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Theoretical Study for Isomerization of Some 2´-Hydroxychalcone Derivative by Using DFT Calculation

Said Abdelqader Said[1*], Omar Adil Shareef [2], Zainab W. Majed[3]
[1] *Department of Chemistry, College of Science, Mosul University.*
[2] *Department of Chemistry, College of Science, Mosul University.*
[3] *Department of New and Renewable Energies, College of Science, Mosul University.*

Abstract

In this work, we present a study about the molecular structure and electrochemical behavior of a series of substituted 2´-hydroxychalcones and their conversion to the corresponding flavanones. The study was performed using density function theory (DFT) based on B3LYP with 6-311G basis set was used in order to investigate the effect of the electronic and structure properties for the isomerization process. Reactants, intermediates and products have an equilibrium state and one transition state that possess one imaginary frequency. The optimized structure, total energies, hardness, polarizability, chemical potential and electrophilicity index were calculated.

The relative energy calculated using DFT corresponds with those calculated in a practical way by the use of HPLC technique, the hardness profile along the reaction path in agreement with maximum hardness principle, and the minimum polarizability principle is obeyed in all cases .

Keywords: DFT; Isomerization ; 2´-Hydroxychalcone ; Flavanone ; Hardness ; Polarizability

Introduction

Chalcones are a generic term given to compounds bearing the (1,3-diphenyl-2- propen-1-ones) which are open-chain flavonoids[1] , that have a framework in which two aromatic rings are linked by a three carbon α,β- unsaturated carbonyl system [2] . Chalcones may exist in two isomeric forms, cis and trans, of which the *trans* form is thermodynamically favourable [3,4] . 2-Hydroxy chalcone and flavanone are a very well-known family of natural products found almost exclusively in the plant kingdom [5,6]. These compounds are often found in fruits (particularly in skin),vegetables and plants tissue [7,8] . Thus, it is a common component in general daily diet of human beings. Contemporary studies report a generous variation of significant pharmacological activities which include antioxidation [9] , antiallergic [10] ,antimicrobial [11], antifungal [12] , antiviral and anticancer properties [13].

The classic method for the synthesis of flavanone, involves the synthesis of the intermediate of 2-hydroxy chalcone which undergoes cyclization to flavanone.

Aromatic compounds are a large class of conjugated π electrons system which are of great importance in many research areas, such as materials science [14] and molecular electronics [15-16].

Density function theory (DFT) has been accepted as an effective and reliable approach in order to compute molecular structure, energies and vibration frequencies for chemical reactions [17] . It provides an efficient method to include correlation energy in electronic calculations [18]. In addition it constitutes a solid support to reactivity model [19]. Reactivity of the molecule is always governed by its thermodynamic and kinetic stability and electronic properties.

DFT has been found to be successful providing insights into the chemical reactivity and selectivity respectively interms of global reactivity parameters such as hardness η ,electronegativity χ local ones [20] , such as Fukui function f(r) and local softness s(r)[21].

While the concept of electronegativity has been introduced by Pauling [22], Pearson introduce the hardness concept about hard-soft acid and base (HSAB) which state that [23] ,"hard likes hard and soft like soft".

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*Corresponding author e-mail saidabdelqader75@gmail.com
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Another hardness-based principle is the maximum hardness principle (MHP) [24], which states that ‘there seems to be a rule of nature that molecules arrange themselves so as to be as hard as possible.

The MHP is a useful parameter [25] in analyzing internal rotation and molecular vibration of different types of chemical reactions, aromatic character, clusters with a magic number of atoms, extra stability of a closed-shell species, dynamic problems, electronic excitation atoms and molecules [26].

For an N electron system with total energy E, external potential υ(r), electronegativity χ and hardness η are respectively defined as the following first order [27] and second order derivative.

$$\chi = -\left(\frac{\partial E}{\partial N}\right)_{\upsilon(r)} \quad ----(1) \quad \text{and}$$

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{\upsilon(r)} ----(2)$$

In the present work we study the reactivity and selectivity for the isomerization of 2-hydroxy chalcones to thier corresponding flavanones and make a comparison between the present study and previous practical kinetic study that conducted by means of HPLC technique.

For this purpose a density function route has been adopted to optimize the geometries of the reactant, product, intermediate, transition state, and then different quantities are calculated for the optimized structure.

Computational Detail

We adopt the density function theory (DFT) method of Becke's three parameters exchange and gradient corrected correlation function of Lee Yang and Par (B3LYP) [28] for optimization of the reactants, transition state (TS), Intermediate (IM) and products, atomic basis function augmented by diffuse function on heavy atoms.

All computational studies were carried out using the density function theory (DFT) methods implemented in the Gaussian 09 suit of program [29].

The molecular properties of the compounds have been computed by DFT using standard 6-311G basis set,

Vibration analysis has been carried out at stationary points under harmonic to check the optimized geometry of reactant, intermediate and product characterized by all real frequency and transition state (TS) characterized by only one imaginary frequency .

To account for the solvent effect, all optimization with continuum model (PCM) was carried out at the B3LYP/6-311G with acetonitrile as the solvent since this solvent was used in the experimental solvent (the reason for selecting this solvent is to compare theoretical results with practical results that obtained using HPLC technique).Apart from the broad range of reliability and applicability of the B3LYP functional predicting energy of activation in the theoretical investigation of reaction mechanism in organic chemistry.

The chemical reactivity descriptor calculated using DFT are total energy (*E*), chemical hardness (η), electronic chemical potential (μ) and electrophilicity (ω).

Chemical hardness measure the resistance to change in the electron distribution or charge transfer and it associated with the stability and reactivity of a chemical system [30].On the basis of frontier molecular orbitals, chemical hardness corresponds to the gap between the HOMO and LUMO, chemical hardness is approximated using equation (3).

$$\eta = (E_{LUMO} - E_{HOMO})/2 \qquad ----3$$

Where E_{LUMO} and E_{HOMO} are the LUMO and HOMO energies. Electronic chemical potential is defined as the negative of electronegativity of a molecule and calculated using equation 4.

$$\mu = (E_{HOMO} + E_{LUMO})/2 \qquad ----4$$

physically μ describes the escaping tendency of electros from an equilibrium system.

The static electric dipole polarizability has been calculated by analytical differentiation of the dipole moment with respect to the electric field.

$$\alpha = \frac{1}{3}\left(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}\right) \qquad ----5$$

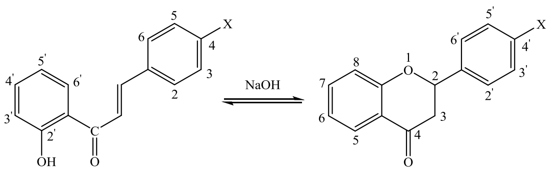
Global electrophilicity index (ω) is calculated using the electronic chemical potential and chemical hardness as shown in equation 6.

$$\omega = \frac{\mu^2}{2\eta} \qquad ----6$$

The index measure the propensity or capacity of a species to accept electrons, it is a measure of the stabilization in energy after a system accept additional amount of electronic charge from the environment.

RESULTS AND DISCUSSION

Isomerization of 2'-Hydroxychalcone-flavanone have been presented in the general scheme, which illustrate the transformation of reactant (R) to the product (P) through an intermediate (IM) and one transition state (TS).



X= 4-Cl, 4-Br , H , 4-CH_3 , 4-$N(CH_3)_2$

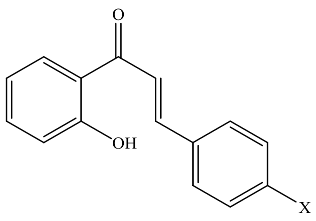
Table (1): Relative energy (E), Hardness (η), polarizability (α), Chemical potential (μ) and electrophilicity index (ω) for compounds under study.

	HOMO	LUMO	η (kcal/mol)	α (au)	*E(kca/mol)*	*μ*(ev)	ω (ev)
***4-Cl* (compd.1)**							
R	-0.24159	-0.09318	46.56364	1.8566333	-746.0082024	-0.16739	0.188786054
TS_1	-0.17924	-0.07150	33.80342	2.94486666	-745.7145819	-0.11987	0.120980188
IM	-0.22210	-0.04816	54.57368	0.852133	-746.0000493	-0.13513	0.1049794
P	-0.24921	-0.07548	54.50778	1.0436	-746.0140092	-0.16485	0.161049452
***4-Br* (compd.2)**							
R	-0.24125	-0.09305	46.49775	1.864566	-2072.471655	-0.16715	0.188523094
TS_1	-0.17913	-0.07013	34.19875	4.347133	-2072.17795	-0.12463	0.142501256
IM	-0.22666	-0.05002	55.4208	0.773	-2072.463394	-0.13834	0.108344404
P	-0.24775	-0.07614	53.84263	0.8890666	-2072.477387	-0.162945	0.1565419
***H* (compd.3)**							
R	-0.24184	-0.09496	46.0836	2.31086	-619.500881	-0.1684	0.193073
TS_1	-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	-619.52824	-0.162405	0.15514
***4-CH_3* (compd.4)**							
R	-0.23542	-0.08853	46.08674	2.1649	-482.2771918	-0.161975	0.178609168
TS_1	-0.17697	-0.06267	35.86163	3.845666	-481.9827305	-0.11982	0.125606583
IM	-0.22042	-0.04508	55.01293	1.0321	-482.2683679	-0.13275	0.10050509
P	-0.24558	-0.07700	52.89198	1.1469666	-482.2893697	-0.16129	0.154315246
***N,N-Di –CH_3* (compd.5)**							
R	-0.20322	-0.08288	37.75668	2.918333	-541.6692919	-0.14305	0.170045725
TS_1	-0.17449	-0.06228	35.22158	5.822766	-541.3734551	-0.118385	0.124844185
IM	-0.20290	-0.04742	48.78185	1.129933	-541.6563992	-0.12516	0.100752673
P	-0.20341	-0.07616	39.92469	1.5124	-541.6723691	-0.139785	0.153554784

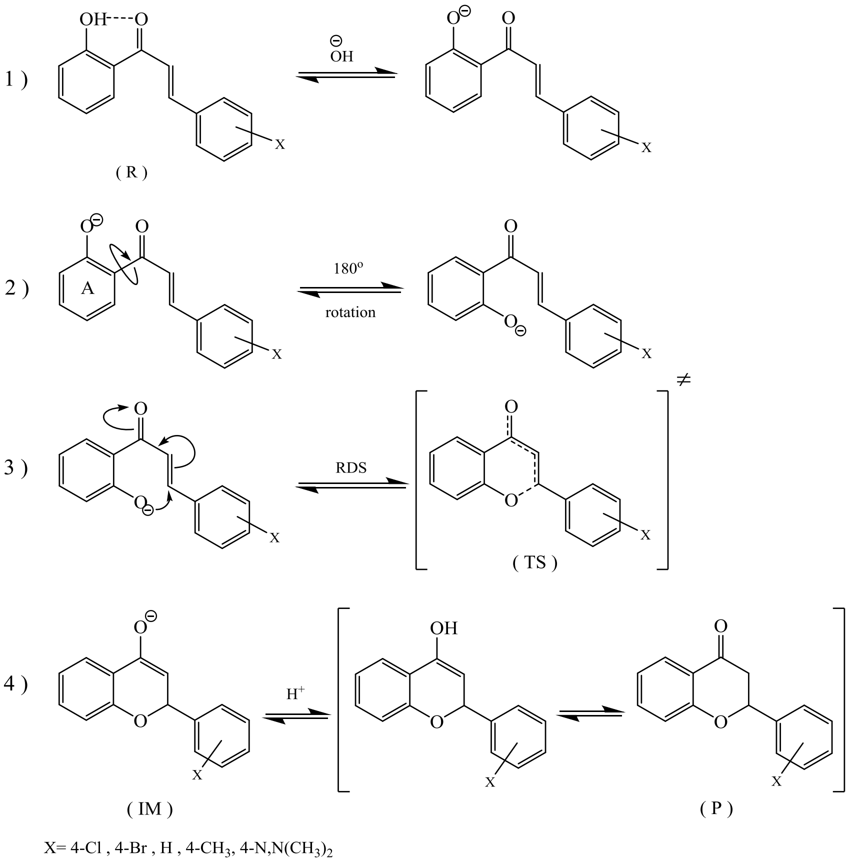
In general reactions that involve electron withdrawing groups (EWGs) have an activation energy lowest than those with electron donating groups (EDGs) relative to the unsubstituted one. Thus the activation energies for compounds 1&2 are -745 and -2072 kcal/mol respectively, while the unsubstituted one possess -619 kcal/mol. In contrast compounds 4&5 activation energy is -482 and -541 kcal/mol . These results can be attributed to electronic factors that effect in the reaction center i.e. β-Carbon:

Since the electron withdrawing groups (4-Cl and 4-Br) activate the reaction center (via increasing electron deficiency at β-carbon) toward nucleophilic attack of the phenoxide ion .

On the other hand electron donating groups represented with 4-CH_3 and 4-$N(CH_3)_2$ have the highest activation energy compared with those of electron withdrawing groups even the unsubstituted one, and here again the electronic factor play an important rule since they inhibit the reaction rate by increasing electron density at the reaction center and strengthen the hydrogen bond (IHB). These results can be illustrated in table (1), and this (or 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(2).



Temp. °C	Compd. No. x 10^4 k/min				
	1	2	3	4	5
25	6.461	2.437	1.294	0.944	0.625
30	8.283	4.834	3.742	2.321	1.613
35	9.629	6.324	4.233	2.756	2.375
40	23.132	13.343	5.017	3.664	2.698
45	26.731	14.562	8.237	7.524	4.371



General scheme mechanism of isomerization process

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

Cleary we can see that the reaction demand lower energy value especially with the electron withdrawing groups (4-Cl & 4-Br derivatives) relative to the unsubstituted one in order to get to the T.S , which transformed to the more stable intermediate with lower energy value (compared with T.S.) that on tautomerization produce the product (most stable flavanone) fig.1 (a , b & c)

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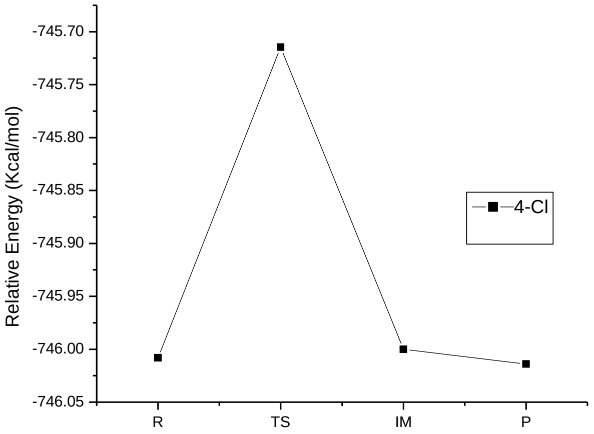


Fig.(1a): relative energy for 4-Cl substitution

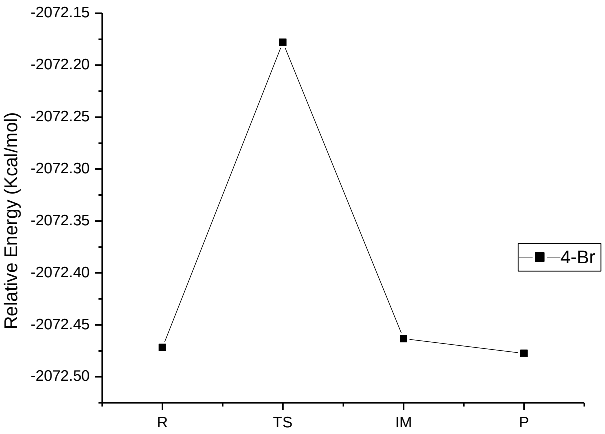


Fig.(1b): relative energy for 4 –Br substitution

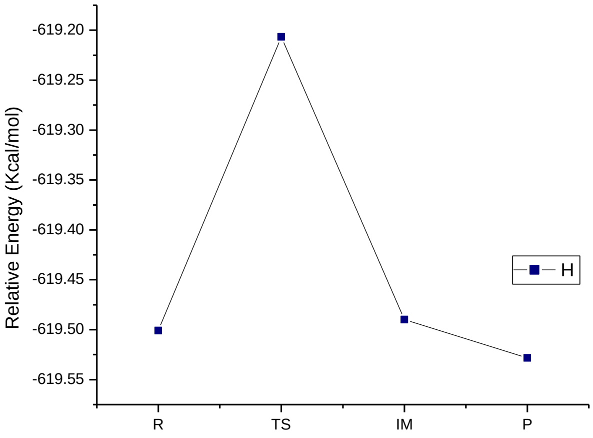


Fig.(1c): relative energy for unsubstituted

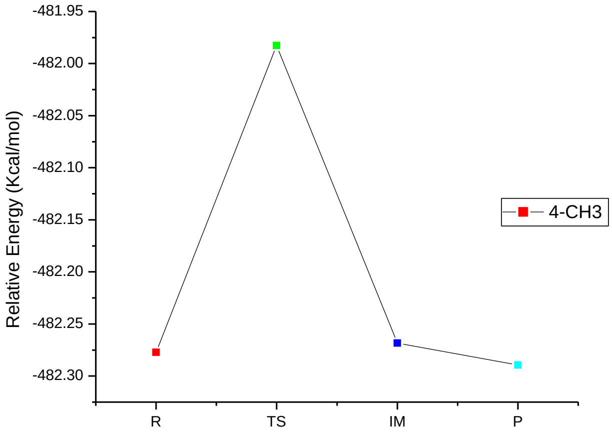


Fig.(1a): relative energy for 4-Cl substitution

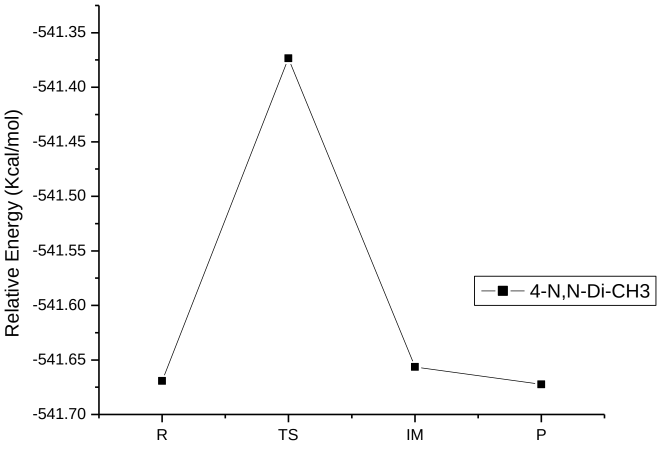


Fig.(1a): relative energy for 4-N,N-Di-CH_3

This in contrast with reactions that involve (EDGs) proceed with the same manner but with higher energy value due to the deactivation of the reaction center fig1 (d & 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.

In general, there is an equilibrium state between the reactant and the product with slightly predomination of the product, since the energy gap between reactant and product is quite small.

These results came with a good agreement with our experimental study, since there is a relatively close ratio between the reactant and product within the first hour of reaction which increased later toward the product as shown in table (3).

Table (3): The relative percent between flavanone and chalcone at a different times

Compd. No.	Retention Time min.		(flavanone:chalcone)%	(flavanone:chalcone)%
	flavanon	chalcone	After 1 hour	After 48 hours
1	2.775	3.204	(63.12:36.88)	(82.56:17.74)
2	1.244	1.504	(57.78:42.22)	(71.28:27.72)
3	2.775	3.204	(46.53:53.47)	(64.53:35.47)
4	2.664	2.963	(41.65:58.35)	(61.03:38.97)
5	2.637	2.673	39.78:60.22)	(58.85:41.15)

The structure of T.S. for these reactions was shown in fig.(2) in which the distance C_8-C_{11} is varied from (1.337 to 1.437 A^o) with slightly difference, due to the partial cleavage of π bond . The other important distance is C_9-O_{10} which varied from (1.208 to 1.308 A^o) with slightly differences due to the different substituents .

In fig.(3) the structure of intermediate was illustrated, which showed that the distance of C_9- C_{10} varies from1.357 to 1.337 A° due to formation of π bond, furthermore the C_9-O_{11} distance is changed from 1.208 to 1.455 A° due to completely cleavage of π bond (i.e. carbonyl group) with slightly difference with the substituted compounds.

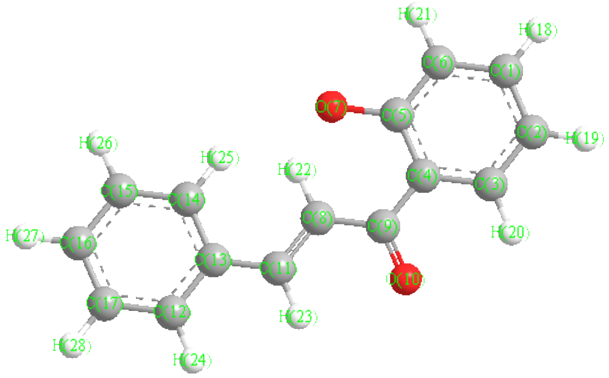


Fig.(2) : Transition state

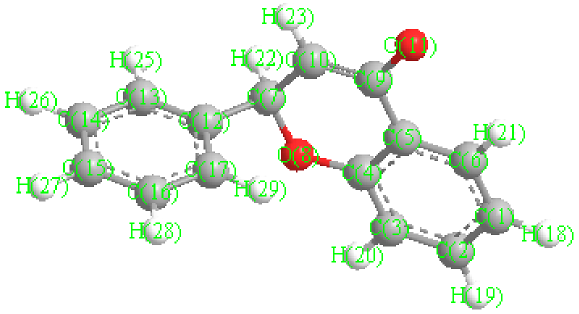
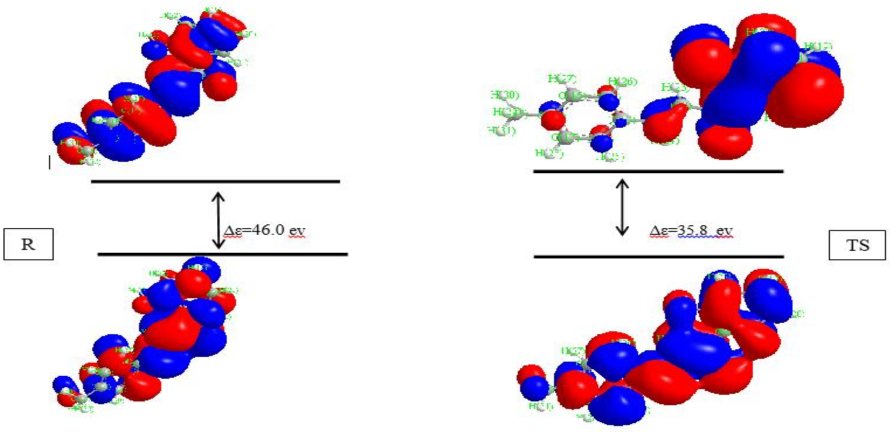


Fig. (3) : Intermediate structure

In fact, the larger the HOMO-LUMO energy gap fig.(4), the harder , the more stable and less reactive molecule [31].Thus flavanone is more stable than chalcone since it posses the larger gap as shown in table 1

The obtained results indicates that compounds with EWGs are harder than those with EDGs i.e. more stable product, consequently the reaction goes faster toward the flavone.



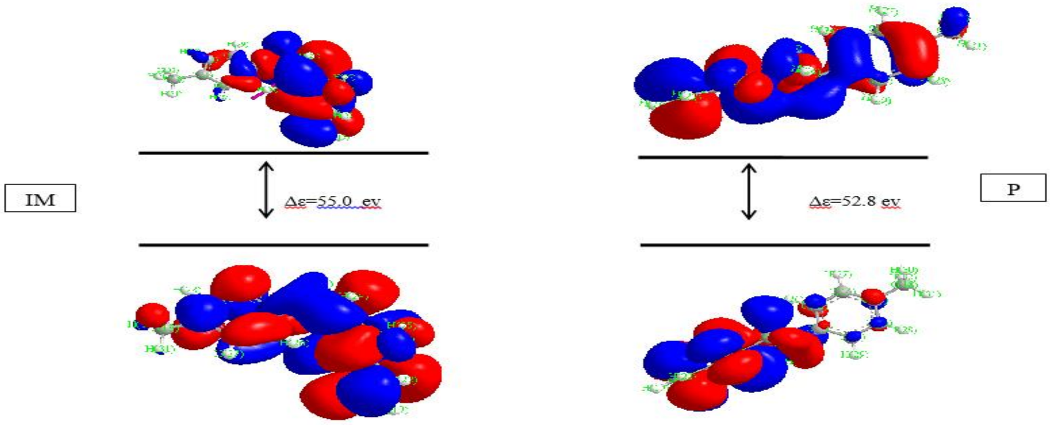


Fig.(4): Frontier molecular orbitals for the isomerization of 2-hydroxy chalcone-flavanone of reactant, transition state , intermediate and product (compound 4)

Thus the hardness for these compounds will follow the sequence 1 > 2 > 3 > 4 > 5 as shown in fig. (5)

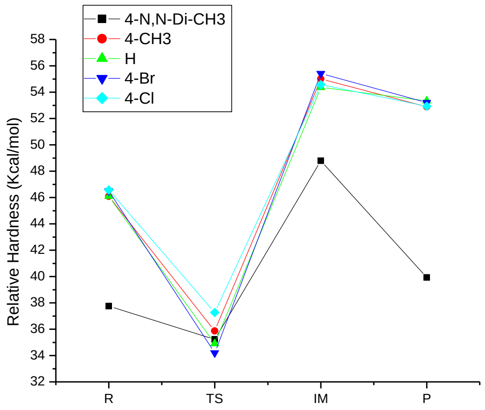


Fig (5): Relative Hardness for all species participating in chalcone-flavanone isomerization.

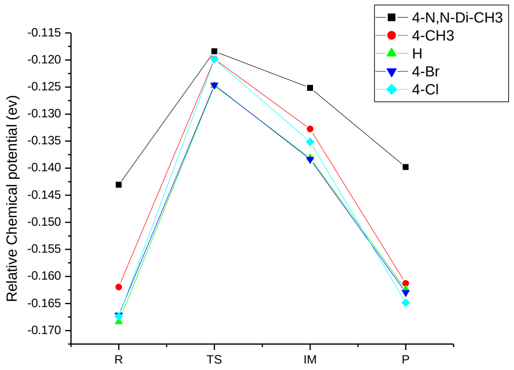


Fig (6): Relative Polarizability for all species participating in chalcone-flavanone isomerization

The minimum polarizability principle (MPP) is valid for these molecules as well.

it is interesting to note that the MPP came with a good agreement fig.(6) for compounds with (EWGs) but there is slightly differences for compounds with (EDGs), since EDGs inhibit the final transformation to flavanone by destabilizing the carbanion (negative charge at α-C), i.e the HOMO is more concentrated in this case. Since the polarizability profile mimics the hardness profile which is a mirror of the latter one, thus the polarizability showed a corresponding behavior as the energy profile. In principle all obtained information regarding the isomerization process (both thermodynamic and kinetic) in terms of hardness/polarizability profile almost in the same way

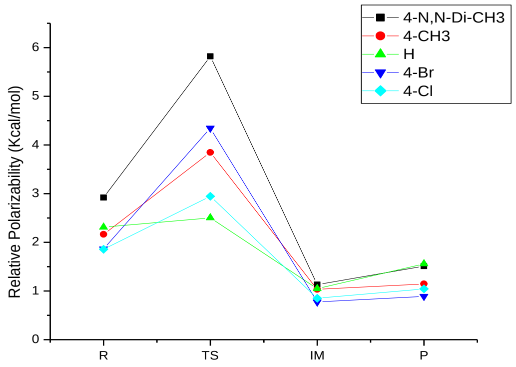


Fig (7): Relative Chemical potential for all species participating in chalcone-flavanone isomerization as would have been obtained from the corresponding energy profile.

Conclusion

Using Density function theory (DFT) with B3YLP /6-311G basis set. Relative energy (E), hardness (η), polarizability (α), chemical potential (*μ)* and electrophilicity index (ϖ) were calculated for the transformation process of 2-hydroxy chalcones to flavanones. The reactions rate were affected by the presences of different substituents, in which electron withdrawing groups enhance the reaction rate since it possess lower activation energy since these groups increase electron deficiency at the reaction center and this in contrast with electron donating groups that have higher activation energy which in turn decrease the reaction rate (i.e. ncleophilic addition) since these groups increase electron density at the reaction center. Furthermore, this study confirm all results that obtained from our previous experimental study.

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References

1- F. Dong, C. Jian, F. Zhenghao, G. Kai and L. Zuliang, Synthesis of chalcones via Claisen–Schmidt condensation reaction catalyzed by acyclic acidic ionic liquids, *Catalysis Communications*, 2008, 9(9): 1924-1927.

2- B. A. Saleh, Structure and vibrational spectra of mononitrated Benzo[a]pyrenes, *Journal of Molecular Structure THEOCHEM*, 2009, 915(47).

3- B. E. AKSÖZ and O. R. ERTAN, Spectral properties of chalcones II, *FABAD Journal of Pharmaceutical Science.*, 2012, 37(4): 205-216.

4- D. I. Batovsk and I. T. Todorova , Trends in utilization of the pharmacological potential of chalcones, *Current Clinical Pharmacol*ogy, 2010, 5(1): 1-2.

5- J. Mierziak, K. Kostyn and A. Kulma, Flavonoids as important molecules of plant interactions with the environment, *Molecules*, 2014, 19: 16240-16265.

6- I. Zhang, Fu-Jian Ji, Y. Gu , X. Yao Zhang and Shi-Xing Qiao , Chalcones derivatives as potent cell division cycle 25B phosphatase inhibitors, *Pharmacological Reports*, 2014, 66: 515–519.

7- D. DiMajo, M. Giammanco, M. LaGuardia, E. Tripoli, S. Giammanco and E. Finotti, Flavanones in *citrus fruit:* structure–antioxidant activity relationships, *Food Research International*, 2005, 38(10): 1161-1166.

8- J. J. Petersona, J. T. Dwyera, G. R. Beecherb, S. A. Bhagwatc, S. E. Gebhardtc, D. B. Haytowitzc and J. M. Holdenc, Flavanones in oranges, tangerines (mandarins), tangors, and tangelos: a compilation and review of the data from the analytical literature, *Journal of Food Composition and Analysis*, 2006, 19: S66–S73.

9- Y. S. El-Sayed and M. Gaber, Studies on chalcone derivatives: Complex formation, thermal behavior, stability constant and antioxidant activity, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 2015, 137: 423-431.

10- T. Yamamoto, M. Yoshimura, F. Yamaguchi, T. Kouchi, R. Tsuji, M. Saito, A. Obata and M. Kikuchi, Anti-allergic activity of naringenin chalcone from a tomato skin extract, *Bioscience, Biotechnology and Biochemistry*, 2004, 68(8):1706-1711.

11- D. Božić, M. Milenković, B. Ivković and I. Cirković, Antibacterial activity of three newly-synthesized chalcones & synergism with antibiotics against clinical isolates of methicillin-resistant *Staphylococcus aureus*, *Indian Journal of Medical Research*, 2014, 140(1): 130-137.

12- D. Gupta and D. K. Jain, Chalcone derivatives as potential antifungal agents: Synthesis, and antifungal activity, *Journal of Advanced Pharmaceutical Technology and Research*, 2015, 6(3): 114-117.

13- M. Das and K. Manna, Chalcone Scaffold in Anticancer Armamentarium: A Molecular Insight, *Journal of Toxicologye*, 2016, Article ID 7651047, 1-14.

14- P. V. R. Schleyer, Introduction: Aromaticity, *Chemical Reviews*, 2001, 101(5), 1115-1118.

15- J. McMurry, Organic Chemistry, (5th edition), Brook / Cole, Thomson Learning, USA, 2000.

16- H. S. Nalwa, Handbook of Organic Electronics and Photonics, CA: American Scientific Publishers, Los Angeles, USA, 2006.

17- A. Beyramabadi and A. Morsali, Intramolecular proton transfer of 2-[(2,4-dimethylphenyl) iminomethyl]-3,5-dimethoxyphenol Schiff-base ligand:A density functional theory (DFT) study, *International Journal of Physical Science*, 2011, 6(7): 1780-1788.

18- P. K. Chattaraj, B. Maiti, HSAB principle applied to the time evolution of chemical reactions, *Journal of the American Chemical Society*, 2003, 125(9): 2705-2710.

19- A. A. Kadhum, H. A. Al-Amiery, A. Y. Musa and A. Mohamad, The antioxidant activity of new coumarin derivatives. *International Journal of Molecular Science*, 2011, 12: 5747-5761.

20- K. D. Sen, Eletronegativity, Structure and Bonding 66; Springer-Verlag, New York, 1987.

21- A. T. Mohi, H. I. Al-Rubaye, F. W. Askar, H. J. Abboud, Synthesis, Theoretical and antimicrobial activity study of new benzimidazole derivatives, *Egyptian Journal of Chemistry*,63(8),2020.

22- L. Pauling, The Nature of the Chemical Bond; Cornell University Press, Ithaca, NY, 1960.

23- (a) R. G. Pearson, Hard and Soft acids and bases, Dowden, Hutchinson and Ross: Stroudsberg, PA, 1973. (b) Pearson R. G., Hard and Soft acids and bases, *Journal of the American Chemical Society*, 1963, 85(22): 3533-3539.

24- S. Pan, M. Solà and P. K. Chattaraj, On the Validity of the Maximum Hardness Principle and the Minimum Electrophilicity Principle during chemical reactions, *The Journal of Physical Chemistry A*, 2013, 117(8): 1843-1852.

25- P. K. Chattaraj, Chemical reactivity theory, *Proceeding of the Indian National Science Academy-Part A*, 1996, 62: 1133.

26- P. K. Chattaraj and A. Poddar, A Density Functional Treatment of chemical reactivity and the associated Electronic Structure Principles in the Excited Electronic States, *The Journal of Physical Chemistry A*, 1998, 102(48): 9944-9948.

27- D. Glossman-Mitnik, A comparison of the chemical reactivity of naringenin calculated with the M06 family of density functional, *Chemistry Central Journal*, 2013, 7:155.

28- Peter M. W. Gill, B. G. Johnson and J. A. Pople, The performance of the Becke-Lee-Yang-Parr (B-LYP) density functional theory with various basis sets, *CHEMICAL PHYSICS LETTERS*, 1992, 197(4,5): 499-505.

29- M. J. Frisch, Gaussian 09, Revision A.02, Gaussian, Inc., PA, Wallingford CT. 2009.

30- J. W. Peters, W. N. B. Lanzilotta, J. Lemon and L. C. Seefeldt, X-ray crystal structure of the Fe-only hydrogenase (CpI) from Clostridium pasteurianum to 1.8 Angstrom resolution, *Science*, 1998, 282: 1853-1858.

31- M. Torrent-Sucarrat, M. Duran, J. M. Luis, and Miquel Solà, Generalizing the breakdown of the Maximum Hardness and Minimum Polarizabilities Principles for Nontotally Symmetric Vibrations to Non-π-Conjugated Organic Molecules, *The Journal of Physical Chemistry A*, 2005, 10(4): 615–621.