

A Density Functional Theory Study of the Isomerization of Substituted 2'-hydroxychalcones to the Corresponding Flavanones

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Summary: The transformation of 2'-hydroxychalcones to their corresponding flavanones was studied theoretically by the use of the density functional theory (DFT) with B3-LYP/ 6-311G basis set to get important information about the role of both of electronic and structural properties in this process. The obtained energies were found to be in agreement with our previous results that obtained from HPLC studies. The estimated hardness, polarizability, and electrophilicity profiles were found to obey the maximum hardness principle (MHP), minimum polarizability principle (MPP), and the minimum electrophilicity principle (MEP) respectively. Flavanone ring closure was found to be the rate-determining step.

Keywords: Chalcones, Flavanones, Isomerization, Hardness, Polarizability, Electrophilicity, MHP, MPP, MEP.

Introduction

Chalcones are compounds that have the framework of the α - β -unsaturated carbonyl system to which attached two aromatic rings [1]. Chalcones exist in two forms cis and trans, the transform is thermodynamically favorable [2, 3]. 2-Hydroxychalcone and flavanone are a family of natural products usually found in the plant kingdom [4, 5]. They are often found in fruits (especially in skin), vegetables, and plant tissue [6, 7]. Hence, it is a common component of the daily diet of human Beings. Recent studies showed variation of significant pharmacological activities include antioxidation [8], antiallergic [9], antimicrobial [10], antifungal [11], antiviral and anticancer properties [12]. However, flavones are usually synthesized from 2-hydroxychalcone via cyclization. The development of density functional theory(DFT) methods and the evolution of fast computers permit the quantitative assessment of reactivity indices such as electronegativity (χ), chemical potential (μ), hardness (η), softness (r), polarizability (α), Fukui function $f(r)$ [13]. Hardness can be defined as the resistance to change electron density or chemical potential. It can be estimated by using Koopman's approximation [14]:

$$\eta = (\epsilon\text{LUMO} - \epsilon\text{HOMO})/2 \quad (1)$$

where ϵHOMO and ϵLUMO are energies of higher occupied and lower unoccupied molecular orbitals respectively.

While the chemical potential represent the ability of the system to exchange electron density

with the environment and to break equilibrium. It can be estimated as follows:

$$\mu = (\epsilon\text{HOMO} + \epsilon\text{LUMO})/2 \quad (2)$$

It can be seen from equation below:

$$\text{Electrophilicity } (\omega) = \mu^2/2\eta \quad (3)$$

That ω is coined from the tendency to acquire an extra electron density μ , and the resistance to exchange electron density with the environment η , and that a good electrophile has a high $|\mu|$ value and low η value [15].

The static polarizability can be obtained as the mean of the diagonalized tensor:

$$\alpha = (\alpha_{xx} + \alpha_{yy} + \alpha_{zz})/3 \quad (4)$$

These reactivity parameters are better described by various electronic structure principles. The maximum hardness principle (MHP). There seems to be a rule of nature that molecules arrange themselves so as to be as hard as possible [16], the minimum polarizability principle (MMP) [17] direction of evolution of any system toward a state of minimum polarizability", and the minimum electrophilicity principle (MEP) [18] where molecules tend to decrease their electrophilicity power during a process to become less reactive species.

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Computational Methods

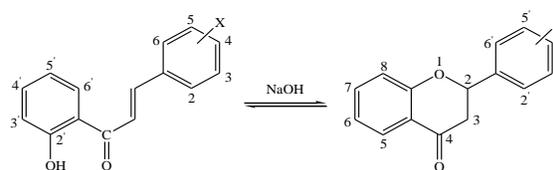
All computations were done using Orca 4.0.0 Geometry optimizations of the title compounds were performed to determine molecular orbitals energies (HOMO-LUMO) of the reactants, products, and transition state (TS) using density functional theory (DFT) with B3LYP functional and polarized double zeta basis set. A potential energy surface scan was performed to obtain a point near the TS. Then Hessian calculations were done to produce imaginary frequency and energy gap of the TS. Molecular hardness, electronic chemical potential, electrophilicity and polarizability have been calculated by applying equations 1, 2, 3, and 4 respectively.

Results and Discussion

Isomerization of 2-Hydroxychalcone-flavanone have been presented in the general scheme (1), which illustrate the transformation of reactant (R) to the product (P) through an intermediate (IM) and one transition state (TS), these species have been discussed within the concepts of hardness, polarizability, electrophilicity and relative energy.

Following the definition of hardness where it represents the resistance of a system to exchange

electron density with the environment. The result obtained for hardness is $\eta_{\text{product-intermediate}} > \eta_{\text{reactant}} > \eta_{\text{TS}}$ for all substituents, the hardness pass through a minimum for the TS, revealing an increase in molecular reactivity, followed by two maxima. This confirms that the hardness follows MHP. Since the intermediate is harder than the reactant. When the hardness was scaled in accordance with $(\eta = \eta/(\mu)^{1/3})$ [19] which showed that the hardness of the product was higher than that of the reactant i.e. MHP is obeyed. The reaction also obeys the MPP. Since the polarizability varies from the maximum for the TS more reactive and minima for the intermediate (table1) i.e. the product is the least polarizable entity less reactive (the profile is shown for each substituent in fig.1). The chemical potential goes from a higher to a lower value for all the substituents table (1), which means the change in the electronic cloud can be regarded as spontaneous. Consequently, the reaction proceeds in the formation of flavanone.



X= 3,4-Di-Cl, 2-Cl, H, 2,4-Di-OCH₃, 4-OCH₃

General equation for the isomerization of substituted chalcones to their corresponding flavanones

Table-1: Hardness (η), polarizability, (α), Relative energy (E), Chemical potential (μ) and electrophilicity index (ω) for studied compounds.

	HOMO	LUMO	η (kcal/mol)	α (au)	E(kca/mol)	μ (ev)	ω (ev)
3,4-Di-Cl (compd.1)							
R	-0.24481	-0.09591	46.71737	2.4655	-1034.405799	-0.17036	0.194913
TS	-0.18079	-0.06594	36.03419	3.3961	-1034.112774	-0.123365	0.132511
IM	-0.22326	-0.05424	53.02689	1.1822	-1034.398139	-0.13875	0.113908
P	-0.25286	-0.07927	54.46614	1.193133	-1034.747418	-0.166071	0.161831
2-Cl (compd.2)							
R	-0.25144	-0.09092	46.5636	1.97466	-746.003375	-0.17505	0.206472
TS	-0.17868	-0.06250	36.45148	3.56984	-745.709705	-0.12059	0.125167
IM	-0.21891	-0.05001	52.98924	1.4678	-745.9964725	-0.13446	0.107049
P	-0.24790	-0.07714	53.57829	1.3988	-746.0419663	-0.16252	0.155250
H (compd.3)							
R	-0.24184	-0.09496	46.0836	2.31086	-619.500881	-0.1684	0.193073
TS	-0.18038	-0.06913	34.90469	2.50352	-619.2065835	-0.124755	0.139899
IM	-0.22475	-0.05148	54.36346	1.048266	-619.4899625	-0.138115	0.110093
P	-0.24741	-0.07740	53.34064	1.5580	-619.728240	-0.162405	0.15514
2,4-Di-OCH ₃ (compd.4)							
R	-0.21926	-0.08538	42.00485	2.0723	-601.9538412	-0.15232	0.1733
TS	-0.17640	-0.05512	38.0516	2.4698	-601.0310485	-0.11576	0.110491
IM	-0.21503	-0.04284	54.02461	1.5553	-601.9420756	-0.128935	0.096546
P	-0.22616	-0.07351	47.89394	1.9983	-601.973871	-0.149835	0.147072
4-OCH ₃ (compd.5)							
R	-0.22638	-0.08725	43.65204	3.30393	-529.4666	-0.156815	0.176748
TS	-0.17647	-0.05869	36.95347	4.02971	-529.1719	-0.11758	0.11738
IM	-0.22535	-0.05042	54.88429	1.60204	-529.4575	-0.137885	0.108685
P	-0.23383	-0.07694	49.22424	2.2013	-529.4841	-0.155385	0.153894

Besides this analysis, the reactivity of the chalcone-flavanone isomerization can be analyzed through the electrophilicity of the species involved, since it showed the validity of MEP in which the product was lower than that of the reactant.

The other side of this analysis is to bring down these theoretical outcomes on the experimental results that were previously found. Although η and ω are both related, η can be considered as dynamic value while ω is a kinetic value.

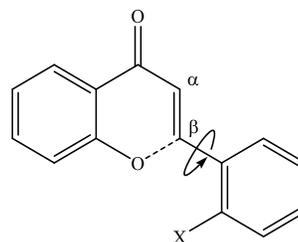
As the difference in hardness between the product and the reactant increase, the occurrence of the reaction is more likely. In this work, $\Delta\eta$ of the chalcone- flavanone isomerization will follow the trend di-Cl > Cl > H > di-OMe > OMe as shown in (table 1). This trend is in coincidence with that of ΔG^\ddagger for this reaction since the less the ΔG^\ddagger of the reaction the greater likelihood of the reaction (Table 2). Furthermore, the product is less electrophilic than the reactant for all compounds due to ring closure (Table 1) i.e. the reactivity decrease.

Table-2: Some physical parameters and entropies of activation.

X	E/kJ.mol ⁻¹	A-factor/min ⁻¹	ΔS^\ddagger /JK ⁻¹ mol ⁻¹ at 308 k	ΔG^\ddagger kJ.mol ⁻¹
(H)	1290.2	-231.47	184.7×10^5	5.9219
(2-Cl)	1162.8	-232.58	138.0×10^4	5.0770
(OCH3)	1622.4	-229.47	634.6×10^5	6.6811
(Di-OCH3)	1468.6	-230.08	283.2×10^5	6.0195
(Di-Cl)	1121.1	-232.79	183.5×10^3	4.7055

In conclusion, it seems from the above context that the theoretical descriptors obtained are in accord with experimental descriptors obtained in the previous study.

In general, reactions that involve electron-withdrawing groups (EWGs) have activation energy lowest than those with electron-donating groups (EDGs). Thus, the activation energies for compounds 1&2 are -1034 and -746 kcal/mol respectively, while the unsubstituted one possesses -619 kcal/mol. In contrast compound 4 activation energy is -601 kcal/mol and finally compound 5 which possesses the highest value -529 kcal/mol. These results can be attributed to both electronic and steric factors that affect on the reaction center i.e. β -Carbon:



Since the electron-withdrawing groups (3,4-Di-Cl and 2-Cl) activate the reaction center toward nucleophilic attack of the phenoxide ion, taking in our account the differences between the two substituents, since the

3,4-Di-Cl substituent possesses the lower value of activation energy compared with 2-Cl substituent, because the latter affects on the reaction center not only by electronic factor but also with steric factors, consequently the reaction is slightly inhibited compared with the Di-Cl substituent.

On the other hand electron-donating groups represented with 2,4 Di-OCH₃ and 4-OCH₃ have the highest activation energy compared with those of electron-withdrawing groups and the unsubstituted one, and here again, the electronic factor affect on the reaction center (i.e. inhibit the reaction rate). These results can be illustrated in (table 1), which came with a good agreement with a previous study which showed that the rate of reactions of compounds with EWGs are faster than those with EDGs as shown in table (3).

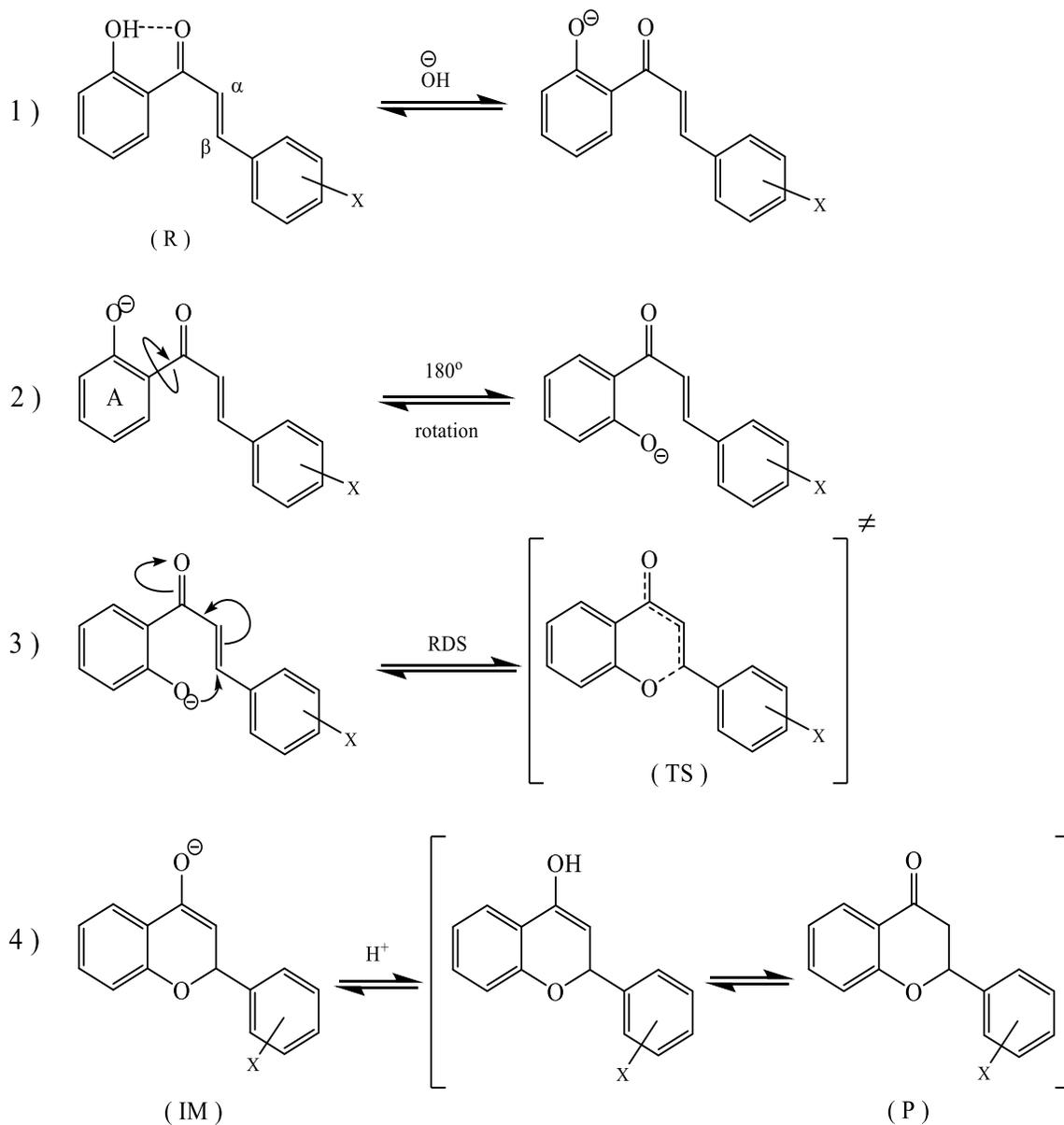
According to the above mechanism the reaction proceeds throughout the formation of one transition state (TS) and an intermediate (IM) that tautomerized to the final product (P).

Clearly, we can see that the reaction demands lower energy value in order to get to the T.S especially with the Di-Cl derivative, which transformed to the more stable intermediate with lower energy value compared with the T.S. that on tautomerization produce the product (most stable flavanone).

The same behavior was shown by 2-Cl derivative but with higher energy value for the same reason that mentioned previously fig. (1a and b).

Table-3: Reaction rate constant for the isomerization of chalcone-flavanone.

Temp. K	Com.1 10 ² k/min	Com.2 10 ² k/min	Com. 3 10 ² k/min	Com. 4 10 ² k/min	Com. 5 10 ² k/min
298	8.35	6.25	6.31	5.46	3.31
303	12.52	11.81	8.86	7.98	6.23
308	15.92	13.77	10.24	9.53	7.36
313	19.54	14.72	13.34	10.86	9.78
318	27.62	19.24	17.89	15.56	13.95



X = 3,4-Di-Cl, 2-Cl, H, 2,4-Di-OCH₃, 4-OCH₃

Scheme-1: Mechanism for the transformation process of chalcone-flavanones.

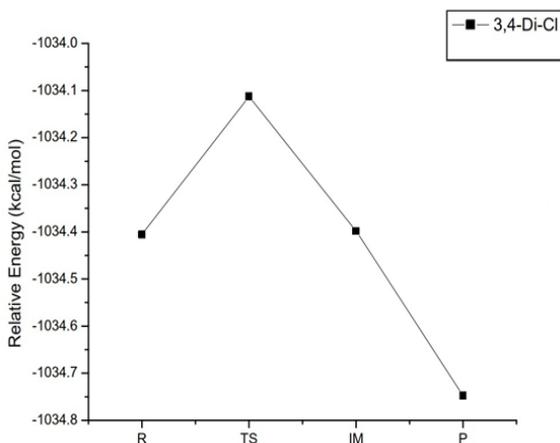


Fig. 1: (a): relative energy for 3,4-Di-Cl substitution.

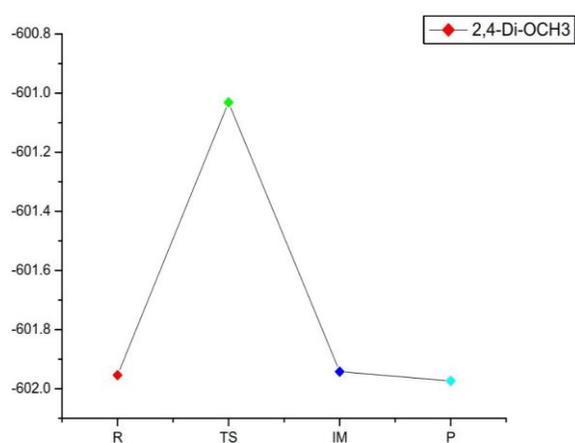
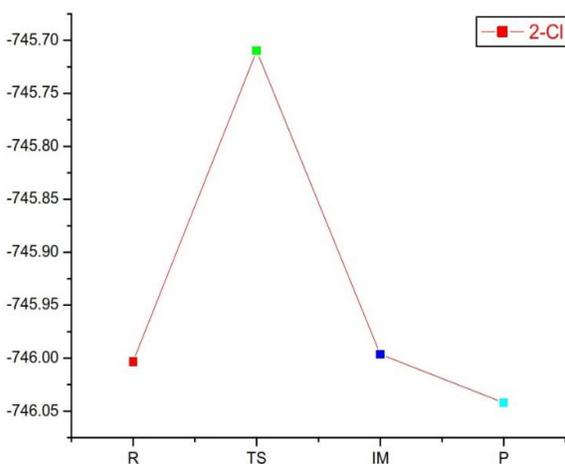
Fig. 1: (d): relative energy for 2,4-Di-OCH₃ substitution.

Fig. 1: (b): relative energy for 2-Cl substitution.

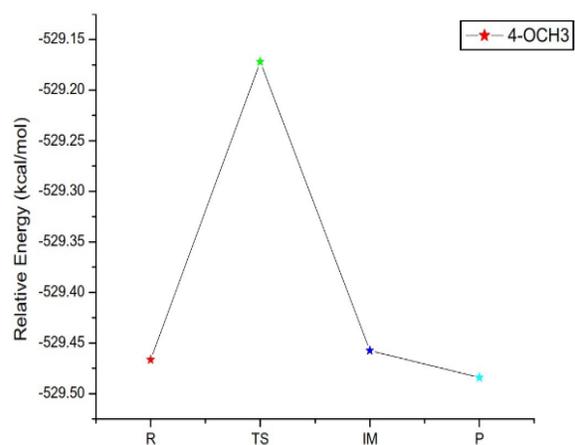
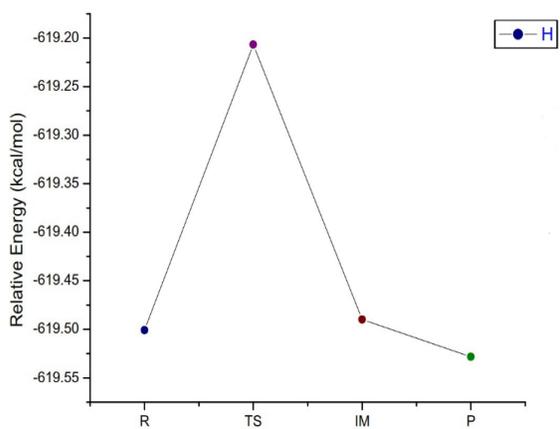
Fig. 1: (e) relative energy for 4-OCH₃ substitution.

Fig. 1: (c): relative energy for 2-Cl unsubstituted.

On the other hand, reactions that involve (EDGs) proceed with the same manner but with higher energy value due to the deactivation of the reaction center Fig. 1 (d and e) respectively, i.e. the barrier highest to pass from the reactant to the intermediates are lower for compounds with EWGs compared with those with EDGs.

Furthermore, since the energy gap between the reactant and product is quite small, an equilibrium state was established between the reactant and the product with a slight predomination of the product.

The present results were confirmed by our previous study which revealed that there is a relatively close ratio between the reactant and product during the first hour of reaction which increased then toward the product as shown in Table (4).

Table-4: Flavanone - chalcone ratio after time.

Comp. No.	R. time (flavanon) min	R. time (chalcone) min	Ratio (flavanone:chalcone)% After 1 hour	Ratio (flavanone:chalcone)% After 48 hours
1	3.78	4.88	(61.64:38.36)	(80.74:19.26)
2	3.43	4.19	(55.80:44.19)	(73.92:26.08)
3	2.86	3.92	(47.63:52.37)	(67.55:32.45)
4	2.87	3.36	(44.72:55.28)	(62.74:37.26)
5	2.76	3.34	(41.62:58.38)	(58.49:41.51)

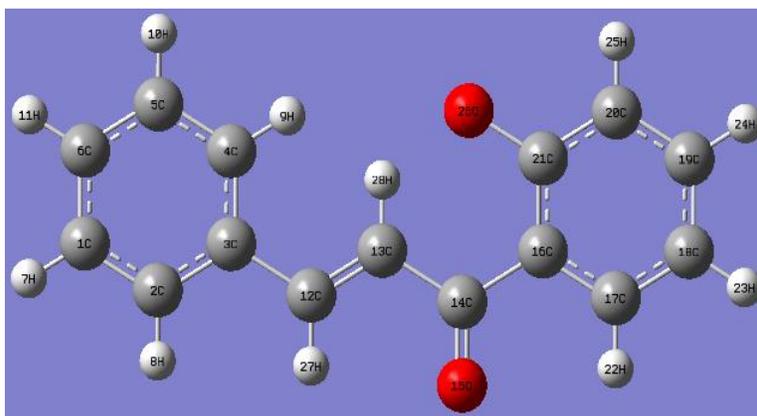


Fig. 2: The transition state.

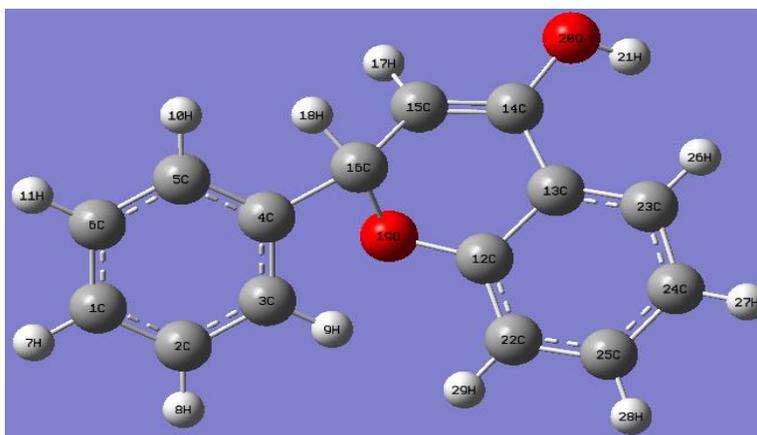


Fig. 3: The Intermediate.

The structure of the TS for these reactions was shown in fig. (2) in which the distance $C_{12}-C_{13}$ is varied from (1.337 to 1.437 Å) with slightly difference, due to the partial cleavage of π bond. The other important distance is $C_{14}-O_{15}$ which varied from (1.208 to 1.308 Å) with slightly differences between the substituents.

In fig.(3) the structure of intermediate was illustrated, which showed that the distance of $C_{14}-C_{15}$ varies from 1.357 to 1.337 Å due to the formation of newly π bond, furthermore the $C_{14}-O_{20}$ distance is varied from 1.355 to 1.455 Å due to the completely cleavage π bond with slightly difference with the substituted compounds.

As we mentioned previously, the larger the HOMO-LUMO energy gap fig. (4), the harder, the more stable and less reactive molecule [20]. Thus, the product (flavanone) is more stable than the starting (chalcone) since it possesses a larger gap as shown in table (1). Furthermore, from the same table, we can note that substituents play an important rule in product stability since compounds with EWGs are harder than those with EDGs i.e. resulting in the formation of a more stable product. As a consequence, the reaction goes faster toward the formation of flavanone Fig. (5).

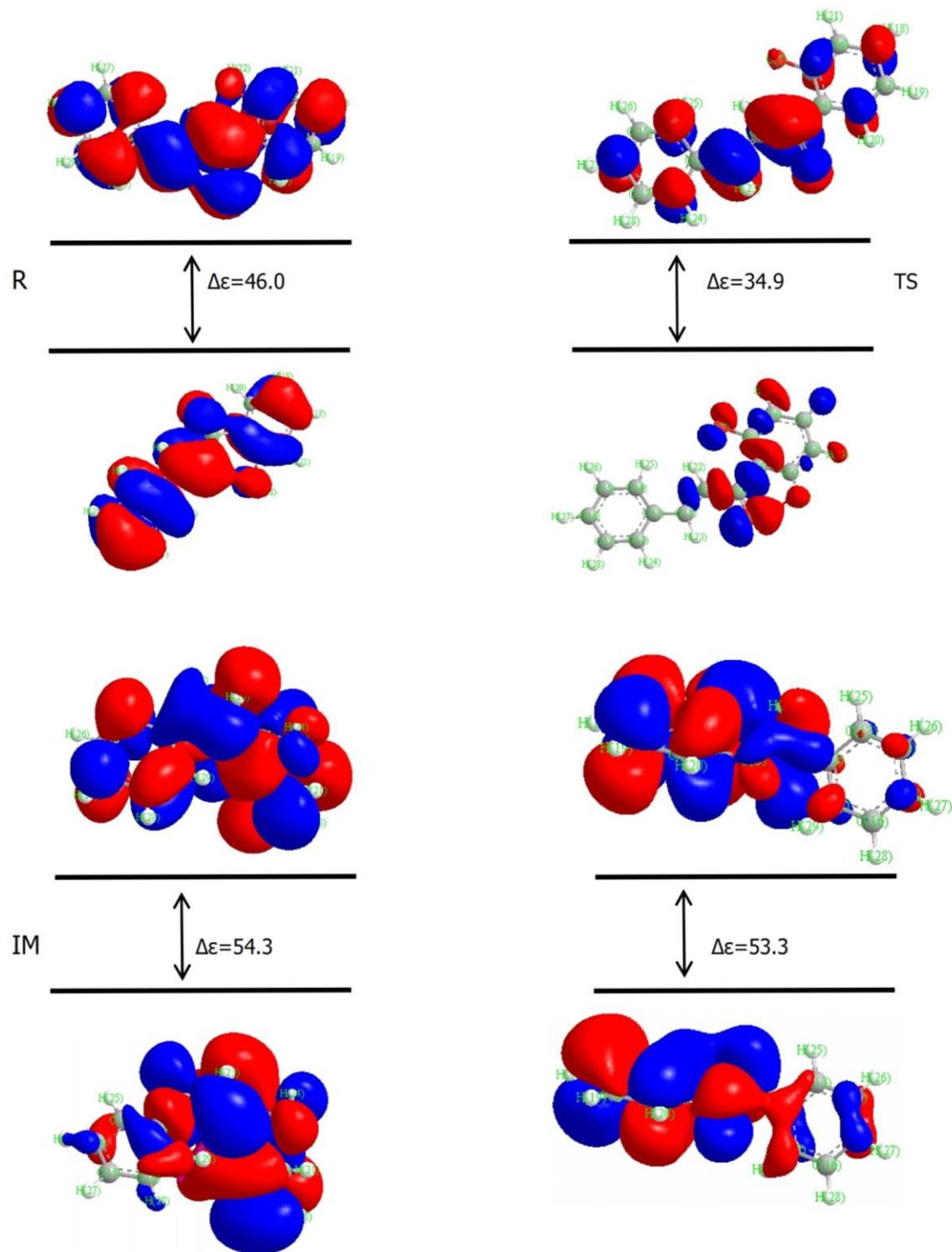


Fig. 4: The molecular orbitals of reactant, transition state, intermediate and product for the isomerization of 2-hydroxy chalcone-flavanone (compound 3).

The minimum polarizability principle (MPP) is valid for these molecules as well, it is worth noting that the MPP came with a good harmony for compounds with (EWGs) but there are slightly differences for compounds with (EDGs) as shown in fig. (6), since EDGs inhibit the final conversion to flavanone by destabilizing the carbanion (negative charge at α -C), i.e the HOMO is more concentrated in this case.

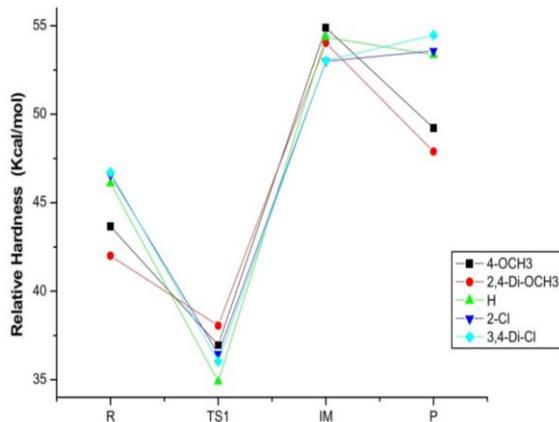


Fig. 5: Relative Hardness for all species participating (that take a part) in chalcone-flavanone isomerization.

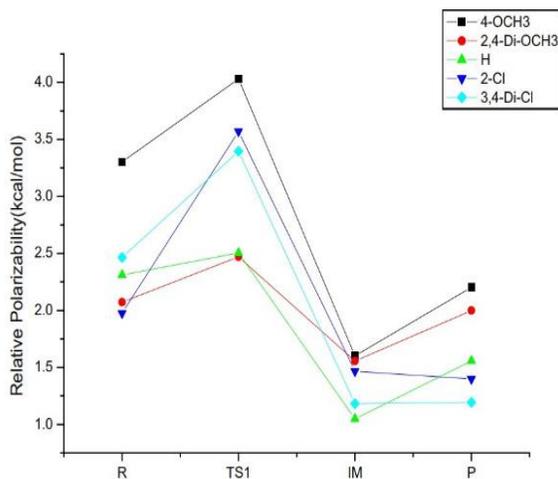


Fig. 6: Relative Polarizability for all species participating (that take a part) in chalcone-flavanone isomerization.

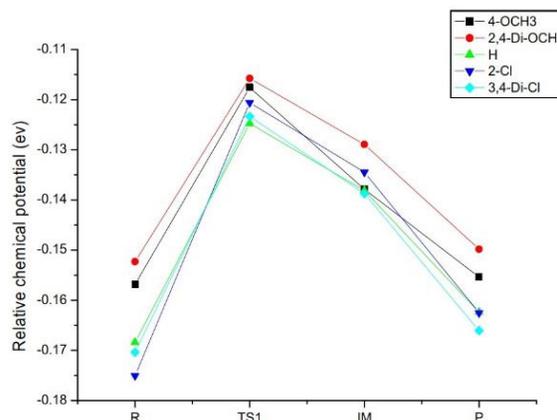


Fig. 7: Relative Chemical potential for all species participating (that take part) in chalcone-flavanone isomerization

The polarizability profile simulates the hardness profile since it is an inverse relationship, while it showed a corresponding behavior as the energy profile. In principle, all obtained information with respect to the isomerization process (both thermodynamic and kinetic) in terms of hardness/polarizability profile almost in the same manner as would have been obtained from the corresponding energy profile.

Conclusion

This study concerned with DFT calculations based with B3LYP/6-311G basis set for the isomerization process of 2-hydroxy chalcones to their corresponding flavanones. We can note that from the obtained data, the electronic nature of the substituents play an important role, since the reaction require lower energy values with (EWGs) thus it goes faster, in contrast with (EDGs) that require higher energy values which in turn inhibit the reaction rate. Furthermore the position of the substituent is also affect on the reaction rate, since ortho substituents inhibit the reaction rate due to the steric hindrance on the reaction center (i.e. β -carbon), thus according to the information that listed in table (1) the reaction rate for these compounds will follow the sequence $1 > 2 > 3 > 4 > 5$.

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