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Density functional theory study of the regio and stereoselectivity in 1,3-dipolar cycloddition reactions between *N*-methyl methylenenitrone and fluorinated dipolarophiles

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A DFT study of the reactivity, regio-, and stereoselectivity of 1,3-dipolar cycloaddition of *N*-methyl-methylenenitrone **1** with (E and Z)-2,4-diethoxy-5-(perfluoroprop-1-en-1-yl)pyrimidine **2E**, **2Z** and (E and Z)-(perfluoroprop-1-en-1-yl)benzene, **3E**, **3Z** in the gas phase and in toluene, has been carried out by using density functional theory (DFT)-based reactivity indices and activation energy calculations at B3LYP/6-31G (d) level of theory. Four reactive channels associated with the *5*- and *4*-regio and *endo* and *exo* stereoselective approach modes of the pyrimidine or phenyl group of these fluorinated vinyls relative to nitrone **1** have been explored and characterized. IRC calculations show that these cycloadditions follow an asynchronous concerted mechanism with a low polar character, displaying *5*-regioselectivity and it is found that the *endo* pathway is preferred, therefore the formation of product with *5-regio* and *endo* pathway is dominant. Also, DFT-based reactivity indices clearly predict the experimental regiochemistry.

1. Introduction

The 1,3-dipolar cycloaddition (1,3-DC) is a chemical reaction between a 1,3-dipole and a dipolarophile to form a five-membered ring [1]. These reactions are one of the most important processes with both synthetic and mechanistic interest in organic chemistry. Nitrones are useful and multipurpose compounds that are widely used in organic chemistry for many applications, i.e. reaction with other molecules (Grignard reagents) [2], trap of free radicals [3], precursors of nitroxides [4], etc. Their reactivity is principally caused by the presence of the carbon–nitrogen double bond, which makes them marvelous 1,3-dipoles in dipolar cycloaddition reactions [5]. In fact, nitrones are capable of reacting with a great variety of dipolarophiles giving rise to a wide range of nitrogen-containing compounds, which are often biologically active specie such as antibiotics, alkaloids, amino sugars, etc. Moreover, the 1,3-DC reactions dominate several interesting attributes, especially, reactivity, regio and stereo selectivity. Reactivity descriptors based on the density functional theory (DFT), like Fukui indices, local softnesses and local electrophilicity, have been widely used for the forecasting of the regio and stereochemistry. For instance, several treatments of 1,3-DC reactions of nitrones with various dipolarophiles can be found in the literature [6–8]. The 1,3-DC reactions of nitrones with alkenes is an important method for preparing isoxazolidines in a regioselective and stereoselective way [9]. Experimentally, it has been found that the cycloaddition reactions of *N*-methyl methylenenitrone **1** with (E and Z)-2,4-diethoxy-5-(perfluoroprop-1-en-1-yl)pyrimidine **2E**, **2Z** and (E and Z)-(perfluoroprop-1-en-1-yl)benzene, **3E**, **3Z** give only 4,5-difluoro-2-methyl-5-substitued-4-(trifluoromethyl)isoxazolidine (*5*-regioisomer) shown in Scheme 1. In addition, the *endo* pathway is preferred [10]. In continuation of our studies on the mechanism and regioselectivity of the 1,3-DC reactions [11–19], we became interested to study these reactions based on activation energy calculations and DFT-based reactivity indices.

2. Computational details

All calculations were carried out with GAUSSIAN03 program suite [20]. Geometry optimization of the reactants was carried out

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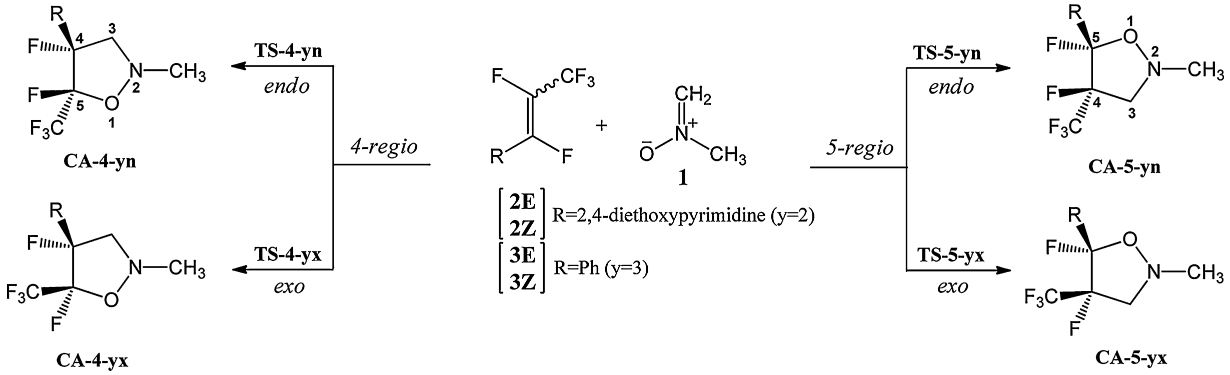

Scheme 1. The regio and stereoisomeric pathways for 1,3-dipolar cycloadditions.

using DFT methods at the B3LYP/6-31G (d) level of theory [21]. The transition states (TSs) for the 1,3-DC reactions have been localized at the B3LYP/6-31G (d) level of theory. Frequency calculations characterized the stationary points to verify that the TSs had one and only one imaginary frequency. The intrinsic reaction coordinates (IRC) [22] calculation was performed in forward and backward path to identify that each saddle point connects to the two associated minima using the second-order González–Schlegel integration method [23,24]. Solvent effects were considered at the B3LYP/6-31G (d) level of theory by geometry optimization of the gas-phase structures using a self-consistent reaction field (SCRF) [25] based on the polarizable continuum model (PCM) of Tomasi's group [26]. Because the studied cycloaddition reactions were carried out in toluene, we selected its dielectric constant at 298.0 K, $\varepsilon = 2.38$.

Reactivity indices, chemical potential (μ) and softness (S) were evaluated within the finite difference approximation, using Eqs. (1) and (2) [27]:

$$\mu = \frac{-(\mathrm{IP}+\mathrm{EA})}{2} \qquad (1)$$

$$S = (\mathrm{IP}-\mathrm{EA})^{-1} \qquad (2)$$

where IP and EA are the vertical ionization potential and electron affinity, achieved by energy difference of the neutral with the cation and anion, respectively.

The global electrophilicity ω for dipoles and dipolarophile was evaluated using Eq. (3) [28]:

$$\omega = \frac{\mu^2}{2(\mathrm{IP}-\mathrm{EA})} \qquad (3)$$

Domingo et al. has introduced an empirical (relative) nucleophilicity index [29], N, based on the HOMO energies obtained within the Kohn–Sham scheme [28], and defined as

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

This nucleophilicity scale is referred to tetracyanoethylene (TCE) taken as a reference.

Very recently, Domingo proposed two new electrophilic, $P_k{}^+$, and nucleophilic, $P_k{}^-$, Parr functions based on the atomic spin density distribution at the radical anion and at the radical cation of a neutral molecule [30]. The electrophilic, $P_k{}^+$, and nucleophilic, $P_k{}^-$, Parr functions, were obtained through the analysis of the Mulliken atomic spin density of the radical anion and the radical cation by single-point energy calculations over the optimized neutral geometries using the unrestricted UB3LYP formalism for radical species. The local electrophilicity indices, ω_k [31], the local nucleophilicity indices, N_k [32] and local softness [33], s were calculated using the following equations:

$$\omega_k = \omega P_k^+ \qquad (5)$$

$$N_k = N P_k^- \qquad (6)$$

$$s^+ = S P_k^+ \qquad (7)$$

$$s^- = S P_k^- \qquad (8)$$

where $P_k{}^+$ and $P_k{}^-$ are the electrophilic and nucleophilic Parr functions [30], respectively.

The atoms in a molecule are open subsystems interchanging energy and electrons, thus the natural thermodynamic quantity is the grand potential $\Omega = E - N\mu$, where E is the energy. Suppose the cycloaddition of molecules A and B to give AB. The interaction of atom i of A with atom k of B is [8]

$$\Delta\ \Omega_i^k = -\frac{1}{2}(\mu_A - \mu_B)2\frac{S_{Ai}S_{Bk}}{S_{Ai}+S_{Bk}} \qquad (9)$$

and illustrates the stabilization owing to the charge transfer between Ai and Bk. Because cycloadditions are concerted reaction, the stabilization upon reactive encounter is owing to two bond-forming interactions $Ai \leftrightarrow Bk$ and $Aj \leftrightarrow Bl$ and is written as $\Delta\ \Omega_{ij}^{kl} = \Delta\ \Omega_i^k + \Delta\ \Omega_j^l$. For the opponent regioisomer, the stability is $\Delta\ \Omega_{ij}^{lk} = \Delta\ \Omega_i^l + \Delta\ \Omega_j^k$ [8].

3. Results and discussion

Our theoretical analyzes of the regio and stereochemistry of these 1,3-DC reactions will be based on activation energy calculations and DFT-based reactivity indices.

3.1. Activation energy calculations

The transition states have been localized for both cyclization modes. In this work, 4/5 and n/x, denote 4/5-regio- and endo/exo stereoseletivity, while, $y = 2$ and $y = 3$ are used for **2** (**E**, **Z**) and **3** (**E**, **Z**) ethenes, respectively (see Scheme 1). The corresponding activation barriers and structures are given in Table 1 and Fig. 1, respectively. An analysis of the geometries at the TS structures, given in Fig. 1, shows that they correspond to asynchronous bond formation processes. The extent of bond formation along a reaction pathway is provided by the concept of bond order (BO) [34]. The BO (Wiberg indices) values of the C–O and C–C forming bonds at TSs are shown in brackets in Fig. 1. These values are within the range of 0.29 to 0.37. These results show that the **TS-5-2n** and **TS-5-2x** are more asynchronous than the **TS-4-2n** and **TS-4-2x**, the **TS-5-3n** and **TS-5-3x** are more asynchronous than the **TS-4-3n** and **TS-4-3x**. In general, the asynchronicity shown by