness η . These two values can be calculated from the energies of the HOMO and LUMO frontier molecular orbitals, with

$$\mu = \frac{\varepsilon_{HOMO} + \varepsilon_{LUMO}}{2} \quad (1)$$

$$\eta = \varepsilon_{HOMO} - \varepsilon_{LUMO} \quad (2)$$

The global electrophilicity index measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment. The electrophilicity [13] is defined as

$$\omega = \frac{\mu^2}{2\eta} \quad (3)$$

High values of nucleophilicity correspond to low values of ionization potential and vice versa. Recently, Domingo et al. have introduced a relative nucleophilicity index Nu based on the HOMO energies obtained within the Kohn-Sham scheme [14 - 16] and defined as:

$$Nu = \varepsilon_{HOMO(Nu)} - \varepsilon_{HOMO(TCE)} \quad (4)$$

The nucleophilicity index Nu is referred to tetracyanoethylene (TCE) as this allows us to conveniently handle a nucleophilicity scale of positive values [17, 18].

Fukui Function (FF) is one of the widely used local density functional descriptors to model chemical reactivity and site selectivity and is defined as the derivative of the electron density $\rho(r)$ with respect to the total number of electrons N in the system, at constant external potential $v(r)$ acting on an electron due to all the nuclei in the system

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N} \right)_{v(r)} = \left(\frac{\partial \mu}{\partial v(r)} \right)_N \quad (5)$$

The condensed FF is calculated using the procedure proposed by Yang and Mortier [19], based on a finite difference method.

$$f_k^+(N) = \rho_K(N+1) - \rho_K(N) \quad \text{for nucleophilic attack} \quad (6)$$

$$f_k^-(N) = \rho_K(N) - \rho_K(N-1) \quad \text{for electrophilic attack} \quad (7)$$

$$f_k^0(N) = \frac{1}{2}(\rho_K(N+1) - \rho_K(N-1)) \quad \text{for radical attack} \quad (8)$$

Where $\rho_K(N)$; $\rho_K(N-1)$ and $\rho_K(N+1)$ are the gross electronic populations of the site k in neutral, cationic, and anionic systems, respectively.

Recently Domingo et al have proposed that Parr functions P_k as given by the following equations can be used to predict local reactivity [20]:

$$P_k^- = \rho_k^{rc} \quad (9)$$

$$P_k^+ = \rho_k^{ra} \quad (10)$$

Where ρ_k^{rc} and ρ_k^{ra} are the atomic spin densities of the radical cation and anion respectively.

When two systems with different electronegativities react together, electrons are transferred from the nucleophilic molecule to the electrophilic molecule until the chemical potentials are equal [21]. The number of electrons transferred ΔN_{\max} is calculated by the following expression [22]:

$$\Delta N_{\max} = -\frac{\mu}{\eta} \quad (11)$$

RESULTS AND DISCUSSION

Analysis of the reactivity indices of the reactants in the base state

The mechanism for the acylation of isocadalene have been theoretically investigated by using DFT methods at the B3LYP/6-311G(d,p) computational level [10, 23]. We identified the transition states and confirmed their existence by the presence of a single imaginary frequency in the Hessian matrix. We analysed the electronic structures of the stationary points and the bond orders (Wiberg indices) [24] using natural bond order method (NBO) [25, 26]. We calculated the values of enthalpies, entropies and free energies using standard statistical thermodynamics.

In figure 2, the energy difference between the two possible HOMO/LUMO combinations is given. A detailed analysis, the energy gap between the HOMO of isocadalene and the LUMO of acyl cation is 0.913 eV, while the energy gap between the HOMO of acyl cation and the LUMO of isocadalene is 12.617 eV indicating that the most favorable interaction is between the HOMO of isocadalene and the LUMO of acyl cation . Thus isocadalene behaves as a nucleophile, while acyl cation is an electrophile.

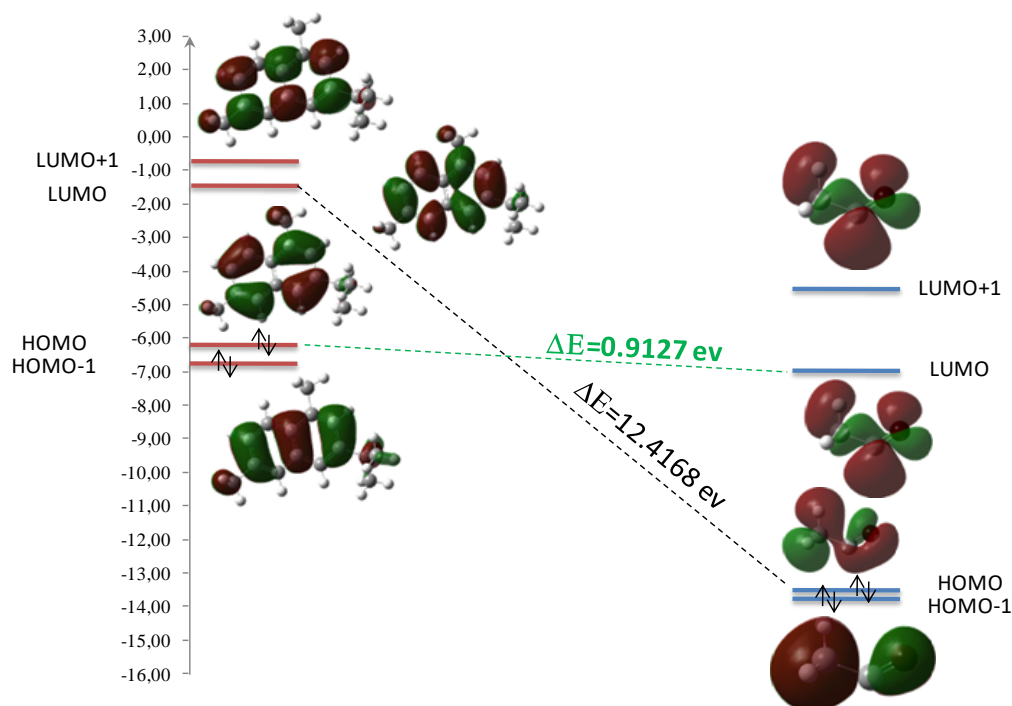


Fig 2: Interaction between the orbital borders HOMO and LUMO of the isocadalene and acyl cation calculated by DFT/B3LYP/6-311G(d,p)

In Table 1, the static global properties, namely, electronic chemical potential μ , chemical hardness η , global electrophilicity ω , global nucleophilicity N_u and global softness S indices, of isocadalene and acyl cation are reported. The electronic chemical potential of acyl cation, $\mu = -10.696$ eV, is lower than that of isocadalene, $\mu = -3.272$ eV, indicating that along a polar cycloaddition reaction path the net charge transfer ΔN will take place from the isocadalene toward the acyl cation. On the other hand, the electrophilicity index of acyl cation is 5.969 eV, a value that lies in the range of strong electrophiles on the electrophilicity scale [27], This result confirms that acyl cation will act as an electrophile whereas isocadalene will act as a nucleophile, in clear agreement with the ΔN analysis performed at the TS. The significant difference in electrophilicity ($\Delta\omega = 4.842$ eV) between isocadalene and acyl cation shows a high normal electronic demand (NED) polarity for this reaction [28].

Table 1: Electronic Calculated global reactivity properties of isocadalene and acyl cation (eV) with charge transfer ΔN_{\max} using B3LYP/6-311G(d,p)

	μ	η	ω	Nu	S	ΔN_{\max}
Isocadalene (1)	-3,272	4,749	1,127	3,722	0,105	0,689
Acyl cation	-10,696	9,583	5,969	-6,119	0,052	1,116

In order to predict the most favourable initial electrophile/nucleophile interaction in this acylation reaction, the nucleophilic f_k^- Fukui functions and P_k^- Parr functions of isocadalene and the electrophilic f_k^+ Fukui functions and P_k^+ Parr functions of acyl cation were analysed.

Analysis of the nucleophilic f_k^- and P_k^- of isocadalene indicates that the C4 carbon atom is the most nucleophilic centre of this molecule, $f_{C4}^- = 0.555 \cdot P_{C4}^- = 0.323$, On the other hand, the electrophilic f_k^+ and P_k^+ of acyl cation indicate that the C1 carbon atom is the most electrophilic site of this molecule, $f_{C1}^+ = 0.452 \cdot P_{C1}^+ = 0.632$ (see fig. 3).

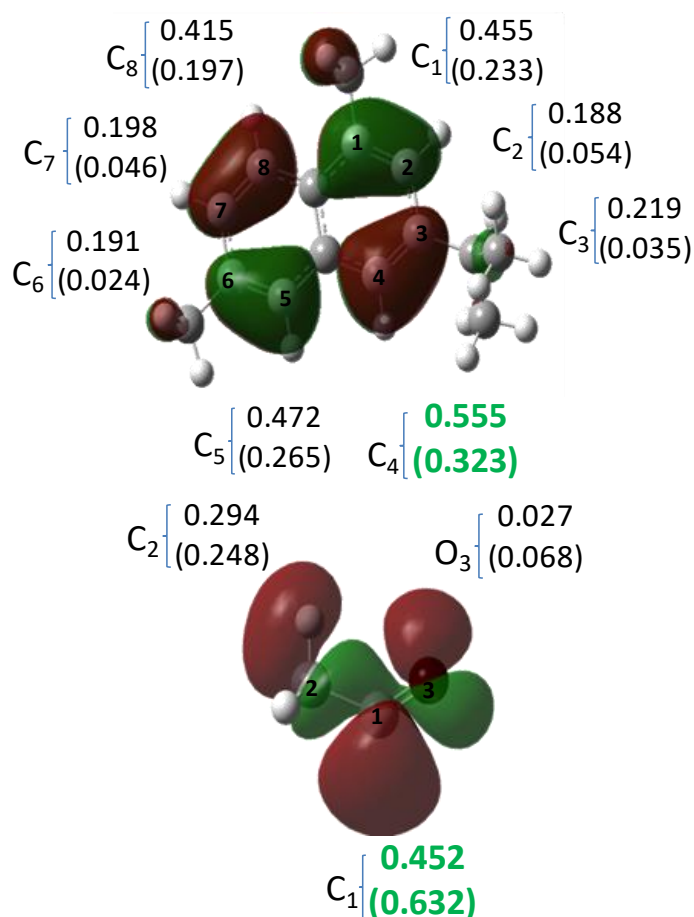
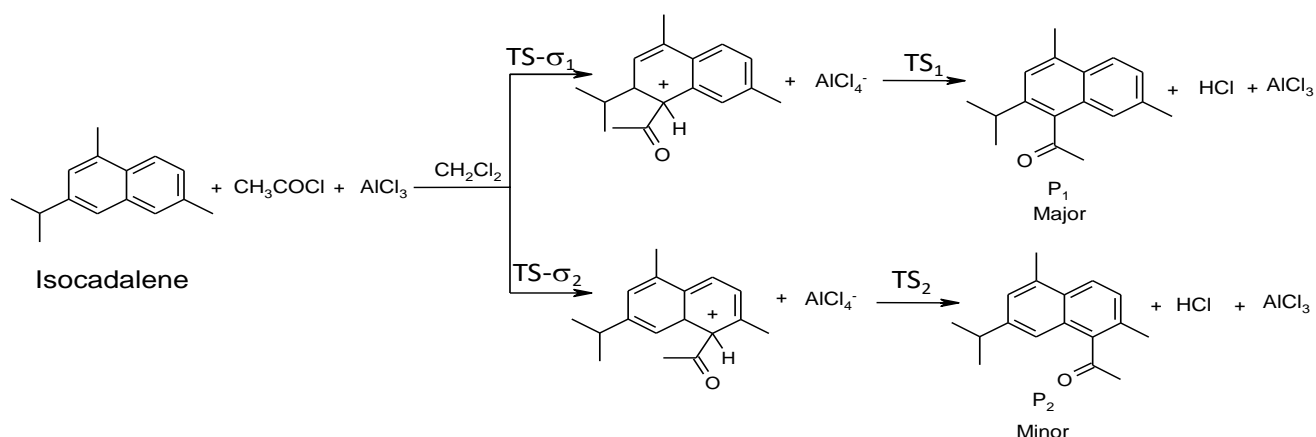


Fig 3: The nucleophilic f_k^- Fukui function and P_k^- Parr functions of isocadalene and the electrophilic f_k^+ and P_k^+ of acyl cation.

Consequently, the most favourable initial nucleophile/ electrophile interaction along the acylation reaction of isocadalene will occur between the most nucleophilic centre of isocadalene, the C4 carbon, and the most electrophilic centre of acyl cation, the C1 carbon. Furthermore, the most favourable regioisomeric

reactive channel will correspond to that associated with the C₄-C₁ bond formation, that suggest a high regioselectivity and in good agreement with the experimental outcomes. (scheme 1)



Scheme 1: Regioisomeric channels associated with the acylation aromatic substitution reactions of isocadalene

Energy profile and geometry analyses of the acylation of isocadalene

In order to show that the acylation preferentially attacked on the C₄ position, we calculated the energies of the reactants, the products and the transition states energies. Figure 4 summarized the total and the relative energies for the EAS reaction of isocadalene.

The theoretical study of reaction paths and transition states on isocadalene acylation allows locating and characterising two TSs (TS- σ_1 and TS1) when the attack affects on C₄ atom and two TSs (TS- σ_2 and TS2) when it is on C₆ atom, thus indicating that it takes place through a two-step mechanism.

The activation energies associated with the two competitive channels are 24.43 (TS- σ_1), 23.68 (TS1), 29.30 (TS- σ_2) and 26.90 (TS2) kcal.mol⁻¹. This isocadalene acylation is completely regioselective as TS- σ_1 is 4.87 kcal.mol⁻¹ lower in energy than TS- σ_2 and as TS1 is 3.22 kcal.mol⁻¹ lower in energy than TS2. Thus, the interaction between isocadalene and acyl chlorides with aluminum trichloride in dichlorocarbene is strongly exothermic; consequently. These energy results indicate that the major products P1 obtained for a stoichiometric quantity is formed by kinetic control in good agreement with the experimental outcomes.

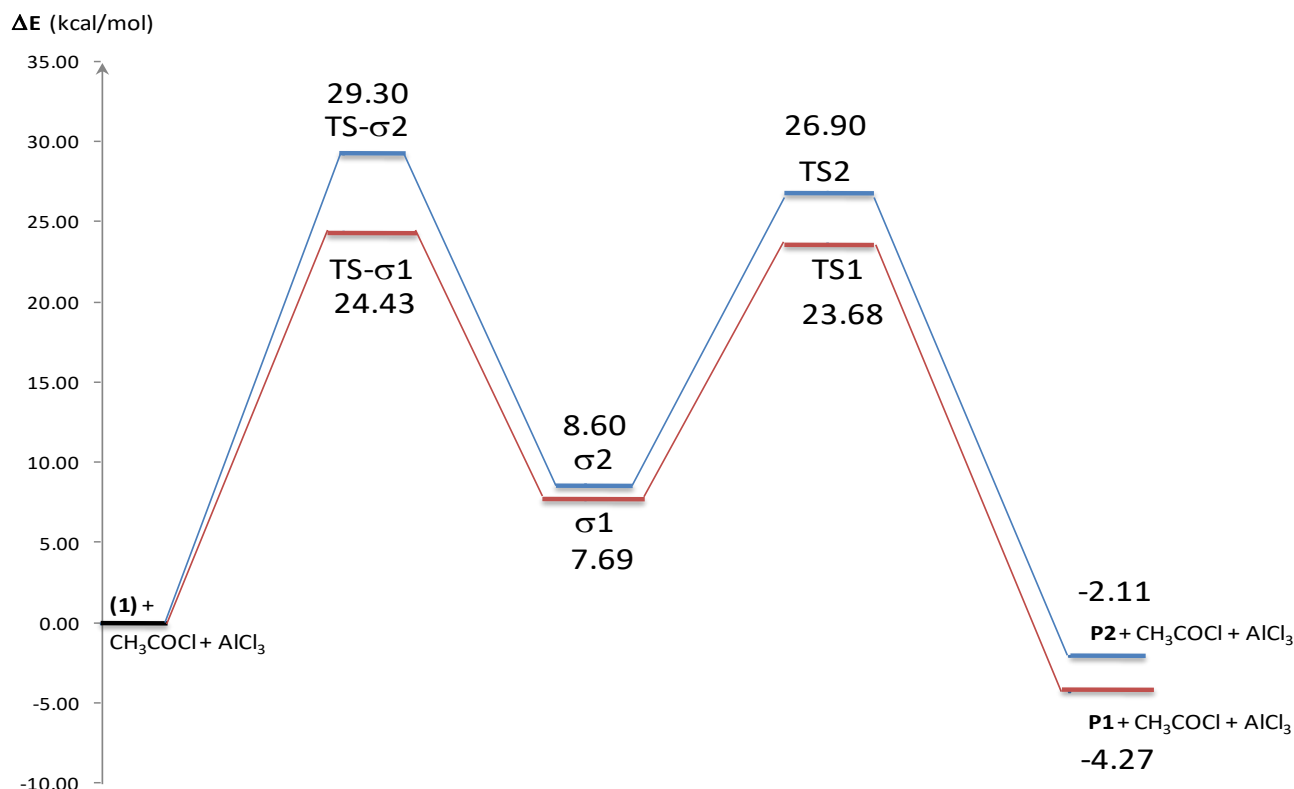


Fig 4: B3LYP/6-311(d,p) relative energy profile of acylation of isocadalene with dichlorocarbene

The activation energies of σ -complexes are 7.69 and 8.60 for σ 1 and σ 2 respectively, showing that the formation of σ -1, isomer was kinetically preferred. Values of relative enthalpies, entropies and Gibbs free energies of the stationary points involved in the isocadalene acylation are summarised in table 2.

Table 2: B3LYP/6-311G(d,p) relative enthalpies, entropies and Gibbs free energies, computed at room temperature and 1 atm, for the stationary points involved in the acylation of isocadalene

	H (u.a)	ΔH (Kcal/mol)	G (u.a)	ΔG (Kcal/mol)
Isocadalene	-582,30016	-	-582,30073	-
CH ₃ COCl	-613,47167	-	-613,50519	-
AlCl ₃	-1623,33270	-	-1623,36861	-
AlCl ₄ ⁻	-2083,80719	-	-2083,84678	-
TS- σ 1	-735,27293	15.32	-735,30608	13.60
TS- σ 2	-735,26274	21.72	-735,30472	14.46
σ 1	-735,29041	4.35	-735,31984	4.97
σ 2	-735,29397	2.12	-735,31806	6.08
TS1	-735,28987	4.69	-735,31042	10.88
TS2	-735,28220	9.51	-735,30944	11.49
P1	-734,95336	-5.02	-735,02076	-39.22
P2	-734,94963	-2.67	-735,01450	-35.29

The products P1 and P2 obtained for a stoichiometric quantity of isocadalene and acyl chlorides with aluminum trichloride in dichlorocarbene are strongly exergonic, by -39.22 and -35.29 kcal/mol respectively and exothermic by -5.02 and -2.67 kcal/mol respectively respectively. Consequently, P1 is thermodynamically preferred to P2, in agreement with the experimental outcomes.

The geometries of the TSs involved in the acylation of isocadalene with acyl cation are given in Figure 5. At the TSs associated with the regioisomeric channels 1, the length of the C4–C1 forming bonds are 2.511 Å at TS1- σ_1 , while at the TSs associated with the regioisomeric channels 2, the distance between the C6 and the C1 atoms is 3.026 Å at TS1- σ_1 . The C4-C1 bond in the TSs associated with the most favorable P1 channels was shorter than the C6-C1 one. These geometric parameters suggested an asynchronous bond formation process along the most favorable P1 regioisomer.

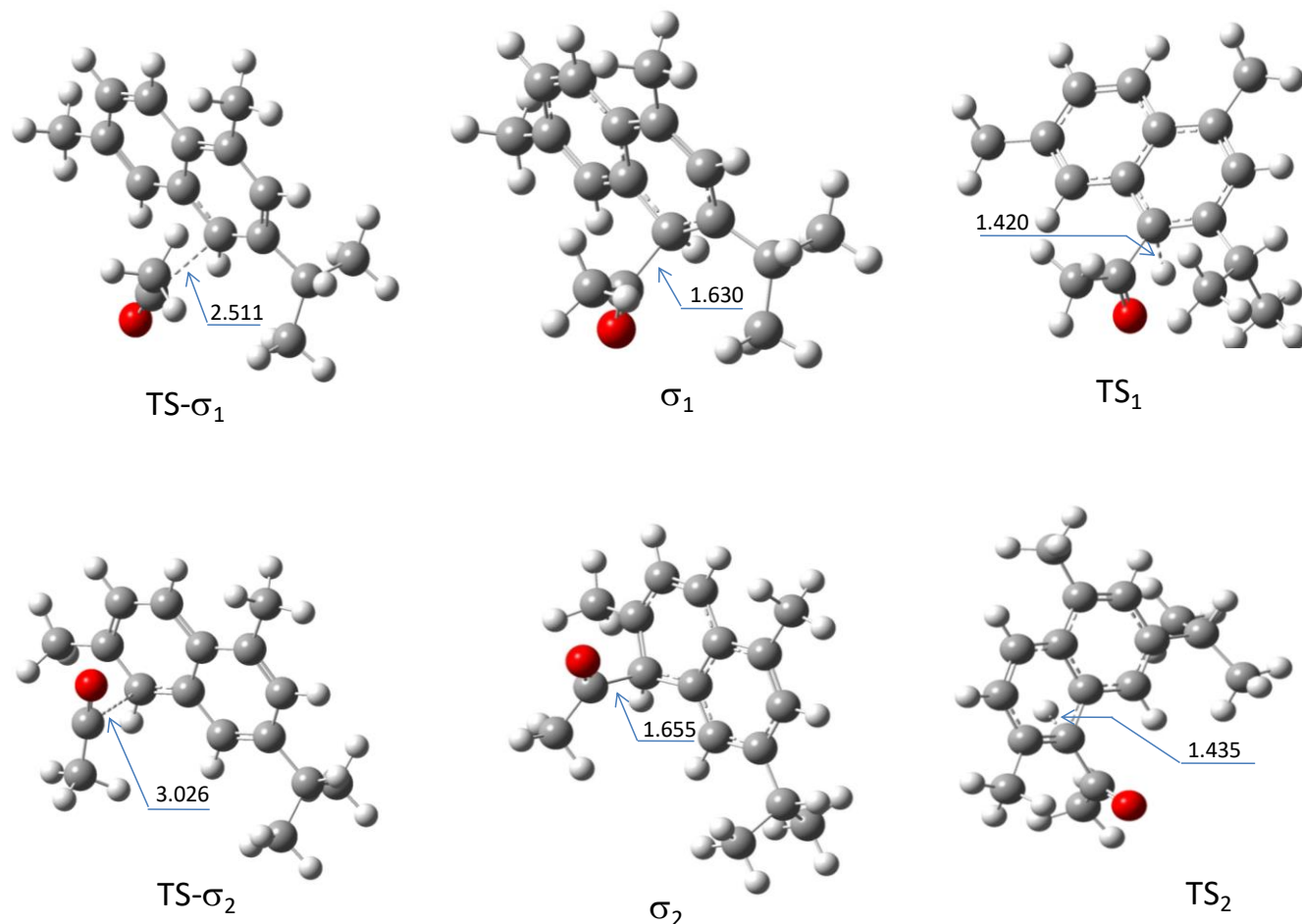


Fig 5: B3LYP/6-311G(d,p) optimized geometries of the TSs involved in the acylation aromatic substitution reactions of isocadalene. Distances are given in Angstroms.

CONCLUSION

The mechanisms of isocadalene acylation have been theoretically investigated by using DFT methods at the B3LYP/6-311G(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 nucleophilic f_k^- Fukui Function and P_k^- Parr functions allows characterising the C4 carbon atom as the most nucleophilic centre of isocadalene, in clear agreement with the regioselectivity found of isocadalene acylation. 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 isocadalene acylation is thermodynamically and kinetically favored in good agreement with experimental observations.

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