

# Topological model to quantify the global reactivity indexes as local in Diels–Alder reactions, using density function theory (DFT) and local quantum similarity (LQS)

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Received: 17 February 2012 / Accepted: 25 July 2012 / Published online: 11 August 2012  
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**Abstract** In this study is presented a Topological model for quantify the global reactivity indexes as local in Diels–Alder Reactions. Using conceptual density functional theory (DFT) and molecular quantum similarity (MQS), by means of six local similarity indexes: Overlap, Overlap-Interaction, Coulomb, Coulomb-Interaction, with their respective Euclidean distances. Using the Topo-Geometrical Superposition Approach (Topo-Geometrical superposition Algorithm) as method of alignment. This allowed us to obtain good results in local similarity indexes. This methodology proved to be an appropriate technique for the intended purpose, found that values of local electrophilic and hardness calculated are in agreement with the theoretical and experimental mechanism of cycloaddition considered here in this work. In addition chemical potential of Overlap and Coulomb proposed reproduce the trend of the values of the Fukui function ( $F^-$ ) of atom C6 in the dihydrofuran derivatives present in the cycloaddition reaction considered. Taking into account that the C6 carbon atom is responsible for the preferred stereochemistry, this evidence allowed us propose this methodology as alternative way to determining of local reactivity indexes using MQS based on the Hirshfeld partitioning. In addition in this contribution was postulated a new perspectives in the chemical reactivity field such as chemical potential, hardness and electrophilicity relative, alternatives to the traditional (chemical potential, hardness and electrophilicity) proposed in the conceptual DFT which allowed us to relate the

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local reactivity indexes proposed with the global considering that the pursuit of local descriptors of reactivity supported on ideas of MQS in Cycloaddition Reactions.

**Keywords** Diels–Alder reactions · Density functional theory (DFT) · Molecular quantum similarity · TGSA · Fukui function · Global and local reactivity indexes

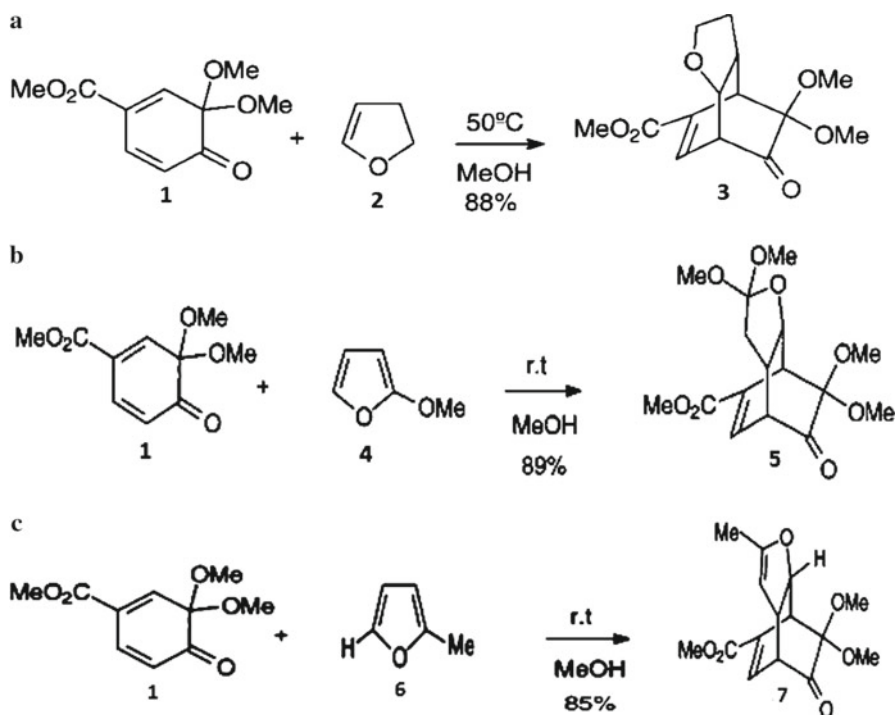
## 1 Introduction

The Diels–Alder reaction is an important reaction in organic chemistry. Since Diels–Alder reaction was discovered some years ago, a large number of experimental and theoretical studies have been developed to obtain information from the mechanism associated with this type of reaction [1–3]. Several rules and theories have been used to understand the nature of this reaction, such as organic frontier molecular orbital (FMO) theory [4], the transition state theory (TST) [5–7] and more recently static reactivity indexes defined within the density functional theory (DFT) [8]. Many studies have been performed to obtain information on the mechanism of Diels–Alder reaction using topological analysis [9–12], showing that the topological analysis is a powerful tool for determining the trajectory of the mechanism and regioselectivity in Diels–Alder reactions.

Not long time ago Domingo and Aurell studied the chemical reaction between masked *o*-benzoquinones and furan derivatives [13]. These authors studied a series of Diels–Alder reactions reported by Liao et al. [14] on cycloaddition reactions between furan derivatives (2, 4 and 6) and the compound 1 (see reactions 1a, 1b, 1c; Fig. 1). Domingo and Aurell concluded that the reaction pathway can take place through a polar stepwise mechanism. To demonstrate this mechanism, in this study we are proposing a methodology with which it is possible to quantify global reactivity indexes in terms of local indexes, this topological analysis is carried out consistently with the polar characteristic of the mechanism proposed in the ref [13].

In this contribution, attention will be focused in the use of theoretical approach based on Quantum Similarity (QS) [15–23] and Density Functional Theory (DFT) based reactivity descriptors [24]. In order to get insight into the factors determining nature of these cycloaddition reactions. First, one can hope that theoretical descriptors could provide indications, or at least trends, as to what factors affect the structural properties of these cycloaddition reactions.

The use of DFT calculation is mainly justified by its superior precision per unit computational cost and the possibility of defining chemical concepts in a precise way using the so-called conceptual DFT [24]. For instance some of these descriptors are: Electronic chemical potential ( $\mu$ ), electrophilicity ( $\omega$ ) hardness ( $\eta$ ) electronegativity ( $\chi$ ) and softness ( $S$ ). Several of such descriptors have been used individually in other studies to understand chemical reactivity and molecular selectivity [31]. In this contribution the basic quantities to be addressed are hardness, electrophilicity and chemical potential at the global level. A detailed discussion of these quantities can be found elsewhere (for detailed accounts see ref [24]). The local property developed in this work is the Fukui function. FF typically is a function that explains the local role of a specific atom within a molecule [24, 31].



**Fig. 1** Cycloaddition reaction of Diels–Alder [13], furan derivatives (Compounds 2, 4 and 6) and masked *o*-benzoquinone (compound MOB 1) are used to propose topological descriptors of reactivity using (DFT) and (MQS)

Molecular similarity indexes measures the similarity between two molecular structures. The idea of similarity index was originally proposed from the point of view of quantum chemistry by Carbó [15–23]. Similarity concept is a universal notion that permeates almost every field of chemistry. Indeed the idea of similarity can be naturally extended to other scientific fields. Typically, the similarity descriptors are applied to compare a certain property among a set of molecular structures.

An important characteristic of the concept of similarity is that similarity never is absolute. This means that there is not absolute measure of similarity. For example when the similarity concept is applied to molecular structures always has biased feature. Notorious efforts to developed algorithms to resolve this problem has been made, in order to estimate the concept of similarity without biased preconceptions [15–23]. In all cases, the similarity concepts and algorithms made to overcome this issue are necessarily associated with some degree of arbitrariness. The present work is concerned with such methodology that is based on similarity indices computed from molecular fields using Carbó approach [15–23]. In the quantum similarity the electron density surrounding each molecule is the most import quantity to be measure [24].

This paper aims at using different field based descriptors such as descriptors rooted in conceptual DFT and molecular quantum similarity (MQS) these descriptors are

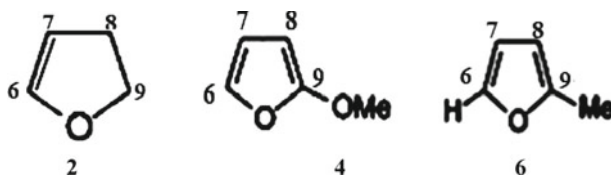
used to assess what information can be obtained from them. More precisely we wish to examine the use of the local reactivity indexes proposed with the global considering that the pursuit of local descriptors of reactivity supported on ideas of MQS in cycloaddition reactions.

In the Fig. 1a–c are shown the reactions considered in the present study.

## 2 Alignment structures and computational details

The Molecular similarity subject has flourishing under the impetus of Carbó. Who has created through it, a theoretical framework for several chemical concepts allowing its qualitative and quantitative use in widely variety of studies [15–23]. Molecular similarity has become an interesting and important topic itself, but also a cornerstone of many important research areas in chemistry. Fields such as structure and substructure heavily depend on the ideas of quantum molecular similarity [15–23].

The problem about how the similarity between different molecules should be addressed is not completely answered so far. The lack of a uniform approach in the characterization of molecular structure is attest to by the multiplicity of methods used to perform Molecular Quantum Similarity (MQS). For this reason many methods have been established to create the best conditions for an optimal overlap including the use of CoMFA and CoMSIA. This idea is widely used nowadays in fields such as biology being used to obtain three-dimensional quantitative structure–activity relationship (QSAR) models [35] in this sense, have been implemented many alignment method among which we can mention the maximum similarity superposition algorithm (MSSA) proposed by Constans et al. [36]. This field-based method takes into account that the optimal alignment provides the maximum value of similarity measures for a given similarity operator, another algorithm implemented in the field of similarity quantum is the Topo-Geometrical superposition Algorithm (TGSA) which was proposed by Girones et al. [37], unlike the (MSSA), this alignment technique considers the optimal alignment of overlap is based on the recognition of a common Skeleton, taking only the kinds of atoms and bond. In this work, a molecular set which has a structural fragment common to all structure was studied. This fragment is also a molecule that is part of the molecular group and not a portion or structural fragment of one of them (Fig. 2).



**Fig. 2** Structure of the Compound dihydrofuran 2, Compound 4 and 6, the compound 2 is used for the alignment with the (TGSA)

## 2.1 Design of molecules, optimization of geometry and calculation of molecular descriptors

The (TGSA) by Carbó and collaborators [23] begins with the recognition of the largest common substructure in the aligned molecules. These types of search algorithms constitute an important field of scientific interest [38].

The structures were optimized with the program Gaussian 98 [39]. The calculation of molecular descriptors, using the (DFT), using the B3LYP/6-31G\* [40] as base of calculation, for the prediction of the total atomic charges and bond distances was used the Chemcraft 1.6 program [43].<sup>1</sup>

## 3 Model equations

### 3.1 Global reactivity indexes

As a detailed presentation and discussion of the DFT based descriptors of the reactivity used in this paper can be found elsewhere [24], only the relevant expressions used for the evaluation of different quantities are given here. The global reactivity indexes can be obtained as:

$$\mu \approx \varepsilon_L + \varepsilon_H \quad (1)$$

$$\eta \approx \varepsilon_L - \varepsilon_H \quad (2)$$

$$S = \frac{1}{\eta} \quad (3)$$

where  $\mu$  is the chemical potential,  $\eta$  global hardness and  $S$  is the global softness. Where  $\varepsilon_L$  and  $\varepsilon_H$  that represent the energies of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), respectively.

Using Eqs. 1 and 3 is possible to determine the electrophilicity ( $\omega$ ) index, defined as:

$$\omega = \frac{\mu^2}{2\eta} \quad (4)$$

where  $\omega$  is another global property and represents the stabilization energy of the system when it is saturated by electrons from the external environment.

The descriptors expressed to Eqs. (1)–(4), also are known as global system descriptors and depend on  $N$  and  $v(r)$  and they provide information on the reactivity and stability of a chemical system [24]. Local properties are obtained taking into account the variation of energy with respect to the external potential, this variation depends on the position ( $r$ ), which is why can be defined as a selectivity index.

<sup>1</sup> ChemCraft 1.6, is a Windows-based graphical program for working with quantum chemistry calculations. It is an affordable and convenient tool for visualization of chemical data and preparing new jobs for calculation. Programming: Grigoriy A. Zhurko, site design, additional support.

However, in order to study selectivity and reactivity it is more advisable to use local reactivity descriptors. Within these we have the Fukui function [24,44,45] which explains the selectivity of a region of a molecule and is defined mathematically as:

$$\langle f(\vec{r}) \rangle = \left( \frac{\delta \mu}{\delta v(\vec{r})} \right)_N = \left( \frac{\partial \rho(\vec{r})}{\partial N} \right)_{v(\vec{r})} = \left( \frac{\partial^2 E}{\partial N \partial v(\vec{r})} \right) \quad (5)$$

The Fukui function is interpreted as the change of chemical potential given an external perturbation, or the variation of the electron density function when the electrons number change. For the calculation of the Fukui function  $f^+$  we used, the condensed approach proposed by Yang and Mortier, using the gross Mulliken [46] charge at atom  $K$ ,  $q_k$ , for the systems with  $N$  and  $N+1$  electrons [47,48]:

$$\langle f_k^+(\vec{r}) \rangle = \int_k [\rho_{N+1}(\vec{r}) - \rho(\vec{r})] = [q_k(N+1) - q_k(N)] \quad (6)$$

$$\langle f_k^-(\vec{r}) \rangle = \int_k [\rho_N(\vec{r}) - \rho_{N-1}(\vec{r})] = [q_k(N) - q_k(N-1)] \quad (7)$$

$$\langle f_k^0(\vec{r}) \rangle = \frac{1}{2} [\langle f_k^+ \rangle + \langle f_k^- \rangle] = \frac{1}{2} [q_k(N+1) - q_k(N-1)] \quad (8)$$

With  $q_k(N)$  denoting the electronic population of atom  $k$  of the system under study, these Fukui functions in the condensate orbital approximation model (AOC) considers only the contribution of the frontier orbitals of an atom [49].

$$\langle f_k^+ \rangle = \int_k \rho_L(\vec{r}) d\vec{r} = q_k^L \quad (9)$$

$$\langle f_k^- \rangle = \int_k \rho_H(\vec{r}) d\vec{r} = q_k^H \quad (10)$$

$$\langle f_k^0 \rangle = \frac{1}{2} [\langle f_k^+ \rangle + \langle f_k^- \rangle] = \frac{1}{2} [q_k^L + q_k^H] \quad (11)$$

Designed  $q_k^L$  and  $q_k^H$  representing the electronic populations on atom  $k$  of the orbitals LUMO and HOMO, respectively.

Dependent of the electronic chemical potential  $\mu$  and the chemical hardness  $\eta$ , which may be approached in terms of the one-electron energies of the frontier molecular HOMO and LUMO,  $\varepsilon_H$  and  $\varepsilon_L$ ,  $\mu \approx \varepsilon_L + \varepsilon_H$  and  $\eta \approx \varepsilon_L - \varepsilon_H$ , respectively

### 3.2 Similarity index

The MQS field was introduced by Carbó [15,16]. He defined the Euclidean distance,  $D_{AB}$ , between the electron densities  $\rho_A(r)$  and  $\rho_B(r)$  of two molecules A and B as:

$$D_{AB} = \int |\rho_A(r) - \rho_B(r)|^2 dr = \int \rho_A^2(r) dr + \int \rho_B^2(r) dr - 2 \int \rho_A(r)\rho_B(r) dr \quad (12)$$

This index can be represented geometrically using the concept of cosine of angle subtended between the density functions taking account that can represent vectors, it can be written as:

$$R_{AB} = \frac{\int \rho_A(r)\rho_B(r) dr}{[(\int \rho_A^2(r) dr) (\int \rho_B^2(r) dr)]^{1/2}} = \frac{Z_{AB}}{\sqrt{Z_{AA}Z_{BB}}} \quad (13)$$

This equation involving the overlap integral  $Z_{AB}$ , often called Molecular Quantum Similarity Measure (MQSM), between the electron densities of molecules A and B.  $Z_{AA}$  and  $Z_{BB}$  are called the Molecular Quantum Self-Similarity Measures of molecules A and B [15,57], respectively.

As the molecules studied have differences in molecular fragments having a skeleton in common, was used (MQSM) of molecular fragments, taking into account the expression:

$$Z_{AA}^x(\Omega) = \int \int \rho_A^x(r_1)\Omega(r_1,r_2)\rho_A^x(r_2)dr_1dr_2 \quad (14)$$

where  $\Omega(r_1,r_2)$  represents the associated operator used in the similarity measure, the use of this type the descriptors upon molecular fragments [57,58] is partly based on the holographic theorem of the electronic density, which assures that the information contained in the total electronic density is also present in the local density of a particular fragment.

### 3.3 Local molecular quantum similarity indexes (LMQSI)

The Hirschfeld Approach was developed [54], to calculate the so-called stockholder charges [55]. Considering that the compound **6** with respect to dihydrofuran **2** only differs structurally by the presence of a molecular fragment (methyl). Assume that these structures differ by the presence of different atoms, carbon (Fig. 1c) of compound **6(C6)**, with the dihydrofuran carbon (**C2**) (Fig. 1a), this assumption is justified by the presence of an additional carbon bond in the compound **6**.

According to Hirshfeld [54], which suggested that the electron density of a molecule can be distributed in contributions at atomic level, obtaining atoms-in-molecules densities by defining the “stock-amount” or weight of an atom (**C6**) in the electron density at  $r$  as:

$$w_{c,6} = \frac{\rho_{c,6}^0(r)}{\sum_X \rho_{X,c,6}^0} \quad (15)$$

where,  $\rho_{c_6}^0(r)$  is the electron density of the isolated carbon (C6) atom in the molecule, and  $\sum_X \rho_{X,c_6}^0$  is the promolecular density of the molecule, obtained as the sum of the isolated atom densities in the same molecular geometry as the actual molecule. If it is furthermore assumed that these weight coefficients remain valid for the true functional density of the molecule. The Hirshfeld atomic electron density of the atom  $a$  in the molecule [54,55], denoted, can be calculated as:

$$\rho_{c_6}(r) = w_{c_6}(r)\rho_{c_6}^0(r) \quad (16)$$

Analogously, for the Compound 2

$$w_{c^2} = \frac{\rho_{c^2}^0(r)}{\sum_Y \rho_{Y,c^2}^0} \quad (17)$$

The numerator of the Carbó index then becomes

$$Z^{local,c^6} = \int w_{c^6}\rho(r)dr = \int \left( \frac{\rho_{c^6}^0(r)}{\sum_X \rho_{X,c^6}^0} \right) \rho_{c^6}(r)dr \quad (18)$$

and, for the Compound 2

$$Z^{local,c^2} = \int w_{c^2}\rho(r)dr = \int \left( \frac{\rho_{c^2}^0(r)}{\sum_X \rho_{X,c^2}^0} \right) \rho_{c^2}(r)dr \quad (19)$$

whereas that the self-similarities  $Z_{c^2c^2}$  and  $Z_{c^6c^6}$  can be written analogously in terms of atomic contributions.

Thus, using Eqs. (18) and (19) in the expression of the Carbó index (Eq. 13), the global index is converted into a local analogue:

$$R_{c^2c^6}^{local} = \frac{\int \left( \frac{\rho_{c^2}^0(r)}{\sum_X \rho_{X,c^2}^0} \right) \left( \frac{\rho_{c^6}^0(r)}{\sum_Y \rho_{Y,c^6}^0} \right) \rho_{c^2}(r)\rho_{c^6}(r)dr}{\left[ \int \left( \frac{\rho_{c^2}^0(r)}{\sum_X \rho_{X,c^2}^0} \right) \rho_{c^2}(r)\rho_{c^2}(r)dr \right]^{1/2} \left[ \int \left( \frac{\rho_{c^6}^0(r)}{\sum_Y \rho_{Y,c^6}^0} \right) \rho_{c^6}(r)\rho_{c^6}(r)dr \right]^{1/2}} \quad (20)$$

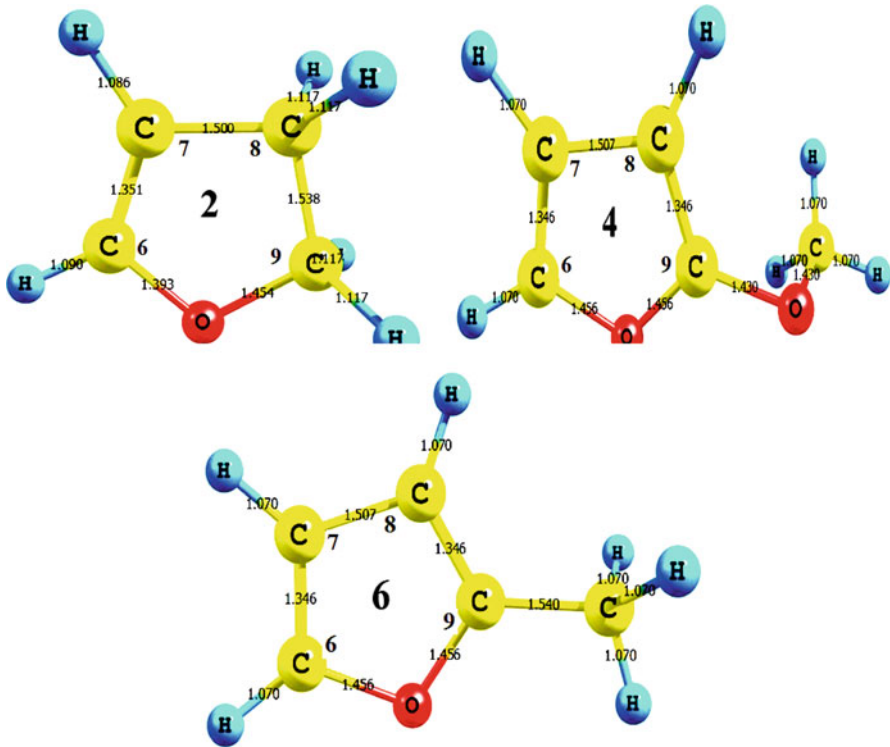
where the global index is partitioned in atomic contributions, allowing have considerations to local level.

## 4 Results and discussion

### 4.1 Topological analysis proposed for Diels–Alder reactions

The interatomic distances among the atoms of the compounds 2, 4 and 6 are analyzed in Fig. 3. The C-C bond distances of these molecular set are different in these





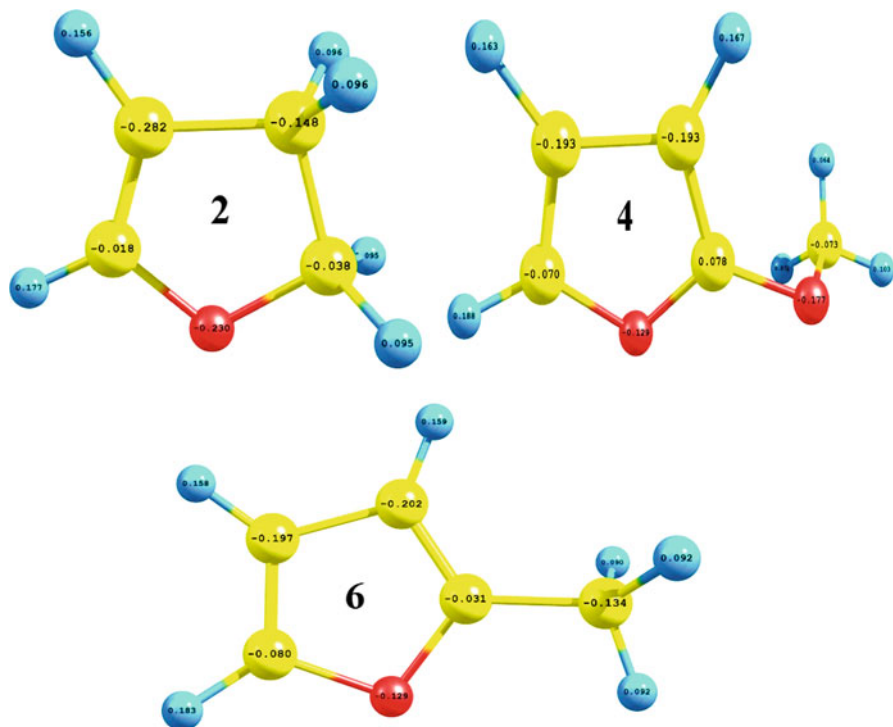
**Fig. 3** Bond lengths (Å), for the Compounds 2, 4 and 6, using Chemcraft 1.6 program [43]

molecules. So, we can assume that this difference or (dis)similarity is due to the presence of substituent groups on compounds 4 and 6 with respect to compound 2. For this reason, in this contribution is proposed a topological analysis characterized by the calculation of molecular quantum similarity local atomic (MQSLA) through the multiplication of MQS index of Carbó with MQSLA using Eqs. (12)–(20) by the absolute value of the total atomic charges shown in the Fig. 4, using Eq. (21), the calculate of the local atomic similarities of the compounds 4 and 6 with respect to compound 2. These results are depicted in Table 2, using the values of the (MQS) of the Table 1.

$$R_{c^2c^n}^{local-Atomic} = MQSLA |C.Atomic| \quad (21)$$

where  $n = 6, 7, 8, 9$ , represent the positions of the local carbon atoms analyzed according to the numbering used for the molecular alignment using TGSA approach (Fig. 2). Taking into account that the compounds analyzed 4 and 6 are derivatives of dihydrofuran 2. We used the Eq. (21) in order to calculate the local atomic physicochemical descriptor which can describe the atomic charges of the compounds 4 and 6 with respect to compound 2, so that Eq. (21) allows us quantify the MQSLA.

The molecular structure of compound 2 (Table 2) has more similarity with the molecule 6 quantified by Quantum Similarity Index of Overlap 0.897 and the Coulomb



**Fig. 4** Total atomic charges (au), for the Compounds 2, 4 and 6, using Chemcraft 1.6 program [43]

**Table 1** Similarity index (Eq. 13) (both analytical and numerical methods) and Euclidean distance (Eq. 3), using global densities for the 2 versus 4 and 6

Molecule(2) <sup>a</sup>	Z(O) <sup>b</sup>	Z(C) <sup>c</sup>	SI(O) <sup>d</sup>	SI(C) <sup>e</sup>	$D_{CP}(O)$ <sup>f</sup>	$D_{CP}(C)$ <sup>g</sup>
4 (Fig. 1b)	4.439	265.142	0.783	0.897	1.648	7.488
6 (Fig. 1c)	5.449	339.606	0.897	0.979	1.007	3.749

<sup>a</sup> Fig. 1

<sup>b</sup> Interaction of Overlap

<sup>c</sup> Interaction of Coulomb

<sup>d</sup> Similarity Index of Overlap

<sup>e</sup> Similarity Index of Coulomb

<sup>f</sup> Euclidean Distance of Overlap

<sup>g</sup> Euclidean Distance of Coulomb

0.979, comparing these two values show that the Coulomb index is the best descriptor of similarity in comparison with the of Overlap value, taking into account that naturally the Carbó index is limited to the range (0, 1], where  $C_{AB} = 1$  means Self-Similarity.

In addition to the calculation of MQSLA indexes, in this work we propose a topological analysis based on the multiplication of global reactivity indexes (electrophilic chemical potential and chemical hardness) with MQS indexes. Taking into account

**Table 2** Calculation of (MQSM) local atomic (MQSLA) Eq. (21)

	Z(O) <sup>b</sup>	Z(C) <sup>c</sup>	SI(O) <sup>d</sup>	SI(C) <sup>e</sup>	D <sub>CP(O)</sub> <sup>f</sup>	D <sub>CP(C)</sub> <sup>g</sup>
Compound 2 <sup>a</sup> versus Compound 4						
$R_{c^2c^9}^{local}$	0.169	10.075	0.029	0.034	0.063	0.285
$R_{c^2c^8}^{local}$	0.657	39.241	0.116	0.133	0.244	1.108
$R_{c^2c^7}^{local}$	1.252	74.770	0.221	0.252	0.465	2.111
$R_{c^2c^6}^{local}$	0.080	4.772	0.014	0.016	0.029	0.134
Compound 2 <sup>a</sup> versus Compound 6						
$R_{c^2c^9}^{local}$	0.207	12.905	0.034	0.037	0.038	0.142
$R_{c^2c^8}^{local}$	0.806	50.262	0.133	0.145	0.149	0.555
$R_{c^2c^7}^{local}$	1.537	95.769	0.253	0.276	0.284	1.057
$R_{c^2c^6}^{local}$	0.098	6.112	0.016	0.018	0.018	0.067

<sup>a</sup> Fig. 1<sup>b</sup> Interaction of Overlap<sup>c</sup> Interaction of Coulomb<sup>d</sup> Similarity Index of Overlap<sup>e</sup> Similarity Index of Coulomb<sup>f</sup> Euclidean Distance of Overlap<sup>g</sup> Euclidean Distance of Coulomb

that the structures considered in this study are derived from dihydrofuran 2.

$$\omega_{2k} \approx \omega R_{c^2c^n}^{local} \approx \frac{\mu^2}{2\eta} R_{c^2c^n}^{local-Atomic} \quad (22)$$

$$\mu_{2k} \approx \mu R_{c^2c^n}^{local} \approx (\varepsilon_L + \varepsilon_H) R_{c^2c^n}^{local-Atomic} \quad (23)$$

$$\eta_{2k} \approx \eta R_{c^2c^n}^{local} \approx (\varepsilon_L - \varepsilon_H) R_{c^2c^n}^{local-Atomic} \quad (24)$$

where  $n = 9, 8, 7, 6$  and  $2k = (\text{Compound 2}) (\text{Compounds 4 and 6})$ , these Eqs. (22)–(24) represent the similarity in molecules fragments, taking into account that the differences of the Compounds 2, 4 and 6 with respect to the furan are the substituent groups, the contributions of similarity in the structures 4 and 6, can be quantified in the local carbon atom C2. (See Fig. 1.) From this point of view, we can suggest that the reactivity indexes of global and local contributions, allow us to obtain topological considerations of the electron density to local level.

In this theoretical model was proposed that the chemical potential, hardness and electrophilicity total can be obtained by the Eq. 25.

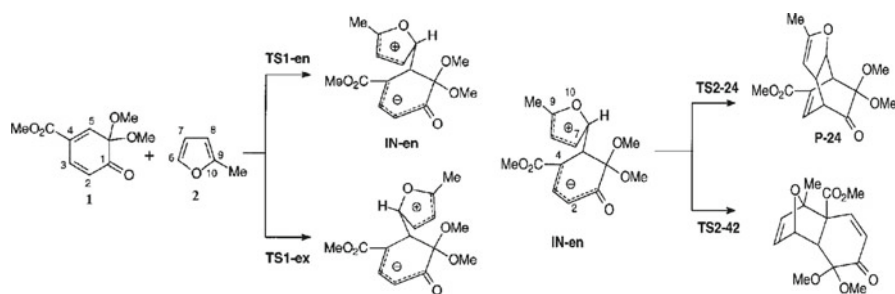
$$U_{2kJ} : \sum_{n:6}^9 R_{c^2c^n}^{local-Atomic} \quad (25)$$

where  $U : \mu, \eta, \omega, 2k: (\text{Compound 2}) (\text{Compounds 4 and 6})$ , and  $J: (\text{O: Overlap and C: Coulomb, respectively})$ ; these results are shown in the Table 3, the total reactivity

**Table 3** Proposed total reactivity descriptors, calculated with the Eq. 25

Molecule	Overlap ( $\mu_{TO}$ )	Coulomb ( $\mu_{TC}$ )	Overlap ( $\eta_{TO}$ )	Coulomb ( $\eta_{TC}$ )	Overlap ( $\omega_{TO}$ )	Coulomb ( $\omega_{TC}$ )
22	-0.039	-0.039	0.247	0.247	0.360	0.360
24	-0.030	-0.035	0.590	0.106	0.497	0.156
26	-0.034	-0.038	0.107	0.118	0.178	0.270

<sup>a</sup> Electronic chemical potential,  $\mu$  and chemical hardness,  $\eta$  values are in atomic units; electrophilicity power values,  $\omega$  are in electronvolts



**Fig. 5** Two of the possible Stereochemical pathways of reactivity between the Compound 1 and 2: (i) The initial attack of compound 2 to 1, corresponding to the endo and exo approach of 2-methylfuran to the position 3 belonging to the diene system MOB1, the product P-24: Cycloaddition {2+4} and (ii) Via P-42 is the Cycloaddition {4+2}. Ref [13]

descriptor provides considerations about the reactivity of the system (C6-C7-C8-C9), used for the analysis proposed in this study (Figs. 1, 2).

#### 4.2 Topological similarity analysis proposed: global reactivity indexes as local in Diels–Alder reactions

An analysis of the potential energy surfaces (PES) was performed by Domingo and Aurell [13] for the reaction between masked o-benzoquinone (MOB) and compound 6. Indicating that this reaction takes place along of the reaction path a cycloaddition mechanism stepwise (Fig. 5). This mechanism is initiated by the nucleophilic attack of the carbon atom unsubstituted C6 of 2-methylfuran to the C5 carbon atom of an intermediary Zwitterion MOB1. Occasionally this can occur after the cyclization of the intermediate along the formation of a new C-C bond, to obtain the final product (Channel TS1-en).

The electronic chemical potential (Table 4) MOB1 ( $\mu = -0.1674$  au for the Compound (1) is less than the chemical potential of compound 6 ( $\mu = -0.0946$  au). Taking into account that the two stereoisomeric reactive channels (the attack on the ortho and meta position) are possible for the furan derivatives (Fig. 5), the C6 position

**Table 4** The static global properties, for derivatives of furan studied (2, 4 and 6, Fig. 2), using Eqs. 1–4

Molecule	$\mu$	$\eta$	$\omega$
1 (Fig. 1)	-0.167	0.145	2.62
2 (Fig. 1a)	-0.080	0.247	0.36
4 (Fig. 1b)	-0.079	0.229	0.37
6 (Fig. 1c)	-0.094	0.236	0.52

Electronic chemical potential,  $\mu$  (au), and chemical hardness,  $\eta$ , values are in atomic units; electrophilicity power values,  $\omega$ , are in electronvolts [13]

of 2-methylfuran is more nucleophilic [58]<sup>2</sup> discarding the study in the C7 position of the compound 2 in the conjugated position MOB2 C5 [59]. With this experimental and theoretical evidence, we calculated the MQS indexes local Table 1, using LMQSI: Overlap-Interaction, Coulomb-Interaction, similarity Overlap, Coulomb similarity, and Euclidean distances of Overlap and Coulomb.

The values of global and local reactivity indexes obtained in this study using the Eqs. (12)–(14) are depicted in Table 5.

The values calculated with the total reactivity index proposed in Eq. 25 for chemical potential, chemical hardness and electrophilicity respectively are depicted in Table 5.

The Fukui values ( $F^-$ ), that represent the susceptibility of be attacked for electrophilic species, Ref [13], for the Cycloaddition studied are displayed in Table 5 (see Fig. 1)

The values of chemical potential calculated for compounds 4 and 6 are shown in Table 5. Note that in all cases the values of  $\mu_{2n} R_{c^2c^6}^{local}$  are higher than  $\mu_{2n} R_{c^2c^9}^{local}$ , where n: compound 4 and 6, are in agreement with the stereochemical preference as is depicted in the Fig. 6, which means that the carbon atom (C6) is more similar than the carbon atom (C9) to allow electrons that flow from the electron cloud, which agrees with observed values of Fukui ( $F^-$ ), this is manifesting in increased susceptibility to form bonds with the MOB 1, the same trend is observed in hardness and electrophilicity index proposed, where we can say the C6 position consistently has the lowest energy of stabilization when it is capable of receiving electrons from the MOB 1.

Comparing the hardness values (Table 5) of the carbon atom C6 and C9 of the compounds 4 and 6, show that the hardness values on the C9 is greater than the C6, indicating that the C6 carbon atom has an enormous opposition to distort the electron cloud favoring the formation of a bond with MOB1, which allows us say that these dihydrofuran derivatives have similar chemical behavior which are confirmed by the Fukui functions (Fig. 6), this is a reason more for the inclusion of the quantum similarity in the chemical reactivity field, taking into account that the search for models to explain the pericyclic reactions is an area of continuing interest [59–64].

<sup>2</sup> The unusual meta regioselectivity for these Cycloaddition has also been studied, optimizing the TS corresponding to the nucleophilic attack of the C7 position of 3b on the C5 position of the MOB 2 along the endo/ortho reactive channel (see the Supporting formation). The ortho TS, which corresponds to an asynchronous concerted process, is 12.7 kcal/mol more energetic than the meta TS1-en, in agreement with the exclusively meta regioselectivity observed for these furan derivatives.

**Table 5** Static local properties proposals, for the derivatives of furan (2, 4 and 6), using the Eqs. (12–14), Tables 1 and 4

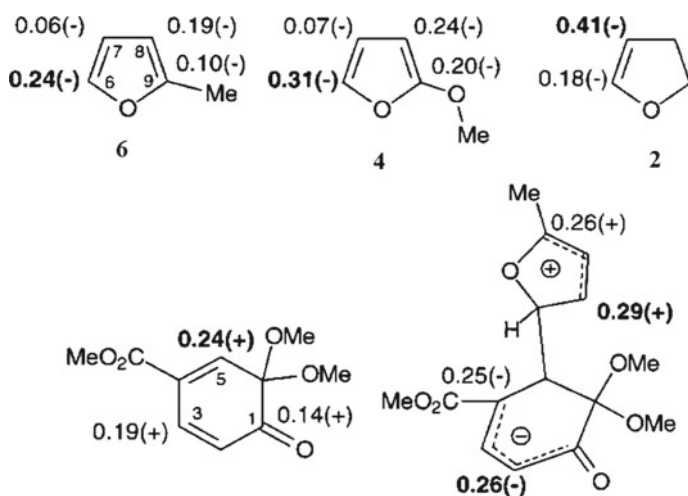
	Z(O) <sup>b</sup>	Z(C) <sup>c</sup>	SI(O) <sup>d</sup>	SI(C) <sup>e</sup>	D <sub>CP</sub> (O)  <sup>f</sup>	D <sub>CP</sub> (C)  <sup>g</sup>
Compound 2 <sup>a</sup> versus Compound 4						
$\mu_{24}R_{c_2c_9}^{local}$	-0.013	-0.809	-0.230*	-0.270*	0.500*	0.023
$\mu_{24}R_{c_2c_8}^{local}$	-0.052	-3.151	-0.930*	-0.011	0.020	0.089
$\mu_{24}R_{c_2c_7}^{local}$	-0.101	-6.004	-0.017	-0.020	0.037	0.169
$\mu_{24}R_{c_2c_6}^{local}$	-0.640*	-0.383	-0.110*	-0.120*	0.230*	0.011
Compound 2 <sup>a</sup> versus Compound 6						
$\mu_{26}R_{c_2c_9}^{local}$	-0.017	-1.032	-0.270*	-0.300*	0.300*	0.011
$\mu_{26}R_{c_2c_8}^{local}$	-0.064	-4.021	-0.010	-0.012	0.012	0.044
$\mu_{26}R_{c_2c_7}^{local}$	-0.122	-7.662	-0.020	-0.022	0.023	0.085
$\mu_{26}R_{c_2c_6}^{local}$	-0.780*	-0.489	-0.130*	-0.140*	0.140*	0.540*
Compound 2 <sup>a</sup> versus Compound 4						
$\eta_{24}R_{c_2c_9}^{local}$	0.042	2.489	0.730*	0.840*	0.016	0.070
$\eta_{24}R_{c_2c_8}^{local}$	0.162	9.693	0.029	0.032	0.060	0.274
$\eta_{24}R_{c_2c_7}^{local}$	0.309	18.468	0.055	0.062	0.114	0.521
$\eta_{24}R_{c_2c_6}^{local}$	0.019	1.786	0.350*	0.400*	0.720*	0.033
Compound 2 <sup>a</sup> versus Compound 6						
$\eta_{26}R_{c_2c_9}^{local}$	0.051	3.187	0.840*	0.910*	0.930*	0.035
$\eta_{26}R_{c_2c_8}^{local}$	0.199	12.415	0.033	0.036	0.037	0.137
$\eta_{26}R_{c_2c_7}^{local}$	0.380	23.655	0.062	0.068	0.070	0.261
$\eta_{26}R_{c_2c_6}^{local}$	0.024	1.509	0.400*	0.440*	0.440*	0.017
Compound 2 <sup>a</sup> versus Compound 4						
$\omega_{24}R_{c_2c_9}^{local}$	0.060	3.627	0.010	0.012	0.023	0.103
$\omega_{24}R_{c_2c_8}^{local}$	0.237	14.127	0.402	0.048	0.089	0.399
$\omega_{24}R_{c_2c_7}^{local}$	0.451	26.92	0.080	0.090	0.167	0.756
$\omega_{24}R_{c_2c_6}^{local}$	0.028	1.718	0.500*	0.580*	0.010	0.048
Compound 2 <sup>a</sup> versus Compound 6						
$\omega_{26}R_{c_2c_9}^{local}$	0.048	4.646	0.034	0.013	0.013	0.051
$\omega_{26}R_{c_2c_8}^{local}$	0.290	18.094	0.048	0.052	0.149	0.199
$\omega_{26}R_{c_2c_7}^{local}$	0.553	34.477	0.091	0.099	0.102	0.381
$\omega_{26}R_{c_2c_6}^{local}$	0.035	2.200	0.500*	0.650*	0.650*	0.024

The Electronic chemical potential ( $\mu$ ) is taken as absolute value, expressing the global reactivity index with respect to the Euclidian Distances between the reactants

<sup>a</sup> Fig. 1

\* (Multiplied by  $10^2$ )

Analyzing compound 2, we can see different results with respect to compounds 4 and 6. For instant the greatest value of the Fukui function in the compound 2 is at the C7 carbon atom meanwhile to compounds 4 and 6 is on carbon 6 (see Fig. 6). This result is in agreement with data shown in Table 3, because the local Electrophilic

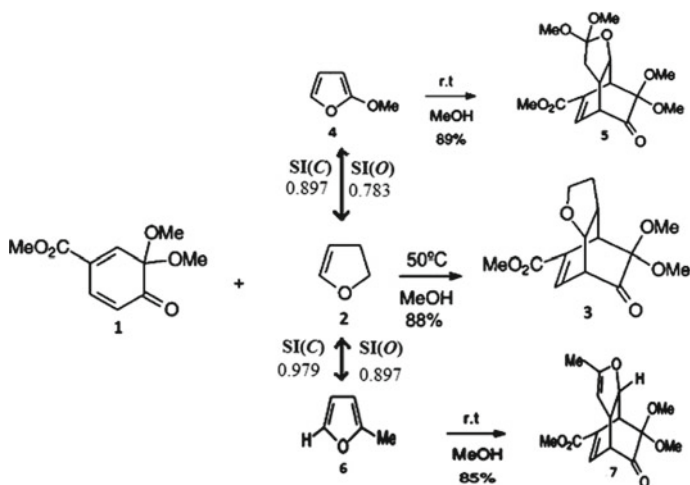


**Fig. 6** Fukui functions for electrophilic ( $F^-$ ) attacks for the furan derivatives 2, 4, and 6, and the intermediate IN-en of Channel TS1-en (Fig. 5), the higher values in the Fukui functions are shown in *bold* [13]

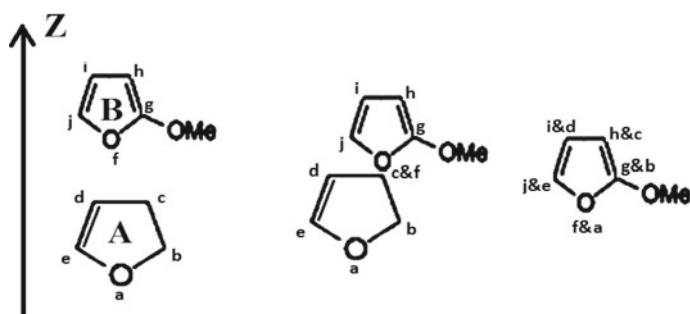
Self-similarity proposed for these derivatives can be associated with the carbon atoms C6 and C7 with a value of ( $\omega_k = 0.36$  eV). For the reactivity descriptors proposed of Overlap and Coulomb. The maximum value  $\omega_{TO}$  is observed when compared the compound 2 with 4 and the lower value is when compared 2 with 6, which agrees with the structural characteristics and the similarity measured of quantum Coulomb index between compounds 2 and 4 (**0.897**), Table 1.

The complementarity between the Fukui functions and local reactivity indexes that is propose in the present work (Tables 4, 5) are in agreement with the results reported by Domingo and Aurell [13] in the analysis of the Fukui functions and with the explanations of the unusual meta regioselectivity found in these dihydrofuran derivatives as is showing in Fig. 5 and the ortho regioselectivity of this type of Cycloaddition. These results lead us to postulate this work as tool for topological analysis, considering the regioselectivity and stereochemistry associated with this type of Cycloaddition.

The total chemical potential proposed and calculated with Eq. 26 is showed in Table 3. With values of: *Overlap*( $\mu_{TO22}$ ) :  $-0.039$ , *Overlap*( $\mu_{TO24}$ ) :  $-0.030$ , *Overlap*( $\mu_{TO26}$ ) :  $-0.034$ , and *Coulomb*( $\mu_{TO22}$ ) :  $-0.039$ , *Coulomb*( $\mu_{TO24}$ ) :  $-0.035$ , *Coulomb*( $\mu_{TO26}$ ) :  $-0.038$  (Table 3). This has the same trends  $\{4 > 6 > 2\}$  that the values found for the Fukui functions of atom C6 in the compounds 2, 4 and 6  $f_2^- : f_4^- : f_6^- : 0.18, 0.31, 0.24$  (see Fig. 6). Considering that the C6 carbon atom is responsible for the preferred stereochemistry (Fig. 5), which allow us say that this set of indexes can be considered as local reactivity indexes associated with the carbon atom C6 in addition, this indexes proposed we can associate with the sensibility in the chemical potential of the Fukui functions with respect to the external distributions and can be expressed mathematically by the relationship [30,65]:



**Fig. 7** Similarity relations that quantify the global reactivity indexes as local in Diels–Alder reactions (Tables 4, 5, 3)



**Fig. 8** The Compound 2 (A) and Compound 4 (B). A is moved along the Z-axis producing higher spatial overlap with B

$$f(r) = \left[ \frac{\delta\mu}{\delta v(r)} \right]_N \quad (26)$$

The Eq. (26) provides the mathematical evidence of the complementarity of the chemical potential with the functions of Fukui that was evidenced in the local reactivity indexes proposed. The relationships of similarity indexes that allow quantify the global reactivity indexes as local are shown in Fig. 7.

Due to that the reactions depicted in Fig. 7 have a large ionic character [13] in this study is analyzed the corresponding reagents with their intermediaries, as a consequence the local Fukui functions of the reagents 2, 4, 6 (Eq. 26), and it is related with the stereochemistry reported for this type of Diels–Alder Cycloaddition through of the reactivity indices proposed (Eqs. 12–15) [13].

The dependence of the MQSM of overlap on the mutual position of both molecules in space is shown in Fig. 8. Molecular alignment thus has important influence on the



MQSM. One of the applications of MQS is the possibility to quantitatively express the similarity and especially to compare and order the degree of similarity over pairs of molecules. These important characteristics of MQSM can be discerned from Fig. 8. Analyzing only the carbon atoms in the molecules (A and B), the first maximum occurs when the first two atoms (c and f in Fig. 8) coincide, all these orientations give rise to interactions of Overlap and Coulomb which are quantified by MQS indexes of Overlap and Coulomb, (see Table 1), giving rise to reactivity indexes proposed in this study from the point of view of the interactions produced by the orientations. The importance of these new techniques lies in the finding of similar characteristics that allow us to correlate structures in organic physicochemical [66].

## 5 Conclusions

In this paper it is postulated that “*a system can be quantified in terms of another*” this can be related with the intrinsic nature of conceptual DFT [67,68]. In this case we expressed a characterization of the global chemical reactivity as a function of local reactivity in Diels–Alder reactions, obtaining consistent results with the behavior of stereochemical experimental and theoretical mechanism for this type of Cycloaddition, Fig. 1.

In this work it is proposed a Topological model for expressing the global reactivity indexes as locals in a series of furan derivatives involved in cycloaddition reactions. For this purpose we used DFT and MQS. The alignment method used is based on the TGSA, this method has been proved to be a good methodology of alignment, taking into account that in the field of the quantum similarity this aspect is very important because its results can depend on it, considering that the similarities in chemical reactivity depends on the molecular properties, and ultimately of the electronic structures, so basically the chemical similarities are manifested in the comparison of molecular behavior, as we can see in the expression of reactivity global indexes as locals. This is consistent with the trend of the Fukui functions and can explaining the charge transfer present in the Diels–Alder Cycloaddition, considered in this study (see Fig. 1).

In this topological model we postulate a new local reactivity indexes that quantify the chemical potential, hardness and electrophilicity (see Eqs. 22–25). These local indexes proposed were characterized taking into account the characteristic tendency of the reactivity indexes such as the Fukui function of species related to interactions with electrophiles ( $F^-$ ). In addition, the chemical potential related with the Overlap and Coulomb indexes proposed in this model reproduce the trend of the values of the Fukui function ( $F^-$ ) of C6 atom in the Cycloaddition reaction (see Fig. 6), considering that the C6 carbon atom in the dihydrofuran derivatives present in the Cycloaddition reaction is responsible for the preferred stereochemistry, justifying the formation of product P-24 along a polar stepwise process (see Fig. 5), allowing the postulation of local reactivity indexes proposed, and presenting an alternative for propose local indexes in the field of quantum similarity in addition to the commonly used based on the Hirshfeld partitioning, taking into account the importance of creating new methodologies that provide new tools to calculate local reactivity descriptors complementary to Fukui functions. This is an important topic, considering that condensed form of

these functions have ambiguities [24,69], proposing new reactivity relationships in the field of pericyclic reactions which has been an area of interest for a long time, specifically in the reactions of 1,3-dipolar cycloaddition [70] in where it is common to find furans acting as dipolarophiles [71], so that new tools of topological analysis can contribute to the clarification of theoretical reaction mechanism of this type of cycloaddition, taking account that this is an area of great interest in organic Physicochemical [72,73].

**Acknowledgments** R.V.R. wishes to thank the Universidad de Cartagena (Cartagena, Colombia), for continuous support to his group. A.M.B. thanks Universidad Nacional Andres Bello (Santiago-Chile), for a PhD fellowship: CONICYT (63100003) is highly appreciated.

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