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DFT study on the mechanism of hetero diels alder reaction of β,γ-unsaturated α-ketoesters and 2,3-dihydrofurane

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ABSTRACT

The reaction mechanism of hetero Diels-Alder reaction of 2, 3 -dihydro furan and β , δ-unsaturated α -ketoesters have been studied using B3LYP method at cc-pVDZ level of theory. The four possible reaction transition states were located with the *ortho* and *meta* regio- and *endo* and *exo* stereoselectivity. Geometry and NBO analysis indicated that the hetero Diels -Alder reactions take place along a concerted mechanism with a polar character.

KEYWORDS

Hetero diels-alder reaction;
Density functional theory;
Regioselectivity;
Stereoselectivity.

INTRODUCTION

Pyran derivatives found in natural and synthetic products, such as cryptocaryalactone, kurzilactone, goniothala min, with a wide range biological activities[1]. They are also used as building blocks in the synthesis of natural products and pharmaceuticals Prins-typ reaction. Hetero Diels-Alder (HDA) reactions of aldehydes with dienes, or α,β -unsaturated carbonyl compounds with electron-rich carbon-carbon double bonds are the most useful routes for the synthesis of pyran and dihydropyran moieties[2-4] Among the numerous methods for synthesizing dihydropyrans, HDA reaction of α,β -unsaturated carbony1 compounds with alkenes have been demonstarted to afford a facile synthesis of these core structures.

The HDA reaction is one of the most important methods for the synthesis of heterocycles. While the asymmetric HDA reactions have been intensively developed in recent years with the main focus on the synthetic aspects, but the number of mechanistic studies has been limited[5]. As, there are many reports regarding to asymmetric HDA reaction of β,δ - unsaturated α -ketoesters with 2, 3- dihydrofuran[6-9], but there isn't any theoretical results about them. In this work, the main attention will be on the development and understanding of the mechanism of some HDA reactions for preparing dihydropyran system. Thought, the theoretical results provide a useful tool; for the interpretation of reaction mechanism, herein, a theoretical study present on the mechanism and regioselectivity of the HDA reactions of 2,3-dihydrofuran (1) with some β,δ - unsaturated α - ketoesters derivaties 2a-f, based on activation energy calculations and DFT based reactivity indices

Computational method

Density functional theory calculations were carried out using the Gaussian 09 package[10]. The relative energies and free energies have been computed at 298 K for the various stationary points at the

B3LYP/cc-pVDZ level. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method[11]. Global reactivity indices were estimated according to the equations recommended by Parr and Yang[12] The global electrophilicity index, ω, is given by the following expression[13].

$$\omega = \frac{\mu^2}{2\eta} \tag{1}$$

In terms of the electronic chemical potential μ and the chemical hardness η, both quantities may be approached in terms of the one-electron energies of the frontier molecular orbitals, HOMO and and LUMO, ε_H and ε_L,[12], as

$$\mu = {\varepsilon_H + \varepsilon_L}\Big/{2} \tag{2}$$

$$\eta = \varepsilon_L - \varepsilon_H \tag{3}$$

Recently, Domingo introduced an empirical (relative) nucleophilicity index,[14] N, based on the HOMO energies obtained within the Kohn Sham scheme,[13] and defined as:

$$\varepsilon_{\mathrm{HOMO}}(Nu) - \varepsilon_{HOMO}(TCE) \tag{4}$$

Nucleophilicity is referred to tetracyanoethylene (TCE), because it presents the lowest HOMO energy in a large series of molecules already investigated in the context of polar cycloadditions. This choice allows us to conveniently handle a nucleophilicity scale of positive values. Recently, Domingo proposed two new electrophilic, P_k^+, and nucleophilic, $P_k^{\text{É}}$, Parr functions based on the atomic spin density distribution at the radical anion and cation of a neutral molecule[15]. The electrophilic, P_k^+, and nucleophilic, $P_k^{\text{É}}$, Parr functions, were obtained through the analysis of the Mulliken atomic spin density. The local electrophilicity indices, ω_k,[16] and the local nucleophilicity indices, N_k[15], calculated using the following expressions:

$$\omega_k = \omega P_{\mathrm{k}}^+ \tag{5}$$

$$N_k = NP_{\mathrm{k}}^+ \tag{6}$$

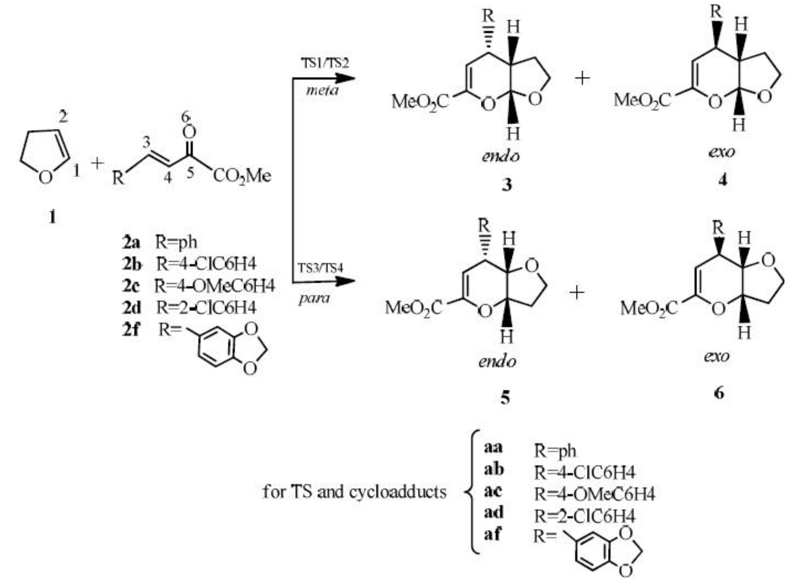
The local electrophilicity and local nucleophilicity index proposed by Domingo[17] to rationalize the regioselectivies of HDA reactions. The transition states were verified by analysis of the internal reaction coordinates (IRC) for both forward and inverse directions[18-19].

RESULTS AND DISCUSSION:

Our theoretical analyzes on the regio- and stereochemistry of these HDA reactions will be based on energy barrier calculations and DFT-based reactivity indices.

Energies

The cycloaddition of 2,3-dihydrofuran 1 with β,γ



Scheme 1 : The calculated possible reaction pathways for the HDA reaction of 2,3-dihydrofuran (1) and β,δ-unsaturated α -ketoesters (2a-f) at B3LYP/cc-pVDZ level

-unsaturated α-ketoesters derivatives (2a-f) can take place along four channels corresponding to *exo*-and *endo* approaches of reactants in two possible regioisomeric senses: the *ortho* and *meta* pathways (see scheme 1). The activation and relative energies corresponding to the stationary points associated with these reactive pathways are summarized in TABLE 1.

An analysis of the stationary points involved in the two regioisometric paths indicates that these HDA reactions have one step mechanism and all cycloaddition pathways are exothermic processes in the range of -35.97 to -89.82 kJmol$^{-1.}$.

The potential energy surface (PES) for these processes indicated that the *ortho* cycloadducts (3 and 4) are more stable than the *meta* ones, 5 and 6, and while in the *meta* pathways the *exo*

Product, 4, has a lower energy than the *endo* ones,3, the large stability of the *endo* cycloadduct is observed for the *meta* pathways of these HDA reactions. Moreover, the low energy differences for 3/4 pairs (about 2 kJmol^{-1}) might suggest that the formation of an equimolar mixture of cycloadducts should be observed.

The analysis of the activation energies and Gibbs free energies for the TSs reveals that the *ortho* approaches are favored over the *meta* ones, TS_1 and TS_4 have lower energies than TS_2 and TS_3, in the range of 2-14 kJmol^{-1}. Therefore, as shown in TABLE 1, the *ortho -endo* pathways are more favorable than *exo* ones, leading to the formation of 3 cycloadduct, which is in agreement with the experimental results[9]. By varying the substituents on phenyl group in β,γ -unsaturated α-ketoesters, the energy barriers changed. While electron-donating substitutents increased energy barriers, electron-withdrawing substituents decreased it, and the lowest energy barriers in favorable pathway related to the phenyl group without any substituents (84.80kJ mol^{-1}). Also, the electron-withdrawing substituents of studied HDA reactions increased the regioselectivity, as in the HDA reactions of 2b and

TABLE 1 : Calculated activation energies ($\Delta E^{\#}$ / kJ mol^{-1}), activation free energies ($\Delta G^{\#}$ / kJ mol^{-1}), reaction energies (ΔE_r / kJ mol^{-1}) and rate constants (k / S^{-1}), of the HDA reactions between 2,3-dihydrofuran (1) and β,δ-unsaturated -ketoesters (2a-f) at the B3LYP/cc-pVDZ level of theory

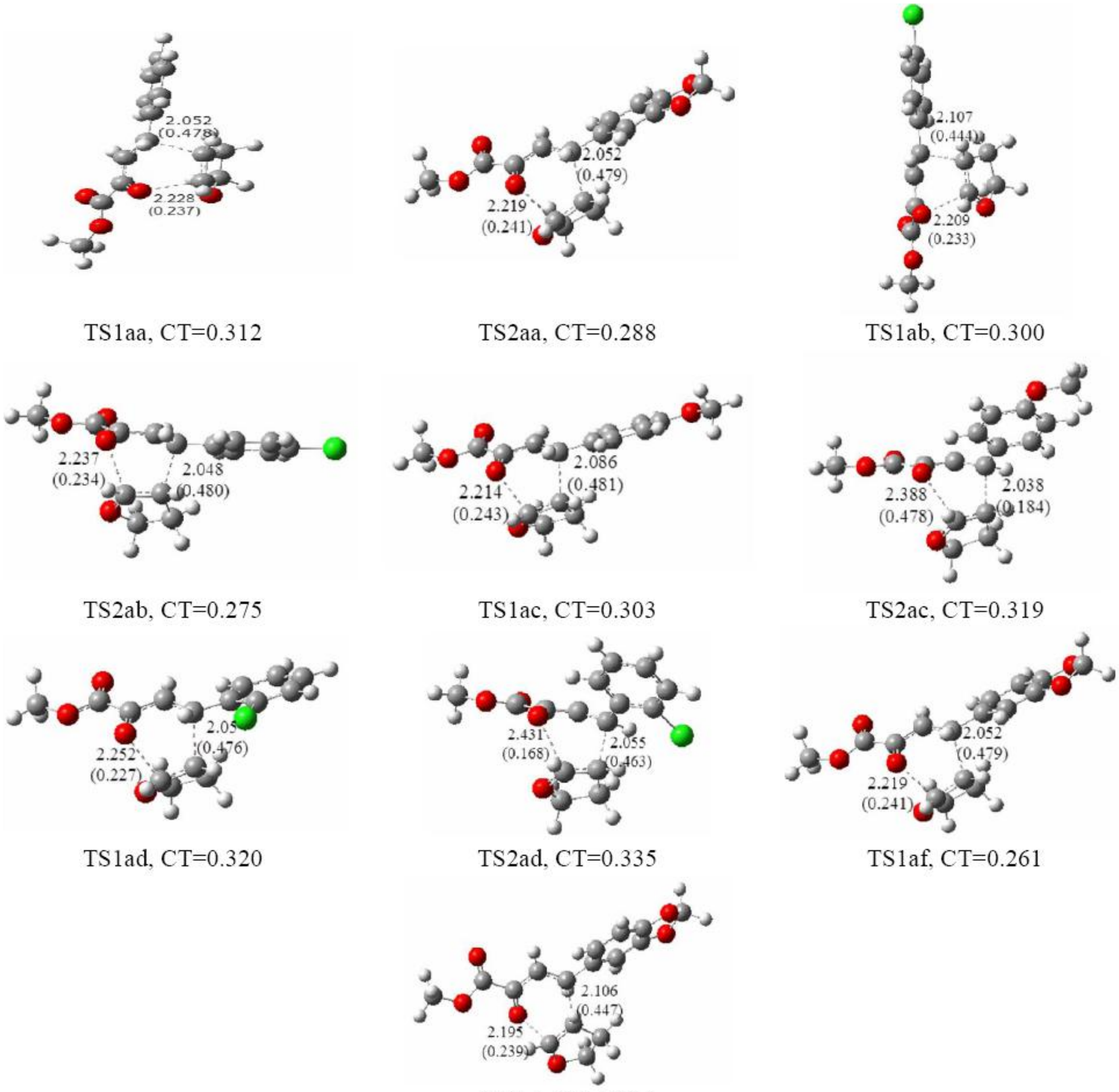
Structure	TS	$\Delta E^{\#}$	$\Delta G^{\#}$	ΔE_r	k
1a+2a →3a-*endo*	TS1aa	84.60	134.81	-69.66	1.45×10^{-14}
1a+2a →4a-*exo*	TS2aa	85.87	135.20	-71.55	1.24×10^{-14}
1a+2a →5a-*endo*	TS3aa	104.87	155.23	-55.14	3.84×10^{-18}
1a+2a →6a-*exo*	TS4aa	102.81	152.93	-48.77	9.68×10^{-18}
1a+2b →3b-*endo*	TS1ab	89.72	145.44	-61.21	1.99×10^{-16}
1a+2b →4b-*exo*	TS2ab	94.40	146.04	-63.09	1.56×10^{-16}
1a+2b →5b-*endo*	TS3ab	112.85	165.80	-47.83	5.37×10^{-20}
1a+2b →6b-*exo*	TS4ab	107.04	160.17	-41.37	5.21×10^{-19}
1a+2c →3c-*endo*	TS1ac	97.66	153.55	-54.40	7.54×10^{-18}
1a+2c →4c-*exo*	TS2ac	123.90	178.26	-56.38	3.51×10^{-22}
1a+2c →5c-*endo*	TS3ac	125.90	174.10	-39.82	1.88×10^{-21}
1a+2c →6c-*exo*	TS4ac	111.66	167.57	-34.08	2.63×10^{-20}
1a+2d →3d-*endo*	TS1ad	88.68	146.24	-68.29	1.44×10^{-12}
1a+2d →4d-*exo*	TS2ad	93.08	150.74	-89.82	2.34×10^{-13}
1a+2d →5d-*endo*	TS3ad	120.05	182.34	-73.40	6.77×10^{-19}
1a+2d →6d-*exo*	TS4ad	107.60	162.38	-54.93	1.59×10^{-13}
1a+2f→3f-*endo*	TS1af	95.93	156.04	-56.76	2.76×10^{-14}
1a+2f →4f-*exo*	TS2af	96.62	156.37	-58.83	2.41×10^{-14}
1a+2f→5f-*endo*	TS3af	116.42	175.57	-41.51	1.04×10^{-17}
1a+2f →6f-*exo*	TS4af	114.23	173.89	-35.97	2.05×10^{-17}

2d with 1, the regioselectivity of *endo* pathways increased to about 32 kJmol^{-1}, but there isn't any significant difference between the energy barriers of the *ortho* - *endo* pathways, 89.22 and 88.68 kJmol^{-1}, respectively. The highest energy barrier and stereoselectivity can be seen in the HDA reaction of 1 and 2c with electron-donating substituent (methoxy group), 25.90 and 26.34 kJmol^{-1}, respectively.

An analysis on the TS geometries shows that they are corresponded to asynchronous bond formation processes. (Figure 2) The extent of bond formation along a reaction pathway is provided by the concept of bond order (BO)[20]. The BO (wiberg indices) and lengths of the C-O and C-C forming bonds at TSs are shown in fig 2. These values are within the range of 0.168 to 0.481. These results show that the TS1 and TS2 are more asynchronous than the TS3 and TS4.

Moreover, the polar nature of the two cyclization modes can be estimated by a charge transfer (CT) analysis at the TSs. The CT values from dienophile 1 to heterodienes 2a-f are between the range 0.261 e to 0.338 e. Therefore the CT calculations show an inverse- electron demand character for these reactions.

DFT-based reactivity indices



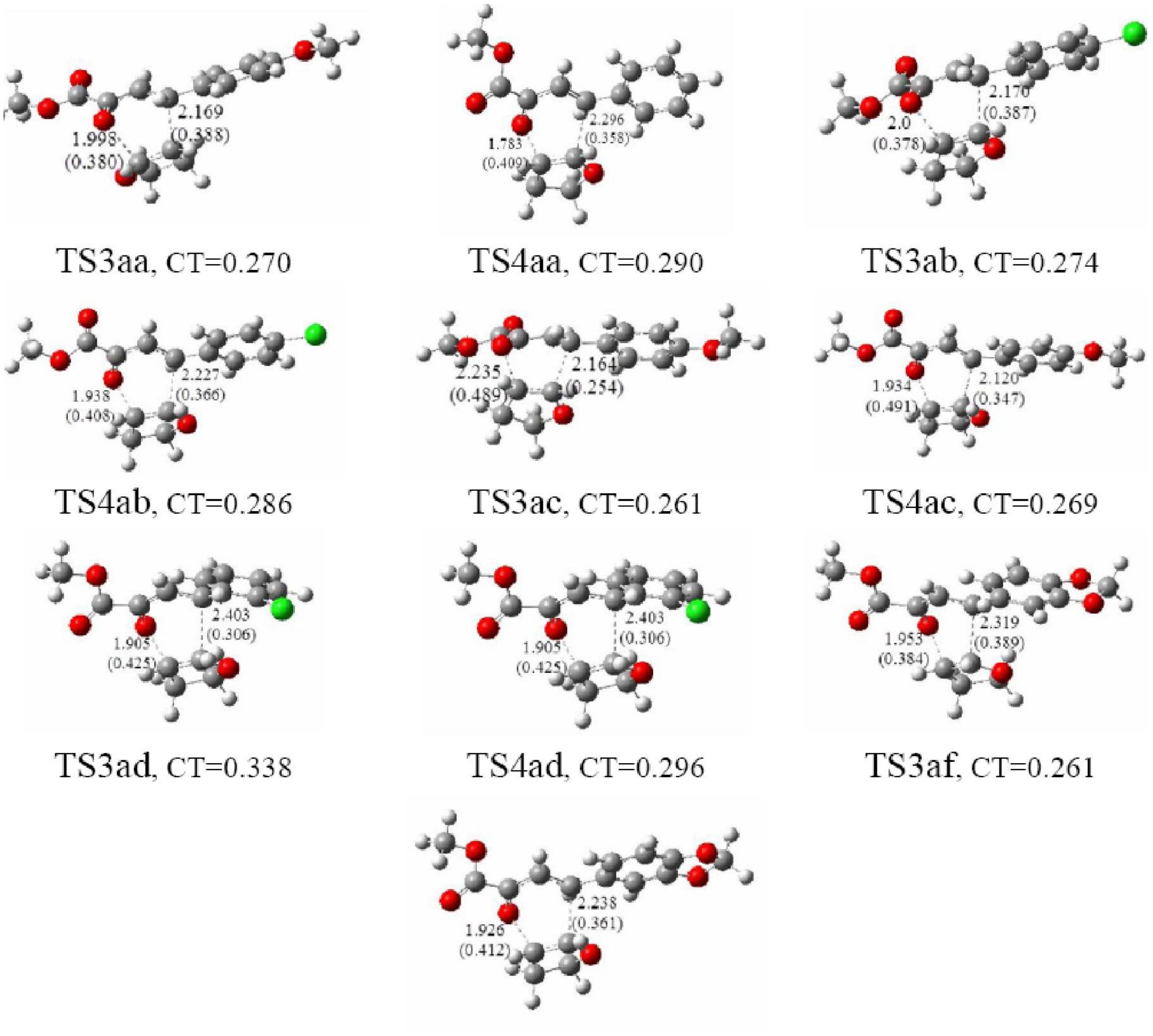
TS1aa, CT=0.312 TS2aa, CT=0.288 TS1ab, CT=0.300

TS2ab, CT=0.275 TS1ac, CT=0.303 TS2ac, CT=0.319

TS1ad, CT=0.320 TS2ad, CT=0.335 TS1af, CT=0.261

TS2af, CT=0.211

Figure 1 : Optimized geometries (B3LYP/cc-pVDZ) of the transition structures involved in the *ortho* patways of HDA reaction between 2,3-dihydrofuran (1) and β,δ-unsaturated -ketoesters (2a-f). Bond distances are given in Å, wiberg bond indices are given in parenthesis and the natural charges (*CT*) of TSs are also given.



TS3aa, CT=0.270 TS4aa, CT=0.290 TS3ab, CT=0.274

TS4ab, CT=0.286 TS3ac, CT=0.261 TS4ac, CT=0.269

TS3ad, CT=0.338 TS4ad, CT=0.296 TS3af, CT=0.261

TS4af, CT=0.211

Figure 2 : Optimized geometries (B3LYP/cc-pVDZ) of the transition structures involved in the *meta* patways of HDA reaction between between 2,3-dihydrofuran (1) and β,δ-unsaturated -ketoesters (2a-f). Bond distances are given in Å, wiberg bond indices are given in parenthesis and the natural charges (*CT*) of TSs are also given

The HOMO and LUMO energies, electronic chemical potential μ , chemical hardness η and global electrophilicity ω of the reactants are given in TABLE 2. As can be seen in TABLE 2, the electronic chemical potential (μ) of, 2,3-dihydrofuran 1 ($\mu = 0.0313$) is higher than those of heterodienes, 2a (-0.1017) 2b (-0.1016), 2c (-0.088), 2d (-0.1017) and 2f (-0.0909), which shows the charge transfer is taking place from dienophile 1 to heterodienes 2a-f, in qualitative agreement with the CT analysis performed at the TS structures.

The global electrophilicity of heterodynes 2a-f are 2.850, 2.850, 2.440, 2.820 and 2.550 eV, respectively. According to the absolute scale of electrophilicity, these compounds may be classified as strong electrophiles. The presence of the electron-donating methoxy group decreases the electrophilicity of 2c. On the other hand, 2,3-dihydrofuran 1 has a very low electrophilicity value, 0.36 eV, being classified as a marginal electrophile.

The difference in electrophilicity of the heterodienes and dienophile pair $\Delta\omega$ for HDA reactions have been used to predict the polar character of the cycloadditions. The $\Delta\omega$ values for these HDA reactions are in the range of 2.09-2.50 eV, which indicate that they will present a polar character at the TS.

The parr indices, local electrophilicity indices

TABLE 2 : HOMO energies / au, LUMO energies /au, electronic chemical potential (μ / au), chemical hardness (η / au) and global electrophilicity (ω / eV) for the reactants obtained with the B3LYP/cc-pVDZ level of theory

Structure	E_{HOMO}	E_{LUMO}	μ	η	ω	N
1a	-0.2079	-0.0313	-0.0873	0.2412	0.430	3.499
2a	-0.2437	-0.1017	-0.1727	0.1420	2.850	2.525
2b	-0.2444	-0.1016	-0.1730	0.1428	2.850	2.506
2c	-0.2229	-0.0880	-0.1555	0.1349	2.440	3.091
2d	-0.2481	-0.1017	-0.1749	0.1463	2.820	2.405
2f	-0.2165	-0.0909	-0.1537	0.1256	2.550	3.265

TABLE 3 : The calculated Parr functions (P/au), local electrophilicity indices (ω_k/eV) and local nucleophilicity indices (N_k /eV) at the reactive sites of C_1 and C_2 atoms of the dienophile 1 and for C_3 and O_6 atoms of the heterodienes 2a-f at the B3LYP/cc-pVDZ level of theory

Structure	Location	P+	P-	ω_k	N_k
1a	C1		0.521		1.311
	C2		0.287		1.003
2a	C3	-0.041		0.117	
	O6	0.214		0.612	
2b	C3	-0.079		0.226	
	O6	0.259		0.741	
2c	C3	-0.098		0.240	
	O6	0.148		0.363	
2d	C3	-0.051		0.144	
	O6	0.246		0.696	
2f	C3	-0.075		0.192	
	O6	0.107		0.274	

and local nucleophilicity indices for the atoms C_1 and C_2 of the dienophile 1 and for the atoms C_3 and O_6 of the heterodienes (2a-f) are given in TABLE 3 (see scheme 1 for atom numbering). Parr functions computed based on the mulliken atomic spin density analysis (TABLE 3). According to the Domingo's model[15, 17], in a polar cycloaddition reaction between unsymmetrical reagents, the more favorable two-center interaction will take place between the more electrophile center characterized by the highest value of the local electrophilicity index ω_k at the electrophile, and the more nucleophilic center characterized by the highest value of the local nucleophilicity index N_k at the nucleophile. According to this model, in the reaction between 1 and 2a-f, the most favorable two-center interaction take place between C_1 of dienophile and O_6 of the heterodynes, 2a-f, leading to theformation of 3 regioisomer which is in agreement with the experimental results[9].

CONCLUSION

Mechanism and regioselectivity for the HDA reactions of the 2,3 dihydrofuran (1) and β,δ-unsaturated -ketoesters 2a-f have been studied using DFT method at the B3LYP/cc -pVDZ level of theory. In these HDA reactions both *endo/exo* stereo- and *ortho*/m*eta* regioselectivity pathways have been studied. The smallest energy barrier associated with the *ortho-endo* pathways of studied HDA reactions. Moreover, DFT-based reactivity indices clearly predict the regiochemistry of the isolated cycloadducts.

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