A competitive Diels-Alder/1, 3-dipolar cycloaddition reaction of1-H-imidazole 3-oxide toward sulfonyl methane. A DFT study on the energetic and regioselectivity

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ABSTRACT

The dual diene/1,3-dipolar character of 1-H-imidazole 3-oxide, **HIO 1**, allows this compound to participate in a competitive Diels-Alder (DA)/1,3-dipolar cycloaddition (13DC) reaction toward C=S double bond of the electro-deficient sulfonyl methane **SFM 2**. The B3LYP/6-311++G(d,p) calculated relative Gibbs free energies indicate that among the studied 13DC and DA reactions, former is completely preferred over the latter in the gas phase as well as in the presence of dichloromethane (DCM). This 13DC reaction takes place through a one-step mechanism to generate corresponding five-membered cycloadduct *via* a quite C1-S5 regioselective fashion which is controlled by theHOMO$_{(HIO\ 1)}$- LUMO$_{(SFM\ 2)}$ interaction.The aromatic character of **HIO 1** which is lost along the studied cycloaddition reaction is responsible for the relatively high activation Gibbs free energies and the endergonic character of these thermodynamically reversible reactions. The quite C1-S5 regioselectivity, resulted from energetic studies, in the investigated 13DC reactioncan be explained usingcalculated electrophilic and nucleophilic Parr functions at the reactive sites of reagents.

Keywords: Diels-Alder and 1, 3-dipolar cycloaddition reactions; Regioselectivity; DFT reactivity indices; FMOs interaction; Parr functions

INTRODUCTION

Among cycloaddition reactions, there are two well-known and very helpful type of reactions namely Diels-Alder (DA) and 1,3-dipolar cycloaddition (13DC) reactions. In a DA reaction, discovered byOtto Diels and Kurt Alderin 1920s [1], an s-cis diene is attacked with a dienophile to generate corresponding six-membered cycloadduct. A 13DC reaction, introduced by Huisgen and co-workers in 1960 [2], makes sense when a 1,3-dipole is attacked by a dipolarophile to afford five-membered cycloadduct. It should be noted that when a compound includes unsaturated bond(s), it can act as either dienophile in a DA reactionor dipolarophile in a 13DC one.

The diversity of functional groups which can be substituted in reagentsskeleton involved in DA and 13DC reactions makes them two of the most valuable synthetic organic reactions [3-5]. In this relation, when adequate substitutions displaying appropriate electronic nature are present in reagents, not only is corresponding DA and/or 13DC reaction considerably accelerated but the regioselectivity can also beimproved [6].

Using frontier molecular orbital (FMO)

theory Fleming explained regioselectivity and reactivity in the DA and 13DC reactions [7]. Considering FMO theory, cycloaddition reactions were classified by Sustmann in three different types: i) one, the normal electron demand (NED) reactions in which the reactivity and regioselectivity are controlled with the HOMO (highest occupied molecular orbital) of diene/1,3-dipole and the LUMO (lowest unoccupied molecular orbital) of dienophile/dipolarophile interaction; ii) two, the inverse electron demand (IED) reactions in which the LUMO of diene/1,3-dipole and the HOMO of dienophile/ dipolarophile interaction controls the reactivity and regioselectivity; and iii) three, in which due to similarity of FMO energy levels of reactants, any HOMO-LUMO interaction between a diene/dienophile and/or 1,3-dipole/ dipolarophile pair can be important in the determining of regioselectivity and reactivity [8, 9].

Nowadays, global and local reactivity indices defined within the conceptual density functional theory (DFT) are widely used as a powerful tool to explain reactivity as well as regioselectivity in cycloaddition reactions. In this way, while global DFT reactivity indices such as global electrophilicity and nucleophilicity explain reactivity, local DFT indexes can nicely elucidate regioselectivity [3-5].

When a reagent can potentially act as both diene and 1, 3-dipole, the study of cycloaddition reaction of such compound toward an unsaturated bond can be much interesting since a 13DC and DA reaction can compete together. One of such compounds comprising both diene and 1,3-dipolarcharacter is 1-H-imidazole 3-oxide which can participate in a competitive DA/13DC reaction toward an unsaturated bond to generate corresponding six- or five-membered cycloadducts. It is worth noting that involvement of dienophiles/ dipolarophiles including C=S double bonds, *e.g.* sulfonyl methane, compared with C=C, C=O, and C=N ones, have usually received less attention while the high reactivity of C=S double bonds in 13DC reactions toward nitrones, diazoalkanes, and thiocarbonyl ylides has well been documented [4]. On the other hand, participation of aromatic compounds such as 1-H-imidazole 3-oxide in cycloaddition reactions demands highly activated unsaturated bonds and harsh reaction conditions. Consequently, a theoretical study on the cycloaddition reaction of1-H-imidazole 3-oxide toward sulfonyl methane presents its exclusive features which can be attractive for experimentalists in particular who are interested in the field of synthesis five-and/or six-membered cyclic compounds *via* cycloaddition reactions.

Herein, a DFT study at the B3LYP/6-311++G(d,p) level is performed on the cycloaddition reaction between 1-H-imidazole 3-oxide, **HIO1**, and sulfonyl methane, **SFM 2**, in order to a complete characterization of energetic as well as the regioselectivity of this process.

COMPUTATIONAL DETAILS
The DFT computations were carried out using the B3LYPexchange-correlation functional, together with the standard 6-311++G (d, p) basis set [10]. Optimizations were performed using the Berny analytical gradient optimization method [11]. The stationary points were characterized by frequency calculations in order to verify that TSs have one and only one imaginary frequency. The IRC paths [12] were traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism using the second order González-Schlegel integration method [13]. Solvent effects of dichloromethane (DCM) in the optimizations were taken into account

using the polarizable continuum model (PCM) as developed by Tomasi's group [14] in the framework of the self-consistent reaction field (SCRF) [15]. Values of enthalpies and Gibbs free energies in DCM were calculated with standard statistical thermodynamics at 298.0 Kand 1.0 atm [10]. The electronic structures of stationary points were analysedby a simple natural population analysis (NPA) [16]. All computations were carried out with the Gaussian 09 suite of programs [17].

The global electrophilicity indexω [18] is given by the following expression, $\omega = \mu^2/2\eta$ based on 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 LUMO, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)/2$, respectively [19]. The global nucleophilicity index$N$ [20], based on the HOMO energies obtained within the Kohn-Sham scheme [21], is defined as $N = \varepsilon_{HOMO}(Nu) - \varepsilon_{HOMO}(TCE)$ in which (Nu) denotes nucleophile. This relative nucleophilicity index refers to tetracyanoethylene (TCE).Nucleophilic P_k^- and electrophilic P_k^+Parr functions [22] were obtained through the analysis of the Mulliken atomic spin density (ASD) of the radical cation of **HIO1** and of the radical anion of dienophile **SFM 2**, respectively. The local electrophilicity index, ω_k, and local nucleophilicity index, N_k, were calculated using $\omega_k = \omega P_k^+$ and $N_k = NP_k^-$ equations [4].

RESULTA AND DISCUSSION

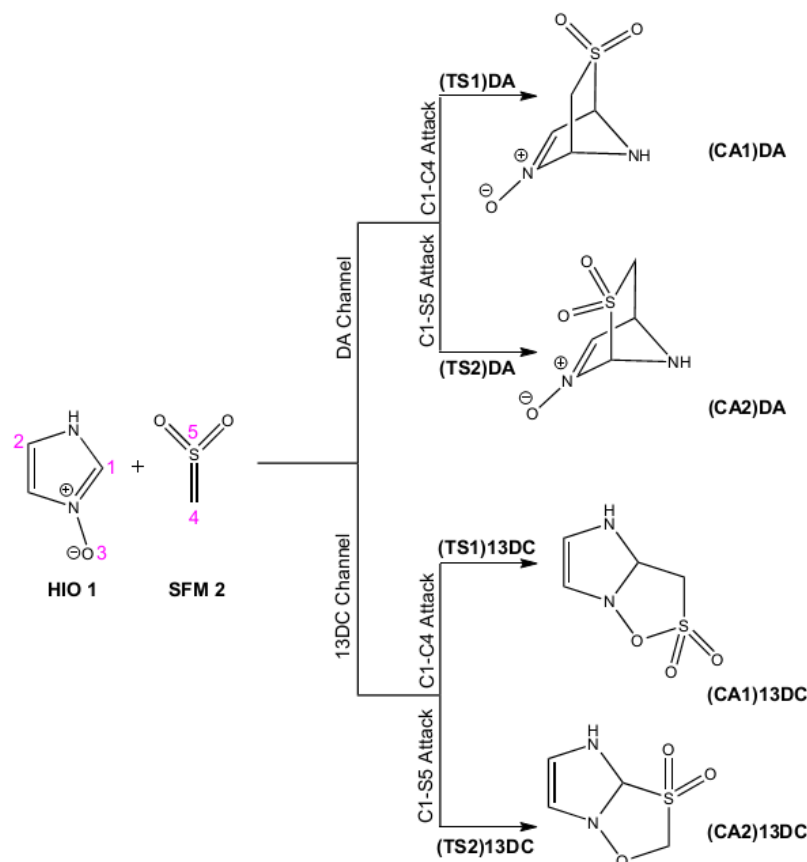The present study is divided into two parts: i) first, the reaction paths involved in the DA and 13DC reactions of **HIO 1** toward **SFM 2** yielding corresponding cycloadducts **CA**sis studied; ii) in the second part, an analysis of the global and local DFT reactivity indices of the reagents involved in these reactions is performed in order to explain reactivity and predict regioselectivity in the DA and 13DC reactions between **HIO 1** and **SFM 2**.

Study of the reaction pathsinvolved in DA and13DC reaction between HIO 1 and SFM 2.

Due to the asymmetry of both reagents, two competitive channels are feasible for each one of the DA and13DC reactions between **HIO 1** and **SFM 2**.As shown in scheme 1, they are related to the two regioisomeric approach modes of the C1 carbon atom of **HOI 1** toward the C4, via C1-C4 attack, or S5, via C1-S5 attack, atoms of **SFM 2**.

Analysis of the stationary points involvedin the considered DA and 13DC reactions evidently indicates that these reactions take place through a one-step mechanism ruling out the existence of any stable intermediate along the corresponding potential energy surfaces (PES). Consequently, four TSs, **(TS1) DA**, **(TS2) DA**, **(TS1) 13DC**, and **(TS2) 13DC** and four corresponding cycloadducts, **(CA1) DA**, **(CA2) DA**, **(CA1) 13DC**, and **(CA2) 13DC** were located and characterized on the PES of these reactions. It is worth noting that because of the cylindrical symmetry of **SFM 2**, *exo* and *endo* stereoisomeric approach modes are meaningless in the studied reactions.

The values of calculated relative enthalpies, ΔH, and Gibbs free energies, ΔG, for the species involved in the DA and 13DC reactions between **HIO 1** and **SFM 2** in the gas phase as well as in the presence of DCM are displayed in Table 1.

Scheme 1. Reaction paths involved in the DA and 13DC reactions of **HIO 1** toward **SFM 2.**

Table 1. B3LYP/6-311++G(d,p) calculated relative[a] enthalpies, ΔH, and Gibbs free energies, ΔG, at 298.0 K and 1.0 atmfor the spices involved in the DA and 13DC reactions between **HIO 1** and **SFM 2** in the gas phase as well as in the presence of DCM

	Gas phase		DCM	
Species	ΔH (kcal/mol)	ΔG (kcal/mol)	ΔH (kcal/mol)	ΔG (kcal/mol)
(TS1) DA	14.2	27.7	15.6	28.7
(TS2) DA	15.4	29.7	17.2	31.1
(CA1) DA	-16.2	-1.0	-12.6	2.28
(CA2) DA	-10.6	4.5	-7.6	7.15
(TS1) 13DC	9.3	22.9	9.6	21.4
(TS2) 13DC	1.9	15.9	4.7	18.8
(CA1) 13DC	-13.3	1.1	-6.2	7.7
(CA2) 13DC	-14.3	0.1	-8.1	6.1

a: Relative to **HIO 1** + **SFM 2**.

As can be seen, while activation enthalpies are 14.2 and 15.4 kcal/mol for **(TS1) DA** and **(TS2) DA**, respectively, these values are 9.3 and 1.3 kcal/mol for **(TS1) 13DC** and **(TS2) 13DC**, respectively. On the other hand, reaction enthalpies imply that formation of the corresponding **CAs** is exothermic; -16.2 **(CA1) DA**, -10.6**(CA2) DA**, -13.3**(CA1) 13DC**, and -14.3**(CA2) 13DC** kcal/mol. Due to the bimolecular nature of DA and 13DC reactions, both activation and reaction entropies are negative acting as an unfavorable factor in the formation of TSs and corresponding CAs. When unfavorable entropy term, TΔS, is summed to the enthalpy changes, a significant increase is produced in both activation and reaction Gibbs free energies (see the third column of Table 1). Calculated relative Gibbs free energies clearly indicate that the 13DC channel is completely preferred over the DA one. On the other hand, while C1-C4 regioisomeric channel is kinetically more favourable reactive channel in the DA reaction, the13DC reaction extremely prefers to take place *via* the C1-S5 regioselective manner. The very slight exergonic character in the case of formation of **(CA1) DA** and endergonic character in the case of formation of other CAs, displayed by the studied reactions, arises from the aromatic character of **HIO 1** which is lost along investigated DA and 13DA reactions and, thus, allows these reactions to be thermodynamically reversible.

When solvent effects of DCM are taken into account, while activation enthalpies (see the fourth column in Table 1) increase as a consequence of stronger solvation of the reactants than TSs, the exothermicity of reactions reduces as a result of stronger solvation of the reactants than CAs. Considering relative Gibbs free energies presented in the last column of Table 1

some appealing conclusions can be pointed out as follows:

- Cycloaddition reaction of **HIO 1** toward **SFM 2** in the presence of DCM, a common solvent used in the organic reactions, demands a relatively harsh reaction conditions.
- In this reaction, 13DC reactive channel is completely preferred over the DA one which takes place in a quite C1-S5 regioselective fashion affording cycloadduct **(CA2) 13DC**.
- Since the aromatic character of **HIO 1**is lost along 13DC reaction toward **SFM 2**this reaction presents an endergonic character such that formation of corresponding cycloadduct becomes a thermodynamically reversible process. Consequently a fast isolation of cycloadducts is required for experimental and presumably synthetic purposes.

The relevant FMOs shape for **HIO 1** and **SFM 2** and their interactions including corresponding energy requirement is sketched in Fig. 1. Based on the FMO theory and Woodward-Hoffmann's symmetry rules [6], the relevant HOMO and LUMO for an s-cis diene and/or 1,3-dipole should, respectively, include one and two nodal plane over the π skeleton of these molecular systems. On the other hand, for a dienophile and/or dipolarophile, while the relevant HOMO should not have any nodal plane, one nodal plane should exist over the π skeleton of the corresponding LUMO. Consequently, as shown in Fig. 2, HOMO-2 of **HIO 1**in which a nodal plane exists over the N(b) atom of diene skeleton, C(a)-N(b)-C(c)-C(d), can interact with the LUMO of **SFM 2**including a nodal plane over the C=S π bond to afford corresponding DA cycloadduct. Such interactions requires an

energy of 5.21 eV (see the blue arrow in Fig. 1). Note that **HIO 1**cannot participate as a 1, 3-dipole using its HOMO-2 since there is not any nodal plane over the π system associated with the 1,3-dipole skeleton, C(a)-N(b)-O(e).Using HOMO in which a nodal plane can be found over the π system of 1,3-dipole skeleton, **HIO 1**is symmetrically allowed to interact with the LUMO of **SFM 2**furnishing corresponding cycloadduct along a 13DC reaction. This interaction which is indicated with a red arrow in Fig. 1 should reach an energy of 3.32 eV. Finally, LUMO+1 of **HIO 1**in which either of diene and 1, 3-dipole skeletons include two nodal planes over corresponding π systems is symmetrically allowed to interact with the LUMO of **SFM 2** to generate corresponding

cycloadducts along a DA and/or 13DC reaction provided that an energy of 7.57 eV (see the green arrow in Fig. 1) is reached.

Among the relevant FMOs interactions between **HIO 1** and **SFM 2**, the least amount of energy is required for the HOMO$_{(HIO\ 1)}$-LUMO$_{(SFM\ 2)}$ interaction implying that, in quite accord with energetic results presented in Table 1, cycloaddition reaction of **HIO 1**toward **SFM 2** should proceed *via* a13DC reaction, instead of DA one, with an NED character.

Optimized geometries of TSs involved in the considered cycloaddition reactions including some selected bond distances and corresponding unique imaginary frequencies are given in Fig. 2.
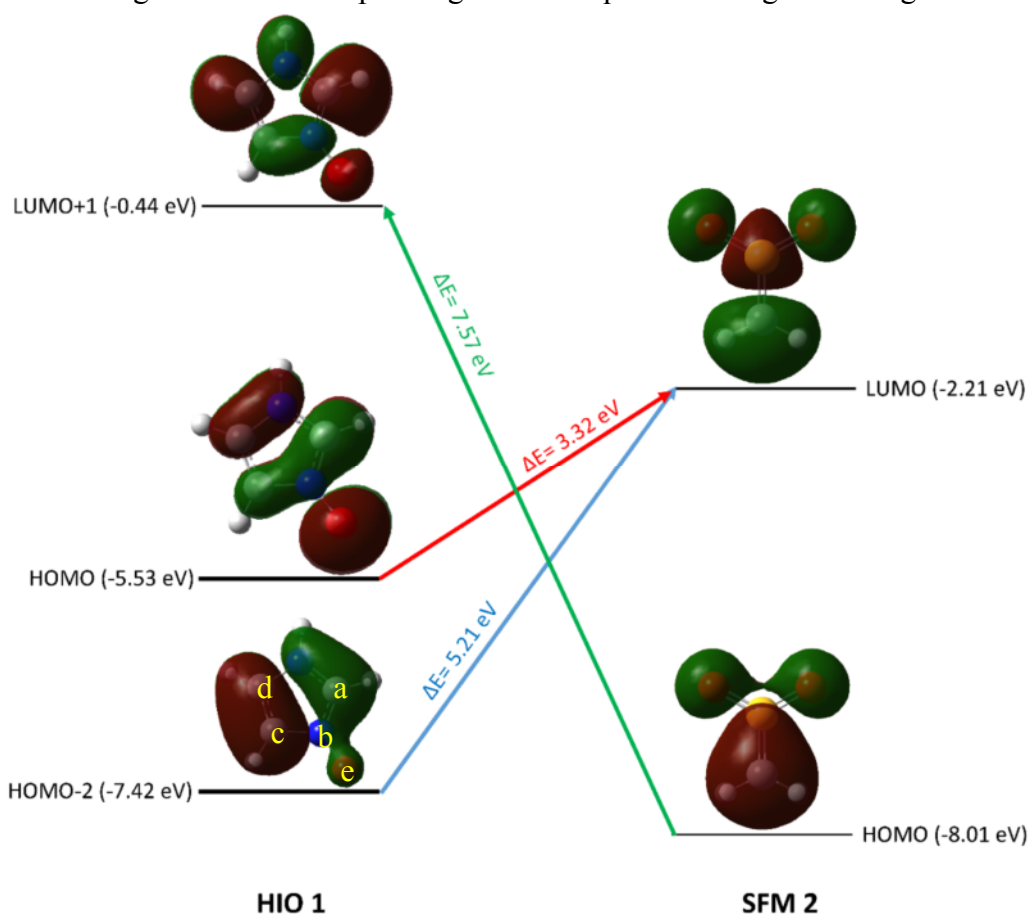

Fig. 1. B3LYP/6-311++G (d,p) relevant FMOs shape for **HIO 1** and **SFM 2** and their interactions including corresponding energy requirement.
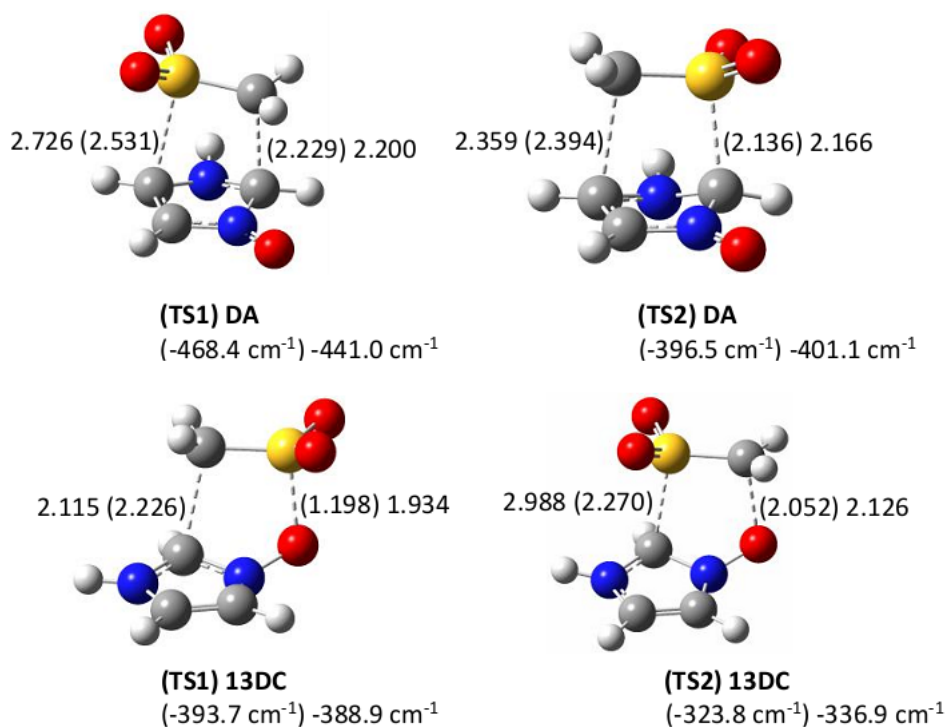
Fig. 2.B3LYP/6-311++G(d, p) optimized geometries of TSs involved in the studied cycloaddition reactions between **HIO 1** and **SFM 2** including some selected bond distances, in Å, and corresponding unique imaginary frequencies, in cm^{-1}. Values in the gas phase and in the presence of DCM are given inside and outside the parentheses, respectively.

DFT analysis based on the global and local reactivity indexes

Global reactivity indices defined within the conceptual DFT [23] are powerful tools to explain the reactivity and regioselectivity in the cycloaddition reactions. The FMO (HOMO and LUMO) energies as well as global indexes, namely, electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω), and global nucleophilicity (N) for **HIO 1** and **SFM 2** are presented in Table 2.

The global electrophilicity index for **HOI 1**, 1.05 eV, and **SFM 2**, 2.25 eV, allows these compounds to be classified as moderate and strong electrophiles, respectively, within the electrophilicity scale [25]. On the other hand, the global nucleophilicity index for **HOI 1**, 3.95 9eV, and **SFM 2**, 1.47 eV, permits them to be
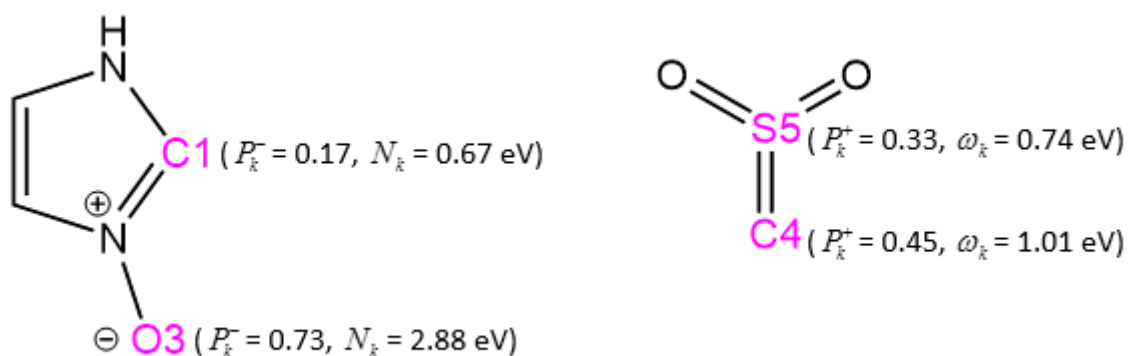
categorized as strong and weak nucleophiles, respectively [26]. When an electrophile-nucleophile pair is approached, the most favorable reactive channel is that associated with the initial two-center interaction between the most electrophilic center of electrophile and the most nucleophilic center of nucleophile. Recently, Domingo has proposed the nucleophilic P_k^- and electrophilic P_k^+ Parr functions derived from the excess of spin electron density reached *via* the GEDT process from the nucleophile to the electrophile.Herein, in order to explain the complete regioselectivity along 13DC reaction between **HIO 1** and **SFM 2** Parr functions including corresponding local reactivity indexes for reactive sites of reagents are analysed. As **HIO 1** and **SFM 2**, respectively, act as nucleophile and

electrophile; the nucleophilic P_k^- Parr function for C1 and O3 atoms of **HIO 1**as well as corresponding local nucleophilicity indices, and electrophilic P_k^+ Parr function

for C4 and S5 atoms of **SFM 2** together with corresponding local electrophilicity indicesare calculated and depicted in scheme 2.

Table 2. B3LYP/6-311++G(d,p) calculated FMO (HOMO and LUMO) energies, electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω), and global nucleophilicity (*N*), in eV, for **HIO 1** and **SFM 2**

	HOMO	LUMO	μ	η	ω	N
HIO 1	-5.53	-0.80	-3.16	4.73	1.05	3.95
SFM 2	-8.01	-2.21	-5.11	5.79	2.25	1.47

Scheme 2.B3LYP/6-311++G (d, p) calculated nucleophilic P_k^- Parr function for C1 and O3 atoms of **HIO 1** (left) as well as corresponding local nucleophilicity indices, and electrophilic P_k^+ Parr function for C4 and S5 atoms of **SFM 2** (right) together with corresponding local electrophilicity indices.

As presented in scheme 2, the local electrophilicity index, ω_k, for C4 and S5atoms of **SFM 2** is 1.01 and 0.74 eV, respectively. On the other hand, the local nucleophilicity index, N_k, for C1 and O3 atoms of **HIO 1** is 0.67and 2.88 eV, respectively. The most electrophilic activation found on C4 carbon atom of **SFM 2**and the most nucleophilic activation found on O3 oxygenatom of **HIO 1** is responsible for the two-center C4-O3 interaction found at the most favorable **(TS2) 13DC** leading to the predominantC1-S5 regioisomeric pathway

(seeScheme 1) along corresponding 13DC reaction. In other words, the regioselectivity predicted according to the calculated local reactivity indexes is in excellent agreement with the regioselectivity resulted from energetic studies (see Table 1).

CONCLUSION
The energetic andregioselectivity of competitive Diels-Alder (DA) and 1,3-dipolar cycloaddition (13DC) reactions between an aromatic diene/1,3-dipole,1-H-imidazole 3-oxide **HIO1**, and electron-deficient dienophile/dipolarophile, sulfonyl

methane **SFM 2**,was theoretically studied using DFT methods at the B3LYP/6-311++G (d, p) level.

The calculated relative Gibbs free energies indicate that among the studied cycloadditions, 13DC reaction is completely preferred over the DA one in both gas phase and in the presence of dichloromethane (DCM) which takes place through a one-step mechanism with a quite C1-S5 regioselectivity. An assessment of interactions between relevant frontier molecular orbitals (FMOs) of **HIO 1** and **SFM 2** evidently clarified that, in complete accord with calculated activation Gibbs free energies, HOMO$_{(HIO\ 1)}$-LUMO$_{(SFM\ 2)}$ interaction proceeds the considered 13DC reaction *via* a normal electron demand (NED) manner. The relatively high activation Gibbs free energies and endergonic character of studied reactions are related to the aromatic nature of **HIO 1** which is lost during reaction.

Analysis of the nucleophilic P_k^- Parr functions in **HIO 1** and the electrophilic P_k^+ Parr functions in **SFM 2** offers an explanation of the complete regioselectivity found in this 13DC reaction. While the O3 oxygenatom of **HIO 1** is the most nucleophilic center, the C4 carbon atom of **SFM 2** is the most electrophilic center. Consequently, the most favorable nucleophilic/electrophilic two center interactions along this 13DC reaction will take place between the O3oxygenatom of **HIO 1** and the C4 carbon atom of **SFM 2**, in complete agreement with the energetic results.

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