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Comparative study between the cycloaddition reaction of diazomethane with alkenes and Aromatic electrophilic substitution of pyrrole: DFT Study.

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ABSTRACT

In this work we used the MEDT method to study the mechanism and regioselectivity of the [2+3] cycloaddition (32CA) reaction between alkenes 1, 2 and 3 with diazomethane yielding a 1-pyrazoline, which participates in two competitive reaction channels, from Gibbs free energies, IRC and density maps of transition state we can concluded that in these 32CA reactions, the diazomethane will participated as strong electrophile via a two-stage one-step mechanism. The regioselectivity experimentally observed was confirmed by the activation energies and local index P0, a investigation of the reactivity and regioselectivity of pyrrole and 2-méthylpyrrole in electrophilic substitution reaction was carried out using density functional theory with B3LYP/6-311G(d,p). Positional selectivity, namely α andβ was predicted using local nucleophilic Parr functions and transition state theory. This study shows that the nucleophilicity is condensed on the α-position and thermodynamically and kinetically favored in good agreement with experimental results.

Keywords: 1, 3-dipolar cycloaddition, pyrrole, 2-méthylpyrrole, regioselectivity, diazomethane, alkenes, MEDT.

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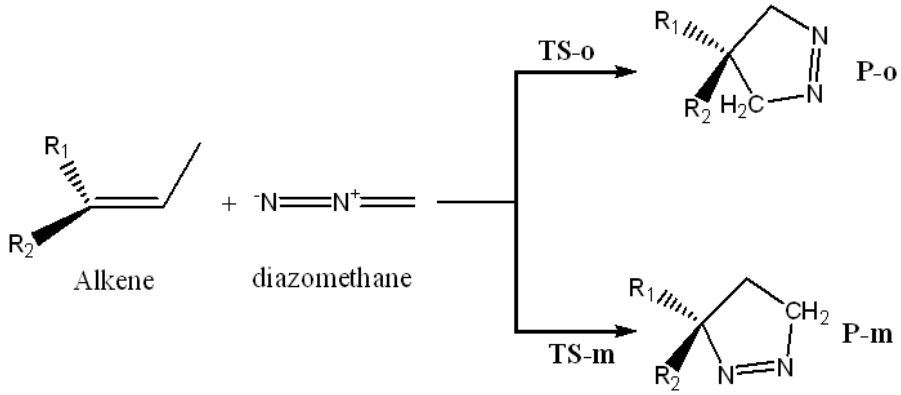
INTRODUCTION

Cycloaddition reactions are reactions relating two partners. Through the reaction, the two partners will unite to form a ring. These reactions additionally involve dipoles having four electrons! Increase in excess of three neighboring atoms [1]. Each dipole has at least one resonance structure in which the opposing charges are in a 1,3 relationship, this structural characteristic which has led to the designation of the (1+3)dipolar cycloaddition [2]. These reactions are a way of preference for the production of 5-membered ring and heterocyclic products [3] and as well utilized for the production of natural compounds like alkaloids, sugar derivatives and pharmacological products for instance pyrazolines having a number of biological activities (anti-inflammatory, analgesic and herbicides) [4]. The pyrazolines products are synthesized using the cycloaddition reactions, because these products have significant pharmacological and biological activities such as: antiviral [5], anti bacterial [6], antifungal [7], to synthesize the pyrazolines, diazoalkanes are used as a dipole which reacts with alkenes or alkynes to give cycle of five atoms (scheme 1).



Sch 1: [2+3] cycloadition reactions between diazomethane and some alkenes.

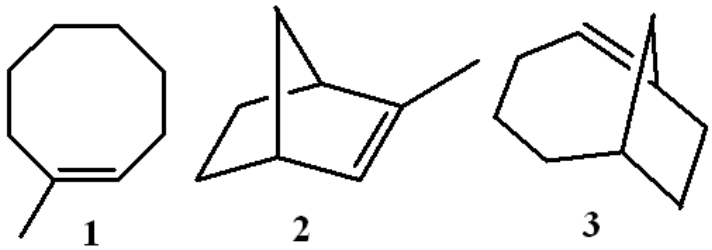
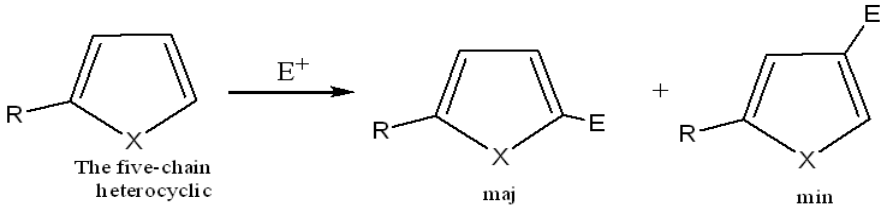


Fig 1: the alkenes study in this work (1) 1-Methyl-cyclooctene, (2) 2-Methyl-bicyclo[2.2.1]hept-2-ene and (3) bicyclo[4.2.1]non-1-ene.

The cycle of five atoms are chemical compounds whose carbon chain, cyclic, has one or more heteroatom, a lot of approach to synthesis these compounds have been developed recent years These molecules unite in one and the same structure the remarkable characteristics of the saturated, partially saturated or aromatic cyclic compounds and those no less interesting of the functional groups built around the heteroatom. The usual techniques for substitution of heterocyclic compounds habitually utilize electrophilic component like a halogen atom, Friedel–Crafts alkylation or nitration. (Scheme 2)



Sch 2 : E= Br^+, R=H, CH3. The five-chain heterocyclic compounds

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In this manuscript, we make use of the novel theory just presented by Domingo, (MEDT) to examine the mechanism and regioselectivity of the cycloaddition reaction between diazomethane and some alkenes experimentally studied by Becker et al [9] (scheme 1), and the electrophilic substitution reaction of pyrrole and methylpyrrole (scheme 2), and compared the our results with experimental upshot.

METHODS OF CALCULATION

The equilibrium geometries have been optimized at the B3LYP / 6-31G (d) calculation level on Gaussian 09 and using Berny's algorithm [10]. Atomic electronic populations and reactivity indices were calculated using natural population (NPA). The transition states, corresponding to the two ortho and meta cyclization modes, were located at the B3LYP/6-31G (d) level by QST2 and QST3, their existence was confirmed by the presence of one and only one imaginary frequency in the Hessian matrix. The IRC [11] was performed and plotted to show that the TS is well connected to both minima (reagents and product). The effect of the solvent was taken into account by a single point calculation on the geometries optimized in the gas phase and using the model PCM (polarizable continuum Model) of Tomas [12]. The global electrophilicity index [13] ω, was given by the following expression, in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities could be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, and as and , respectively. The empirical nucleophilicity index N [14-15] based on the HOMO energies obtained within the Kohn-Sham [16], and defined as the nucleophilicity was referred to tetracyanoethylene (TCE). This choice allowed us to handle conveniently a nucleophilicity scale of positive values. Electrophylicand nucleophilic Par functions were obtained through analysis of the Mulliken atomic spin density (ASD) of the radical anion and radical cation of the reagents [17- 36]. The local electrophilicity and the local nucleophilicity indices were evaluated using the following expressions and [17-47].

RESULTS AND DISCUSSION

This part has been divided in two sections: (1) DFT study reaction between diazomethane and alkenes (1, 2, 3 and 4). (2) Next, The investigation of the regioselectivity in electrophilic substitution reaction of the pyrrole and 2-methylpyrrole.

Theoretical study of the cycloaddition reaction of diazomethane and alkenes (1, 2, 3 and 4)

This section has been divided in three elements: (1) an analysis of the conceptual DFT indices of the reagents involved in cycloaddition reaction between diazomethane and alkenes (1, 2, 3 and 4). (2) Next, Relative Gibbs free energy for the stationary points of the cycloaddition reaction of diazomethane and alkenes (1, 2, 3 and 4) are explored and analyzed, (3) finally, transition states geometries are analyzed.

Analyze of the global DFT indices of reagents involved in cycloaddition reaction between diazomethane and alkenes (1, 2, 3 and 4).

The global DFT indices, namely the electronic chemical potential μ, chemical hadrnessη, electrophilicityω and nucleophilicity N, are given in table 1.

Table 1: Electronic chemical potential μ, chemical hardness η, electrophilicityω and nucleophilicity N calculated using DFT B3LYP/6-31G (d) (eV)

system	μ	η	w	N
diazomethane	-3.64	4.72	1.40	3.52
1	-2.55	6.91	0.47	3.51
2	-2.56	6.87	0.49	3.53
3	-3.23	5.48	0.95	3.55

We can concluded from table 1 the electronic chemical potentials of the alkenes 1, 2 and 3 -2.55, -2.56, -3.23 and -3.16 respectively are slightly higher than the electronic chemical potential of the diazomethane 1.40 (eV). The values of the chemical potentials are in favor, slightly, of the nucleophilic

character for the alkenes, the eletrophilicity w index of diazomethane 1.40 (eV) is much higher than the eletrophilicity of the alkenes 1, 2, 3 and 4 0.47, 0.49, 0.95 and 0.71 respectively. Which means that the diazomethane acts as an electrophile whereas the alkenes 1, 2 and 3 acts as a nucleophile.

Recently, Domingo et al. [37] proposed that the electrophilic and nucleophilic Parr functions, derived from the changes of spin electron-density, the most favorable reactive channel is that involving the initial two-center interaction between the most electrophilic and nucleophilic centers of the two reactants. We therefore analyzed the electrophilic Parr functions for reagents in order to predict the most favorable electrophile/nucleophile two-center interaction in these reactions and so explain the regioselectivity which was found experimentally (Figure 2).

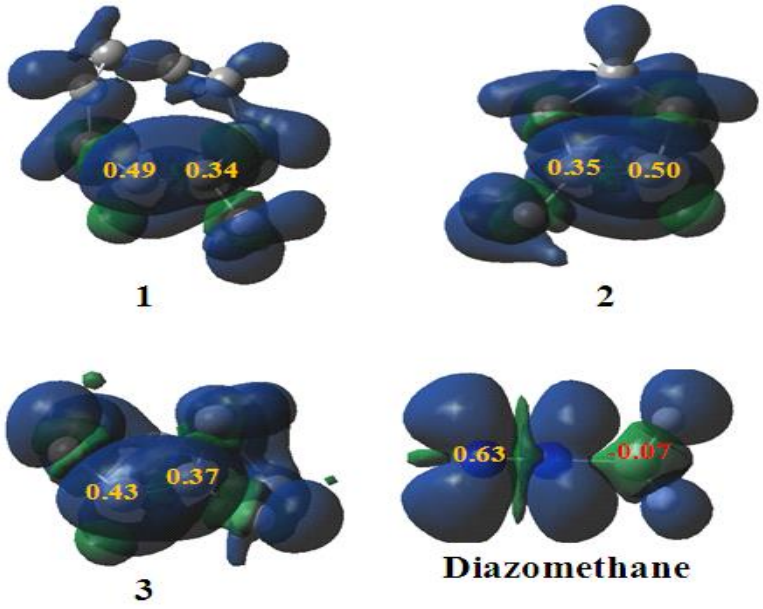

Fig 2 : Electrophilic Parr functions of diazomethane and nucleophilic Parr of alkenes (1, 2 and 3).

Analysis of the electrophilic Parr functions of the alkenes (1, 2, and 3) indicates that the carbon no substituted atom is the most nucleophilic center of these molecules, 0.49, 0.50, 0.43 and 0.49 respectively, while analysis of the electrophilic Parr functions of the diazomethane indicates that the N2 nitrogen atom is the most electrophilic center, 0.78. Consequently, the most favored nucleophilic/electrophilic two-center interaction along an asynchronous single bond formation will take place between the carbon no substituted of the alkenes (1, 2 and 3) and the N nitrogen atom of the diazomethane.

Kinetic study of the Diels-Alder 1,3-dipolar cycloaddition reaction of the alkenes (1, 2, 3 and 4) and diazomethane.

The presence of a non-symmetric dipole and the presence of one double bond the 1,3-DC reaction between the diazomethane and alkenes (1, 2 and 3) can take place through two regioisomiric approach modes, namely meta and ortho. (Scheme 1).

Table 2: Relative Gibbs free energy (ΔG kcal mol^{-1} K^{-1}) computed in gas and diethylether, for the stationary points involved in the 1,3-DC reaction between the diazomethane and alkenes (1, 2, 3 and 4).

SYSTEM	G	ΔG	G (GAS)	ΔG
1+DIAZO	-501.108427	-----	-501.105099	-----
TS1-o	-501.047187	38.42	-501.044721	37.88
TS1-m	-501.049163	37.18	-501.046690	36.65
1-o	-501.123656	-9.55	-501.118633	-8.49
1-m	-501.126366	-11.25	-501.121583	-10.34
2+DIAZO	-460.631972	-----	-460.628683	-----

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TS2-o	-460.565873	41.47	-460.563387	40.97
TS2-m	-460.569541	39.17	460.567005	38.70
2-o	-460.655422	-14.71	-460.650499	-13.68
2-m	-460.659768	-17.44	-460.655045	-16.54
DIAZO+3	-499.895522	-----	-499.892132	-----
TS3-o	-499.854234	25.90	-499.852032	25.16
TS3-m	-499.854573	25.69	-499.852032	25.16
3-o	-499.938806	-27.16	-499.933624	-26.03
3-m	-499.941701	-28.97	-499.936709	-27.97

It can be seen from table 1 that the values of the activation energies TS1-m, TS2-m and TS3-m corresponding to the meta cyclization 37.18, 39.17 and 25.90 respectively are always lower than those TS1-o, TS2 -o and TS3-o 38.42, 41.47 and 25.69 respectively corresponding to ortho cyclization. This shows that the metaregioisomers are more kinetically favored than the orthoregioisomers.

The formation of the 1-m, 2-m and 3-m products is exothermic by 11.25, 17.44 and 28.97 kcal/ mol, respectively, and the formation of the 1-o, 2-o and 3-o products is exothermic by 9.55, 14.71 and 27.16 kcal/mol, respectively, which shows that the meta regioisomers are more thermodynamically favored than the orthoregioisomers and this exothermic character of this 32CA reaction makes the cycloaddition irreversible.

Inclusion of solvent effects destabilizes all transition state, but stabilizes formation of the products in the gas phase calculations. Consequently, solvent effects increase the activation energies by 0.8 kcal mol−1 for all transition state; while for the formation of all the products they are decreases by 1 kcal mol-1 (see Table 2). Thereby, inclusion of solvent effects slightly increases the activation energies and decreases the exothermic character of this 32CA reaction but does not change the low selectivity obtained in gas phase.

The geometry of the transition states TS 1-m, TS 2-m, TS 3-m, TS 1-o, TS 2-o and TS 3-o are shown in Fig. 3.

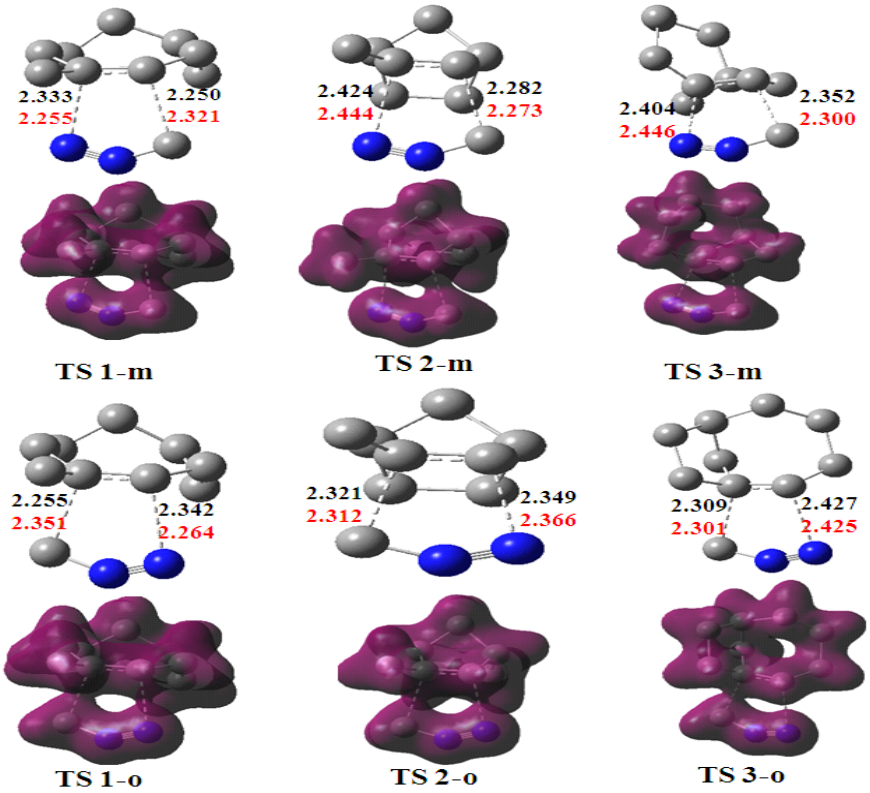

Fig 3: B3LYP/6-31G(d) optimized geometries of the TSs involved in the 1,3-DC reaction between the diazomethane and alkenes (1, 2 and 3). Distances are given in Angstroms. Distances in diethylether are given in red.

Gas-phase optimized TSs involved in involved in the 1,3-DC reaction between the diazomethane and alkenes (1, 2 and 3), including some selected distances, are given in Fig. 3. At the TSs associated with the 1,3-DC reaction between the diazomethane and alkenes (1, 2 and 3), the distances between the atoms involved in the formation of the C–C and C–N single bonds are: 2.250 °A (C1–C8) and 2.333 °A (N3–C8) at TS1-m, 2.342 °A (N3–C8) and 2.244 °A (C1–C1) at TS1-o, 2.312 °A (C1–C8) and 2.398 °A (N3–C1) at TS2-m, and 2.349 °A (N3–C8) and 2.321 °A (C1–C1) at TS2-o, 2.352 °A (C1–C) and 2.404 °A (N3–C1) at TS3-m, and 2.427 °A (N3–C) and 2.309 °A (C1–C1) at TS3-o, 2.374 °A (C1–C) and 2.349 °A (N3–C1) at TS4-m, and 2.427 °A (N3–C) and 2.309 °A (C1–C1) at TS4-O.

Some appealing conclusions can be drawn from these geometrical parameters; (i) the more favorable TS-m is associated with a highly asynchronous bond-formation process; (ii) this 32CA reaction takes place via a two-stage one-step mechanism.

Theoretical investigation of the regioselectivity of the pyrrole and 2-methylpyrrole in electrophilic substitution reaction

The present part has been study aromatic electrophilic substitution reactions of the five-ring heterocycles to understand high regioselectevity of these reactions.

Analysis of the reactivity indices of the reactants

The global DFT indices, namely the electronic chemical potential μ, chemical hadness η, electrophilicity w and nucleophilicity N, of the pyrrole, 2-methylpyrrole and Br2 are gathered in table 3.

Table 3: B3LYP/6-31G(d) electronic chemical potential, chemical hardness , electrophilicity and nucleophilicity in eV.

System	μ	η	N	ω
1	-2.39	6.77	3.58	0.42
2	-2.26	6.48	3.85	0.39
Br_2	-6.06	3.75	1.42	4.90

The electronic chemical potential of the compounds 1 and 2, μ= -2.39 and μ=-2.26 (eV) respectively are higher than that of Br2 μ= -6.06 (eV). Thereby indicating that along a polar reaction the global electron density transfer (GEDT) will go from pyrrole and 2-methylpyrrole to words Br2, the values of the electrophilicity w indices of the reagents are: 0.42 (1), 0.39 (2) and 4.90 (Br2) (eV). According to the electrophilicity scale, while Br2, is classified as strong electrophile, the pyrrole and 2-methylpyrrole are as poor electrophiles, on the other hand, the nucleophilicity N indices of the reagents, 3.58 (1), 3.85 (2) and 1.42 (Br2) (eV). Indicate that the Br2 are marginal nucleophiles as well as pyrrole and 2-methylpyrrole are strong nucleophiles. Because of these, the Br2 will be electrophile so; pyrrole and 2-methylpyrrole are nucleophiles.

The local reactivity indices of the heterocyclic compounds 1-2.

The Parr function has been for last year a powerful tool to understand the regioselectivity in polar organic reactions. The nucleophilic Parr function maps are illustrated in figure 4.

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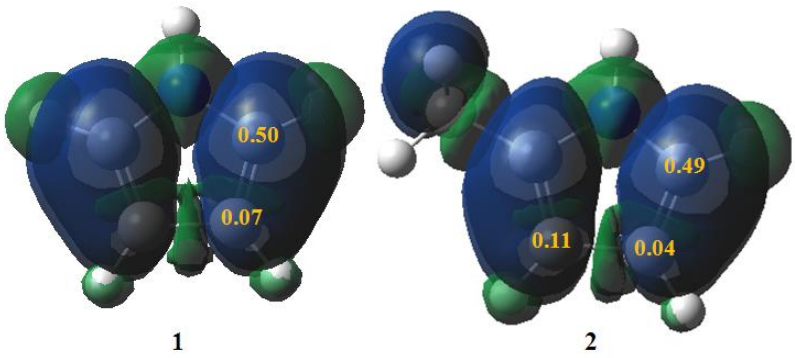


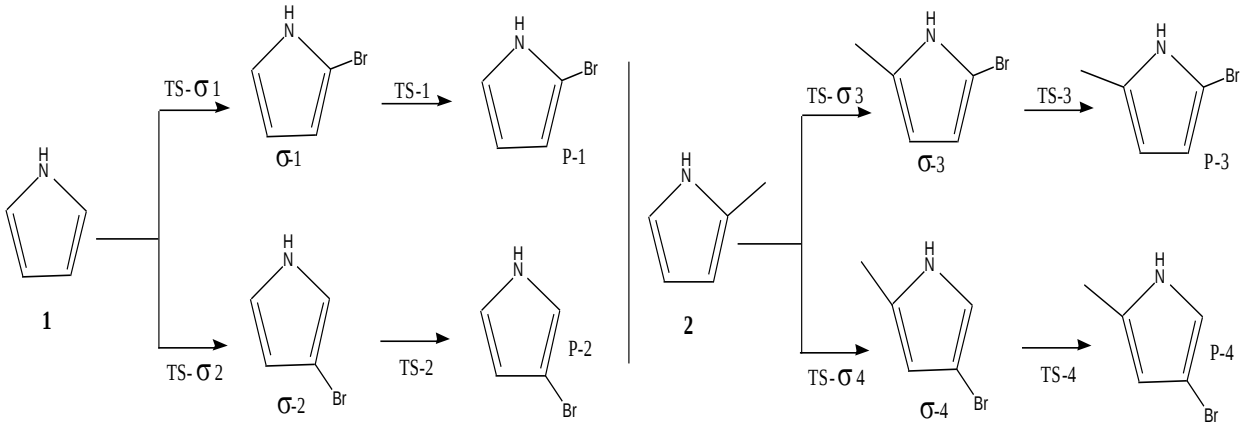
Fig 4: B3LYP/6-311G(d,p) 3D maps of the nucleophilic Parr function of the heterocyclic compounds 1-2.

The most favorable reactive channel is that where the two-centre interaction is developed between the most electrophilic centre of the electrophile and the most nucleophilic centre of the nucleophile. The electrophilic P_k^+ and the nucleophilic P_k^- Parr functions have been reported as derived from the charges of spin electron density. The most favorable single bond formation arises between the most ellectrophilic and nucleophilic centre of the reagents.

The analysis of the nucleophilic Parr function P_k^- for heterocyclic compounds indicates that the α-carbon atom of the compounds 1-2: 0.50 (α-1) and 0.49 (α-2) are most nucleophilic centers than the β-atom 0.07 (β -1), 0.04 (β -2). Hower, β-carbon atom does not participate in the eletrophilic aromatic substitution with electrophiles group. Note that α-carbon is nine more time electrophilicitty activated than β-carbon. The fact that the eletrophilic aromatic substitution reaction of the pyrrole 1 and 2, will be preferred in α-position, in good agreement with experimental observations.

Thermodynamic and kinetic study of the aromatic electrophilic substitution reactions of pyrrole and 2-methylpyrrole.

Due to the non-symmetry of both reagents, the aromatic electrophilic substitution reactions of pyrrole and 1-methylpyrol can take place through two competitive reactive channels, related to two regioisomeric approach modes (scheme 3).



Scheme 3: Regioisomeric reactive pathways associated the aromatic electrophilic substitution reactions of pyrrole and 1-methylpyrol.

The values of the Gibbs free energy G and the relative Gibbs free energy (ΔG), of the stationary points involved in the aromatic electrophilic substitution reactions of pyrrole and 2-methylpyrrole are recapitulated in table 4, the energy profile of the aromatic electrophilic substitution reactions of the pyrrole and 2-methylpyrrole is presented in figure 5.

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Table 4: Relative Gibbs free energy (ΔG kcal mol−1 K−1) for the stationary points involved in the aromatic electrophilic substitution reactions of pyrrole and 2-methylpyrrole.

system	G	ΔG
1+Br_2	-5358.51002	----------
TS σ-1	-5358.48056	18.48
σ-1	-5358.50915	00.54
TS1	-5358.47862	19.70
P1	-5358.58722	-48.44
TS σ-2	-5358.47942	19.20
σ-2	-5358.50529	02.96
TS2	-5358.47733	20.51
P2	-5358.57595	-41.37
2+Br_2	-5397.83949	----------
TS σ-3	-5397.81768	13.68
σ-3	-5397.83869	0.50
TS3	-5397.81503	15.35
P3	-5397.92719	-55.02
TS σ-4	**-5397.81258**	**16.89**
σ-4	**-5397.80855**	**3.14**
TS4	**-5397.83215**	**17.16**
P4	**-5397.91598**	**-47.99**

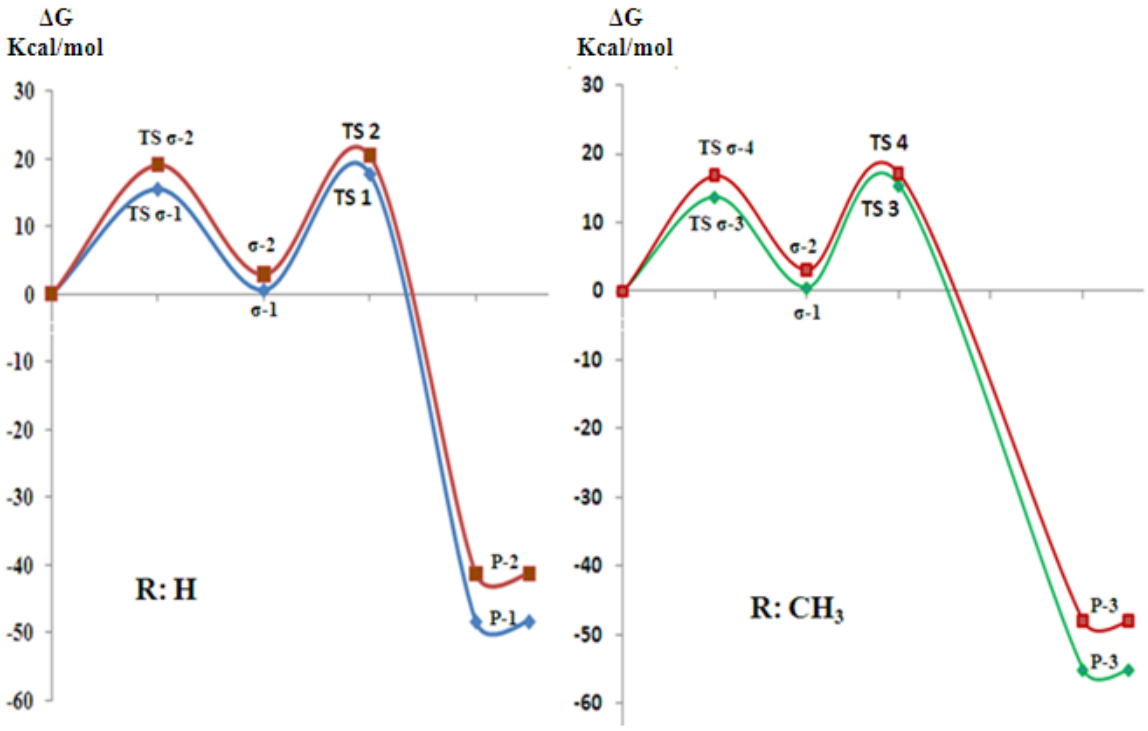

Fig 5: Energy profile (ΔG, in Kcal mol−1) of the aromatic electrophilic substitution reactions of pyrrole and 2-methylpyrrole.

We can observe as of figure 5 and table 4 that the activation energies of the σ- intermediates related by the two reactive channels of the aromatic electrophilic substitution reaction of the pyrrole and 2-methylpyrrole are 18.48, 19.20, 13.68 and 16.89for TS- σ1, TS- σ2, TS- σ3 and TS- σ4 respectively, demonstrating that the formation of the intermediates σ-1 and σ3, isomers were kinetically favored.

In addition the value of TS1 (19.70 eV) is smaller than the value of TS2 (20.51 eV) and the value of TS3 (15.35 eV) is inferior to the value of TS4 (17.16 eV) signifying that the formation of the product are P1 and P3 kinetically very favored. The reactions being exothermic by between 41.37 and 55.02 Kcalmol-1, these results indicate that the product P1 and P3 are kinetically and thermodynamically preferred in good conformity with the experimental outcomes.

The geometries of the TSs involved in the competitive reaction channels are presented in figure 3.

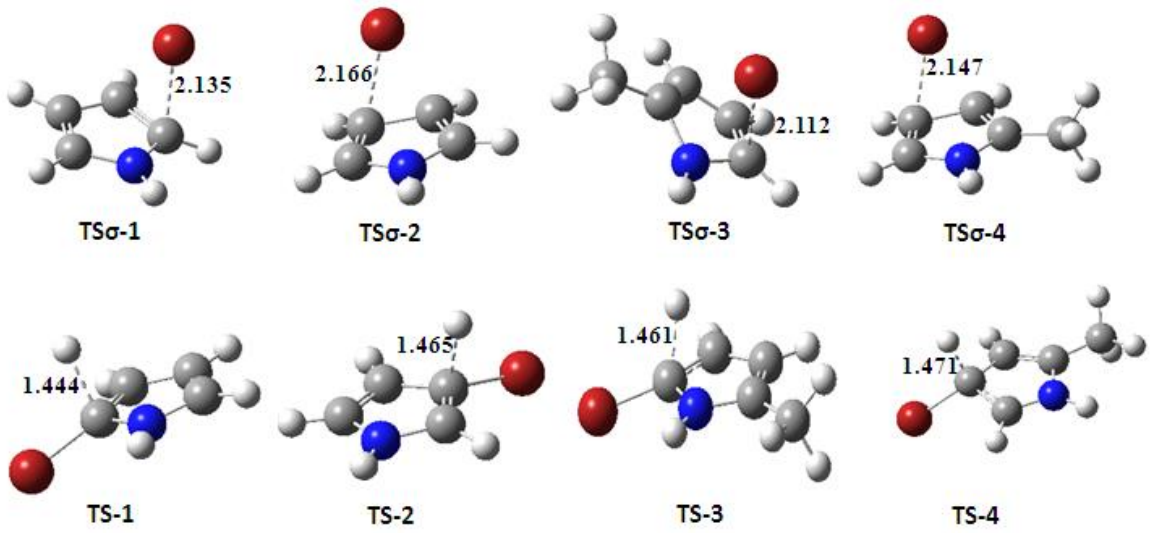

Figure 6: DFT/6-311G(d,p) optimized structures of the TSs in the aromatic electrophilic substitution reactions of pyrrole and 1-methylpyrrole. Lengths are given in Angstroms.

The lengths of the Br–C2, Br–C3 newly created bonds at the TSs associated with the 1, 2, 3 and 4 channels are 2.135, 2.166, 2.112 and 2.147 Å at TS-σ1, TS-σ2, TS-σ3, and TS-σ4 respectively, indicating that the formation of the Br–C2 bond is very favorable and we can conclude that formation of the products P1 and P3 are favored, in good accord with experience.

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