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Regioselectivity of 1,3-dipolar cycloadditions between aryl azides and an electron-deficient alkyne through DFT reactivity descriptors

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Abstract Conceptual density functional theory, including chemical hardness, electronic chemical potential, global and local electrophilicity index and Fukui functions, is used to predict reactivity and regioselectivity of 1,3-dipolar cycloadditions (13DCs) between five aryl azides (1–5) and an electron-deficient alkyne at the B3LYP/6-31G(*d*,*p*) level. Two reaction paths (a) and (b) are considered which result in the corresponding regioisomeric 1,2,3-triazoles $P(1\text{-}5)_a$ and $P(1\text{-}5)_b$, respectively. All the 13DCs proceed via rather asynchronous TSs and the path (b) is clearly more synchronous than the path (a). All the reactions are high exoergic [$\Delta G^\circ = -45.1$ to -51.4 kcal/mol for path (a) and -47.7 to -55.9 kcal/mol for path (b)] with the moderate and nearly similar activation barriers ($E_a = 15.4$–16.7 kcal/mol) referring a relatively low regioselectivity. All reactivity descriptors but one clearly suggest that path (a) is somewhat preferred over path (b). FMO interactions occur between $\mathrm{HOMO}_{13\mathrm{DP}}$ and $\mathrm{LUMO}_{\mathrm{DPh}}$ due to the corresponding lower energy gap. All the reactions considered in this work classified as polar 13DCs with NED character. Our theoretical results are in good agreement with those reported experimentally.

Keywords 1,3-Dipolar cycloadditions · Conceptual DFT · Fukui function · Gazquez–Mendez rule · HSAB

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Introduction

1,3-Dipolar cycloadditions (13DCs) constitute one of the most important classes of organic reactions and are among the most versatile and powerful preparative methods for the synthesis of five-membered heterocyclic compounds [1]. A 1,3-dipole (13DP) can add onto asymmetric dipolarophiles (DPhs) in two different pathways; however, in many cases, the regiochemistry proceeds mainly through one reaction path, which is lower in energy [2–4]. The controversies between the concerted $4\pi_s + 2\pi_s$ mechanism in which two new σ bonds are formed rather simultaneously of Huisgen [5] and the stepwise biradical mechanism of Firestone [6] for 13DC have been solved helping numerous experimental and computational investigations. The concerted mechanism is favored for the reactions of the unsubstituted 13DPs with alkenes or alkynes while the other mechanism becomes likely when the 13DPs and DPhs are substituted by radical stabilizing groups [7].

The first organic azide, phenyl azide, as an explosive and hazardous compound [8] is one of the most important 13DPs applied in the regioselective 13DCs [9, 10]. Phenyl azide and its analogues undergo the azide-alkyne Huisgen cycloaddition, a classic example of click chemistry. Although azides are not the most reactive 13DPs available for reaction, they are preferred for their relative lack of side reactions and stability in typical synthetic conditions. Several 1,4,5-trisubstituted 1,2,3-triazoles were prepared by 13DC reactions of some 2-substituted phenyl azides to dimethylacetylene dicarboxylate under regular stirring at room temperature or under microwave irradiation [11].

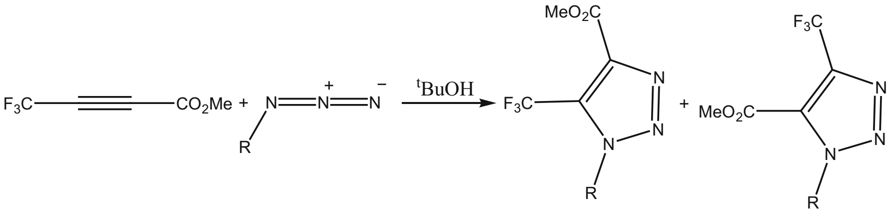
Houk et al. [12] applied frontier molecular orbital (FMO) perturbation theory for interpretation of regioselectivity in the concerted 13DCs. Based on FMO, three types of concerted 13DCs can occur. One is the FMO interaction between the highest occupied molecular orbital (HOMO) of the 13DP and the lowest unoccupied molecular orbital (LUMO) of the DPh (normal electron demand, NED). A 13DP of this class is referred to as a HOMO-controlled dipole or a nucleophilic dipole, which includes azomethine ylide, carbonyl ylide, nitrile ylide, azomethine imine, carbonyl imine and diazoalkane [13]. A second type is dominated by the reaction between the HOMO of the DPh and the LUMO of the 13DP (inverse electron demand, IED). A dipole of this class is referred to as a LUMO-controlled dipole or an electrophilic dipole, which includes nitrous oxide and ozone [14]. Finally, in the third type of 13DC, the HOMO of the 13DP can interact with LUMO of the DPh; alternatively, the HOMO of the DPh can interact with the LUMO of the 13DP. This two-way interaction arises because the energy gap in either direction is similar. A dipole of this class is referred to as a HOMO–LUMO-controlled dipole or an ambiphilic dipole, which includes azides [15]. Any substituent on the DPh would accelerate the reaction by lowering the energy gap between the two interacting orbitals; i.e., an electron-withdrawing substituent (EWG) would lower the LUMO while an electron-donating substituent (EDG) would raise the HOMO. Despite some exceptions such as ozonolysis of olefins and addition of nitrile oxides to alkynes [16], many more substrate combinations result in no cycloadduct formation when 13DP and DPh are simply mixed. To accelerate these types of reactions, two complementary strategies focus on modulating the reactivity of the DPh. In the first strategy, Lewis acids are included to lower the LUMO of the DPh. Under such conditions the dipole reacts through its HOMO to generate the cycloaddition product [17]. Alternatively, additives that increase the electron density of the DPh can accelerate cycloaddition via an inverse demand cycloaddition interaction. This approach is less common than the Lewis acid-based methods [18] but is most notably operative in the copper-catalyzed synthesis of triazoles from alkynes and azides [19]. In general, the regioselectivity is mainly dependant on the functional groups on the alkyne, and the reactivity of the 13DC reaction is dominantly controlled by $\mathrm{HOMO}_{13\mathrm{DP}}$–$\mathrm{LUMO}_{\mathrm{alkyne}}$ interactions. So, an EWG on the alkyne will accelerate the reaction with diazo compounds usually under very mild conditions. However, the balance of factors, strong electrostatic effects and closed shell repulsions may result in some complications which make the regioselectivity to be not straightforward at all times [20].

Nevertheless, this is a fact that, unlike within the molecular orbital (MO) theory, molecular orbitals do not exist entirely in the DFT, and MOs used as an approximation to the resolution of Schrödinger's equation have no physical existence. Consequently, DFT-based MOs employed to explain the reactivity in organic chemistry within FMO theory should be used with care [21].

Thus, it should be useful to find out the utility of several reactivity descriptors for the elucidation of the regioselectivity, concurrently. To the best of our knowledge, theoretical investigations on the 13DCs of unsymmetrical alkynes with substituted phenyl azides have not been addressed [22]. Hence, the main goal of this study is examination of various reactivity descriptors based on density functional theory (DFT) on this reaction to validate their applicability in such important organic reactions (Fig. 1). The comparison of our calculated results with those of experimentally observed would be decisive in this work.

Methodology

All gas phase Gaussian 03 [23] quantum chemical calculations are done using the B3LYP exchange–correlation functional [24, 25] together with the standard 6-31G* basis set [26]. This level of theory had been confirmed by numerous theoretical studies on the related cycloaddition reactions [27–32]. Geometry optimizations for



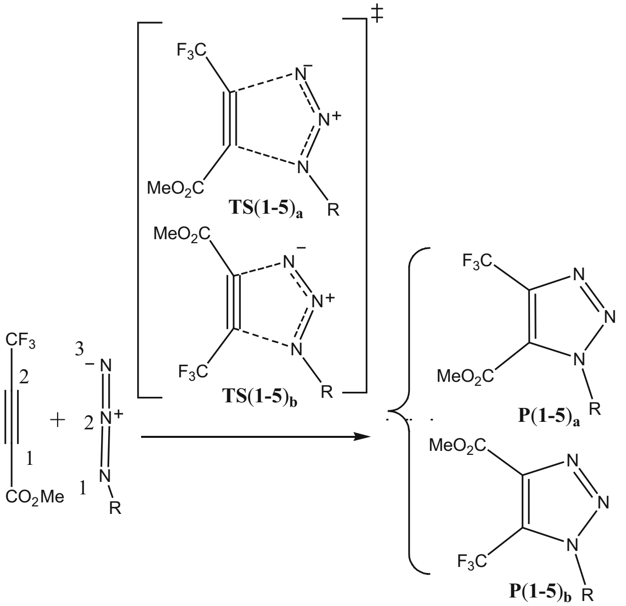
R=C_6H_5, *p*-ClC_6H_4, *m*-FC_6H_4, *p*-CNC_6H_4, *m*-CNC_6H_4

Fig. 1 The experimentally reported 13DC of aryl azides with methyl 2-perfluoroalkynoates to perfluoroalkylated 1,2,3-triazoles [22] the reactant, transition state, and product of all the studied reactions are carried out by the Berny analytical gradient method [33]. To verify the nature of the stationary species and evaluate the activation energy barriers, frequency calculations are performed at 298 K and 1 atm. For minimum state structures, only real frequency values and for the TSs, only a single imaginary frequency value is accepted. In the calculation of the condensed Fukui function, the atomic electronic populations of neutral, cationic and anionic systems are analyzed by natural population analysis (NPA) at the optimized geometries of the corresponding neutral systems [34] with the use of the NBO program version 3.1(link 607, Gaussian 03).

Results and discussion

13DC reactions of methyl 2-trifluoromethylalkynoate with 13DPs 1–5 can take place along two regioisomeric pathways (a) and (b), leading to the formation of methyl 5-(trifluoromethyl)-3-aryl-3H-1,2,3-triazole-4-carboxylates P(1-5)$_a$ and methyl 5-(trifluoromethyl)-1-aryl-1H-1,2,3-triazole-4-carboxylates P(1-5)$_b$, respectively, after passing through their corresponding TSs (Fig. 2).

The B3LYP/6-31G*-optimized structures of the TSs associated with these reactions along two regioisomeric pathways are given in Fig. 3.



R=C_6H_5 (**1**), *p*-ClC_6H_4 (**2**), *m*-FC_6H_4 (**3**), *p*-CNC_6H_4 (**4**), *m*-CNC_6H_4 (**5**)

Fig. 2 Two possible reaction pathways (a, b) along with the atom numbering for five 13DCs (1–5) under study

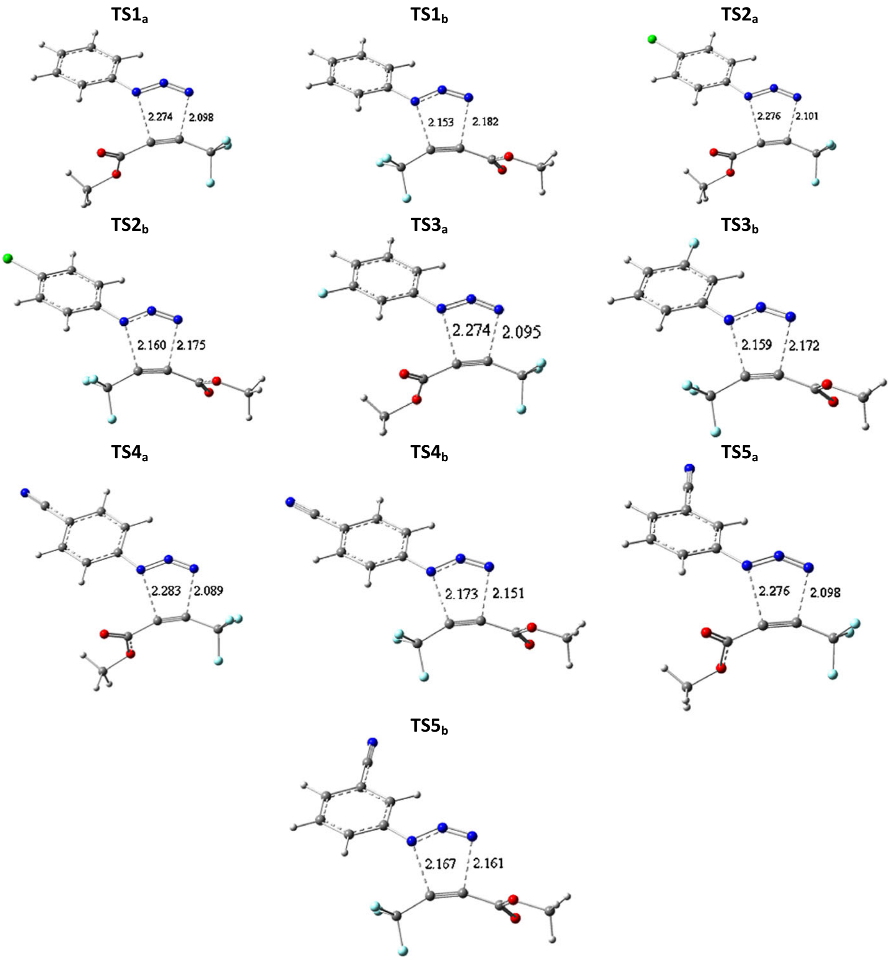


Fig. 3 The B3LYP/6-31G*-optimized structures of transition states corresponding to the 13DCs between alkyne and 13-DPs 1–5 (bond lengths are given in Å)

In general, the linearity of both alkyne and azide moieties are diminished going from the reactants to TSs which denote the product-like nature of TSs based on the Hammond's postulate. The most important geometrical parameter considered in these two reaction paths is the difference between the lengths of the two newly formed sigma bonds: $\Delta r_a = |r_{N1-C1} - r_{N3-C2}|$ and $\Delta r_b = |r_{N1-C2} - r_{N3-C1}|$. These calculated Δr values provide a simple index to assess the synchronicity of the process. Meanwhile, Δr is zero for fully synchronous processes and the deviation from zero is reflected in the asynchronicity of the processes. Accordingly, our calculated Δr values indicate that all the 13DCs proceed via rather asynchronous TSs ($\Delta r_a = 0.175$–0.194 Å, ca. 8 %, and $\Delta r_b = 0.021$–0.05 Å, ca. 1 %) and the path (b) is clearly more synchronous than the path (a) and the highest asynchronous nature is observed for reaction 4 ($\Delta r_a = 0.194$ Å). Another interesting point on the geometry of TS structures is the regularity in the path (a) for having larger bond lengths of C_1–N_1 compared to the C_2–N_3 ones. On the other side, such regularity is not observed in the TS structures of path (b) since TSs 4_b and 5_b are different from the TSs 1_b–3_b for having larger lengths of N_1–C_2 compared to the N_3–C_1 ones.

The potential energy surface (PES) involving activation energies (E_a) as well as the standard Gibbs free energy changes (ΔG^0) of all 13DC reactions along two regioisomeric pathways are presented in Fig. 4.

Our data show that all the reactions are high exoergic [$\Delta G^0 = -45.1$ to -51.4 kcal/mol, for path (a) and -47.7 to -55.9 kcal/mol, for path (b)]. Moreover, all the 13DC reactions along path (b) are more exoergic than their corresponding reactions along path (a) by 1–2 kcal/mol. On the other hand, calculated activation barriers of path (a) are insignificantly smaller than those of path (b). These thermodynamic and kinetic data besides the similarity in the steric effects of all reactions denote a low regioselectivity for such 13DC reactions between aryl azides with alkyne [22].

In parallel to the energetic data, chemical selectivity and reactivity can be provided based on conceptual DFT in terms of global electronic descriptors such as electronic chemical potential (μ), hardness (η) and softness (S) [17, 35]. Since DFT is becoming an efficient and computationally cost effective tool for the study of electronic structures, it is worthwhile to find out how DFT-based reactivity concepts

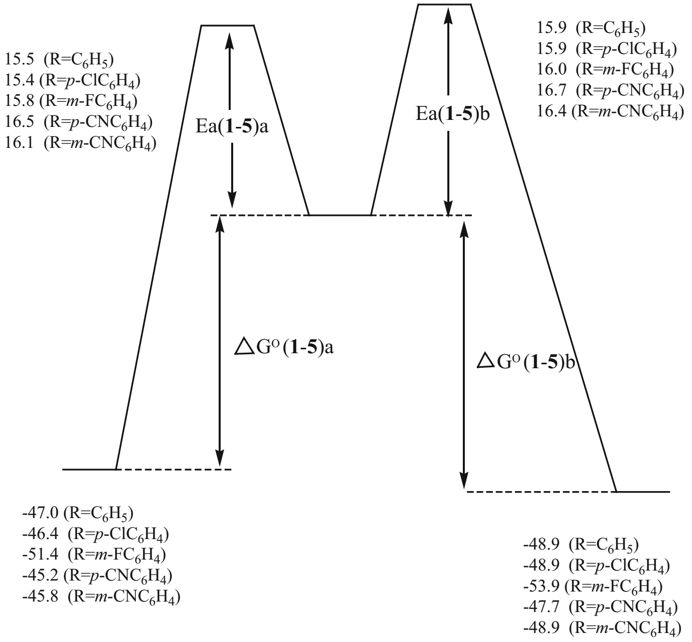


Fig. 4 The B3LYP/6-31G*-calculated PES (kcal/mol) corresponding to all 13DC reactions along two regioisomeric pathways (a, b)

can be used for the interpretation of reaction mechanisms and especially the regiochemistry in the present 13DC reactions [36]. The conceptual DFT has become a powerful tool to study polar organic reactions [37]. Hence, a brief review of employed descriptors is presented hereafter. For an N-electron system with total energy E and external potential v, electronic chemical potential is defined as the first-order derivatives of $E(\mu = (\partial E/\partial N)_v)$ [38, 39]. Moreover, hardness and softness are second-order derivatives of $E\left(2\eta = S^{-1} = (\partial^2 E/\partial N^2)_v = (\partial \mu/\partial N)_v\right)$ [40, 41]. Furthermore, following Koopmans' theorem [42], the chemical potential and hardness can be rewritten as: $\mu = \frac{1}{2}(\varepsilon\mathrm{HOMO} + \varepsilon\mathrm{LUMO})$ and $\eta = \frac{1}{2}(\varepsilon\mathrm{LUMO} - \varepsilon\mathrm{HOMO})$, where εHOMO and εLUMO are the highest occupied and lowest unoccupied molecular orbital energies, respectively. Pearson showed that many electronic systems arrange themselves, in their ground or valence states, to be as hard as possible (the maximum hardness principle, MHP) [43]. In connection with the MHP, Chattaraj and Sengupta proposed a minimum polarizability principle (MPP), which states that the natural direction of evolution of any system is toward a state of minimum polarizability, α [44]. The static electric dipole polarizability is the relative propensity of a charge distribution, like the electron density of a molecule, to be distorted from its normal shape in the presence of an electric field and, for this work, is calculated under the equation of $\alpha = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz})$ where α_{xx}, α_{yy}, and α_{zz} are the diagonal elements of the polarizability tensor. Another global index is the electrophilicity power of a system in terms of its electronic chemical potential and hardness. The electrophilicity index was introduced by Parr et al. [45] and can be expressed as $\omega = \frac{\mu^2}{2\eta}$. This property is a measure of energy lowering due to the maximal electron flow between donor and acceptor. Together with the global electrophilicity ω index, the global nucleophilicity N index is also used to study reactivity [46]. Finally, Noorizadeh et al. [47] showed that in the Diels–Alder cycloadditions, the major product has always less electrophilicity than the minor product and the electrophilicity index can be used as an indicator for regioselectivity which is named the minimum electrophilicity principle (MEP).

Recently, a number of reports were published on the mechanism of 13DC reactions by Domingo et al. For instance, they established good correlations between the pseudodiradical (pr) character, the hardness η, and the nucleophilicity N index of the tri-atom-component's TACs with the feasibility of these nonpolar reactions through analysis of 12 TACs participating in 13DC reactions towards ethylene and acetylene [48]. This study made it possible to establish a useful classification of 13DC reactions into zwitterionic (zw)-type reactions involving TACs with a high zw character, and pr-type reactions involving TACs with a high pseudodiradical character. Moreover, a set of seven non-substituted TACs participating in 13DC reactions has been studied using the reactivity indices defined within the conceptual DFT at the B3LYP/6-31G(d) level of theory and it was concluded that the substitution is required in both, TACs and the ethylene species, in order to experimentally perform these zw-type 13DC reactions under mild conditions [49]. Finally, the participation of azomethine ylides (AYs) and carbonyl ylides (CYs) in 13DC reactions has been analysed at the DFT B3LYP/6-31G(d) level where the asymmetric substitution broke the pseudodiradical character of the simplest TACs, modifying their electrophilic and nucleophilic behaviors [50].

Therefore, in this study, the obtained frontier molecular orbital energies, polarizability, hardness and electrophilicity values for all the studied regioisomers are presented in Table 1.

These data show that while MHP and MEP rules predict the regioisomers of path (a) as the major cycloadducts, the MPP predicts an entirely inverse situation in favor of path (b). Again, these global reactivity indexes denote a low regioselectivity on the 13DC reactions of aryl azides with alkynes under study.

Another method for explanation of the regiochemistry of concerted reactions proposed by Gazquez and Mendez based on a local version of the hard-soft acid–base theory (HSAB principle) [51, 52]. The Gazquez–Mendez rule indicates that the interaction between any two chemical species will occur through the centers with nearly equal softness. To predict the regioselectivity using this rule, it is necessary to determine the type of electron demand character of the reactions. To gain this objective, four properties are considered: HOMO–LUMO gaps between the two reactants, calculated μ and ω of reactants, and charge transfer (CT) analysis in the transition states (Table 2).

It is important to know that for calculation of these parameters, the actual HOMOs and LUMOs are used (relevant HOMO and LUMO). Inspecting the reactant FMOs reveals that in our 13DCs, the theoretical and actual molecular orbitals are the same since both the reactants should have one node in their FMOs which is apparent in the pictures (Fig. 5).

Considering the visualized molecular orbitals of the reactants and their FMO energies, two possible interactions consisting of $\mathrm{HOMO_{13DP}}$–$\mathrm{LUMO_{DPh}}$ and/or $\mathrm{HOMO_{DPh}}$–$\mathrm{LUMO_{13DP}}$ can take place, both of which are symmetrically allowed. The energy differences between the two possible HOMO/LUMO combinations show that for all the cycloadditions, the main interaction occurs between $\mathrm{HOMO_{13DP}}$ and $\mathrm{LUMO_{DPh}}$ due to the lower energy gap (Fig. 6). However, the differences among five interactions appear unimportant and range from 4.31

Table 1 FMO energies, chemical hardness, electrophilicity index and polarizability (all in au) for products of 13DC reactions under study

Cycloadduct	ε_H	ε_L	η	ω	α
$P1_a$	−0.2639	−0.0612	0.2027	0.0652	138.870
$P1_b$	−0.2633	−0.0709	0.1925	0.0725	136.562
$P2_a$	−0.2624	−0.0690	0.1934	0.0710	153.905
$P2_b$	−0.2613	−0.0774	0.1839	0.0780	151.175
$P3_a$	−0.2659	−0.0673	0.1986	0.0699	139.650
$P3_b$	−0.2614	−0.0754	0.1860	0.0762	137.328
$P4_a$	−0.2777	−0.0892	0.1885	0.0893	160.652
$P4_b$	−0.2776	−0.0910	0.1866	0.0910	157.640
$P5_a$	−0.2811	−0.0807	0.2004	0.0816	157.032
$P5_b$	−0.2788	−0.0865	0.1923	0.0867	154.837

Table 2 FMO energies (au), electronic chemical potential (au), chemical hardness (au), chemical softness (au^{-1}) and electrophilicity index (au) for reactants in 13DCs

	HOMO	LUMO	μ	η	S	ω
DPh	−0.3004	−0.0701	−0.1853	0.2303	2.1714	0.0745
13DP1	−0.2280	−0.0382	−0.1331	0.1898	2.6345	0.0466
13DP2	−0.2321	−0.0465	−0.1393	0.1856	2.6934	0.0522
13DP3	−0.2358	−0.0448	−0.1403	0.1910	2.6181	0.0515
13DP4	−0.2483	−0.0703	−0.1593	0.1780	2.8090	0.0713
13DP5	−0.2505	−0.0669	−0.1587	0.1836	2.7230	0.0686

(13DP1) to 4.90 eV (13DP5). Consequently, based on the HOMO–LUMO gaps, the 13DC reactions considered in this work have the NED character.

On the other hand, calculated μ values of all 13DPs 1–5 (ranging from −0.1331 to −0.1593 au) are more positive than that of DPh (–0.1853 au) which is indicative of electron flow from the 13DPs to the dipolarophile DPh (Table 2). This finding is referring again to the NED character of these reactions. The largest μ pertains to the 13DP4 with a para-CN substituent. Besides the moderate electrophilicity values encountered for all reactants, 13DP4 is also the most electrophilic (ω = 0.0713 au) and the softest dipole among all. The polar character of the studied reactions can be measured by the difference in the absolute electrophilicity power (Table 2). Hence, 13DC reactions of 13DPs 1–5 with the alkyne have a rather low polar character and the reaction of 13DP1 has the highest polarity with Δω = 0.641 eV.

The last method for determining the electronic nature of the scrutinized reactions is charge transfer (CT) analysis in the transition states. CT analysis with the NPA method shows that a relatively low net charge transfer takes place from the DPs to the DPh which, again, is in agreement with the NED character of the 13DCs (Table 3).

These data show that values of the CT are between 0.0504e and 0.0817e for all studied TSs in both paths (a) and (b). The values of CT are clearly smaller than those of previously reported Diels–Alder reactions [53]. These results indicate that the reactions can be classified as polar 13DCs, with a more polar nature in the path (a).

In the last step, calculation of Fukui functions, f(r), in the reaction sites of reagents is presented. The Fukui function is the most fundamental and useful local reactivity indicator in chemical DFT. It defines the reactivity and selectivity of a specific site in a molecule as the differential change in electron density due to an infinitesimal change in the number of electrons at a constant external potential v(r) [54]. An other definition of Fukui function is the response of the chemical potential μ of a system to a change in the external potential v(r) [55]. $f(r) = \left[\frac{\partial\rho(r)}{\partial N}\right]_{v(r)} = \left[\frac{\delta\mu}{\delta v(r)}\right]_{N}$. The condensed forms of Fukui functions of an atom, say k, in a molecule with N electrons, depending on the type of electron transfer, have been proposed by Yang and Mortier [56]: $f_k^+ = [\rho_k(N+1) - \rho_k(N)]$ for

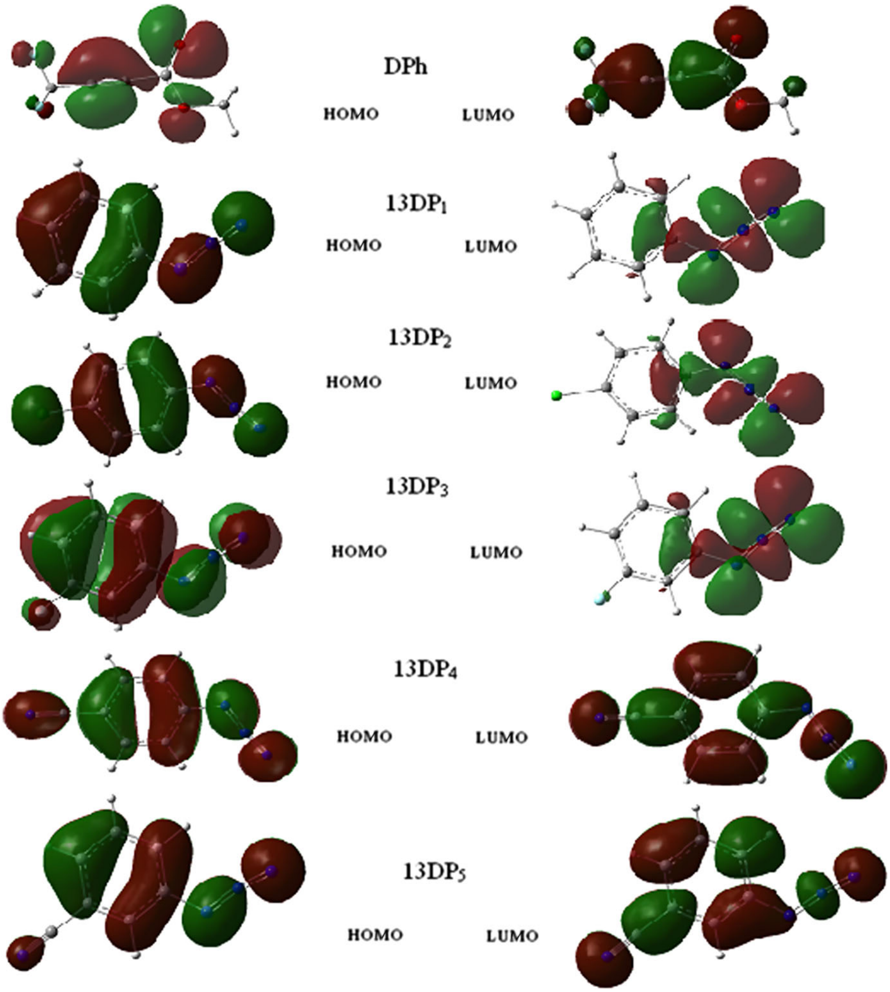


Fig. 5 The visualized FMOs of reactants in this study

nucleophilic attack; $f_k^- = [\rho_k(N) - \rho_k(N-1)]$ for electrophilic attack, and $f_k^o = \frac{1}{2}[\rho_k(N+1) - \rho_k(N-1)]$ for radical attack, where $\rho_k(N)$, $\rho_k(N-1)$, $\rho_k(N+1)$ are the gross electronic population of the site k in neutral, cationic and anionic systems, respectively. Since the electronic mechanism of the studied reactions is NED, Fukui functions for electrophilic (f_k^-) and nucleophilic (f_k^+) attack at the reaction sites (k) are calculated for 13DPs and DPh, respectively, and collected in Table 4.

The local softness, s_k^α, and local philicity index, ω_k^α, condensed to reaction sites are easily obtained by their global quantities and condensed Fukui functions. Three different types of s_k^α and ω_k^α can be readily defined as [57]: $s_k^\alpha = Sf_k^\alpha$ and $\omega_k^\alpha = \omega f_k^\alpha$ where $\alpha = +$ and $-$ refer to nucleophilic and electrophilic attack, respectively.

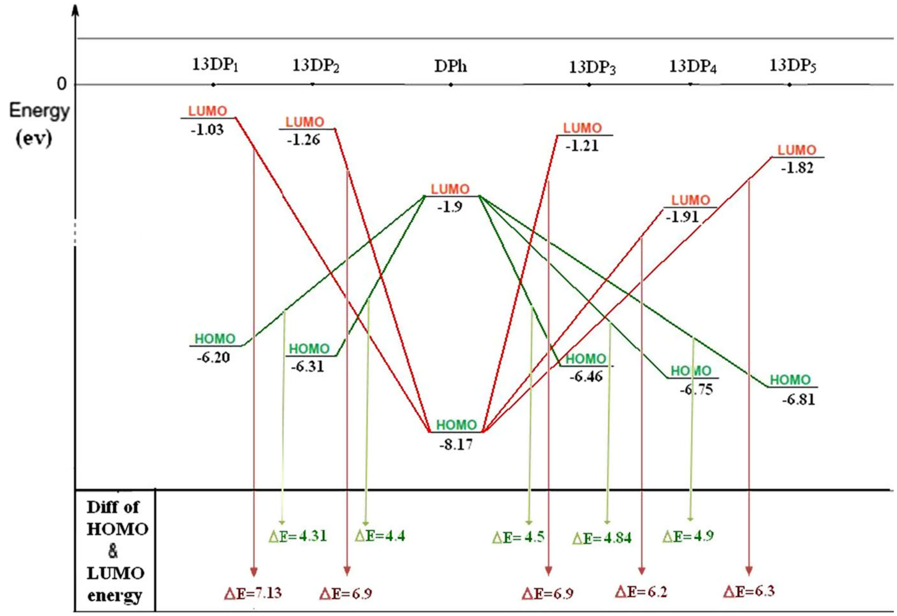


Fig. 6 Possible FMO interactions in the 13DCs between alkyne (DPh) and 13DPs 1–5

Table 3 Charge transfer (e) from 13DPs 1–5 to DPh in the studied reactions

13DP	1	2	3	4	5
Path a	0.0817	0.0726	0.0693	0.0542	0.0555
Path b	0.0787	0.0718	0.0658	0.0504	0.0538

Table 4 Fukui function, local softness and local philicity power in the reaction sites of reactants

	13DP1		13DP2		13DP3		13DP4		13DP5		DPh	
	N1	N3	N1	N3	N1	N3	N1	N3	N1	N3	C4	C5
f^{+}	0.152	0.237	0.127	0.212	0.154	0.231	0.141	0.216	0.161	0.232	0.075	0.261
f^{-}												
s^{+}	0.402	0.625	0.343	0.572	0.44	0.605	0.397	0.606	0.439	0.632	0.163	0.568
s^{-}												
ω^{+}	0.019	0.029	0.018	0.030	0.021	0.031	0.028	0.043	0.030	0.043	0.012	0.0242
ω^{-}												

Now, using local softness s(r) values and the Gazquez–Mendez rule concept, the Δs values for both pathways are computed according to the formula: $\Delta s_a = \left(s^{-}_{\mathrm{N1}} - s^{+}_{\mathrm{C1}}\right)^2 + \left(s^{-}_{\mathrm{N3}} - s^{+}_{\mathrm{C2}}\right)^2$ and $\Delta s_b = \left(s^{-}_{\mathrm{N1}} - s^{+}_{\mathrm{C2}}\right)^2 + \left(s^{-}_{\mathrm{N3}} - s^{+}_{\mathrm{C1}}\right)^2$(Fig. 2). It is recommended that the reaction channel with lower activation energy corresponding to the predominant product is associated with a smaller Δs value. The values of Δs_a and Δs_b are given in Table 5.

It is clear that values of Δs_a are smaller than those of Δs_b for all the studied reactions. Therefore, the Gazquez–Mendez rule based on NPA charges predicts that path (a) would be chosen over the alternative path (b).

According to Chattaraj's polar model [44], prediction of the regioselectivity using local descriptors is possible. In this model, the most favored interactions take place between highest values of local electrophilicity powers between reaction sites (Fig. 7). The values of the local nucleophilicity powers, ω^-, for atoms N_1 and N_3 of 13DPs 1–5 and the local electrophilicity powers, ω^+, for atoms C_1 and C_2 of DPh, are shown. This figure evidently shows that Chattaraj's model also predicts regioselectivity of these 13DCs in favor of path (a).

It is worth mentioning that local reactivity in polar reactions can also be studied within the conceptual DFT through the analysis of the electrophilic and nucleophilic Parr functions based on the spin density distribution at the radical anion and at the radical cation of a neutral molecule which allow for the characterization of the most electrophilic and nucleophilic centers of molecules, and for the establishment of the regio- and chemoselectivity in polar reactions [58].

In summary, all the conceptual DFT reactivity indexes (except for MPP) denote relatively more reactivity in path (a) of the 13DCs which results in the formation of methyl-5-(trifluoromethyl)-3-aryl-3H-1,2,3-triazole-4-carboxylates, P1–5_a. The regioselectivities in the 13DCs discussed here could be determined from the relative energies of the two TSs associated with the two modes of cycloadditions. Due to the similarity of Arrhenius pre-exponential factor and entropy values, the relative amounts of the two cycloadducts can be assumed to be proportional to the Arrhenius exponential factor [$\exp\left(\Delta E_a^{\#}\right)/RT$]. Consequently, the calculated product ratios, P1–5_a/P1–5_b, appear to be insignificant just by 2.6 times in favor of P1–5_a. Low regioselectivity pertaining to these 13DCs are in good agreement with the results of X-ray crystallography and ^{19}F nuclear magnetic resonance (NMR) spectra reported by Zhang et al. [22] where they found that all the path (a) regioisomers P1-5_a are preferred by 2.1–2.4 times over the corresponding path (b) regioisomers P1-5_b.

Interestingly, the fact that the MPP index fails to explain the observed regiochemistry of 13DC reaction is in line with some earlier reports in the literature. In 2006, Noorizadeh and Maihami argued that that, in many cases, the MHP and MPP cannot predict the major regioisomer of a Diels–Alder reaction [47], and, in 2013, Blair and Thakkar reported that careful scrutiny of 2386 experimental

Table 5 Calculated values of ΔS_a and ΔS_b for reaction between 13DPs 1–5 and DPh

	13DP1	13DP2	13DP3	13DP4	13DP5
ΔS_a	0.060	0.032	0.078	0.056	0.080
ΔS_b	0.241	0.218	0.212	0.225	0.237

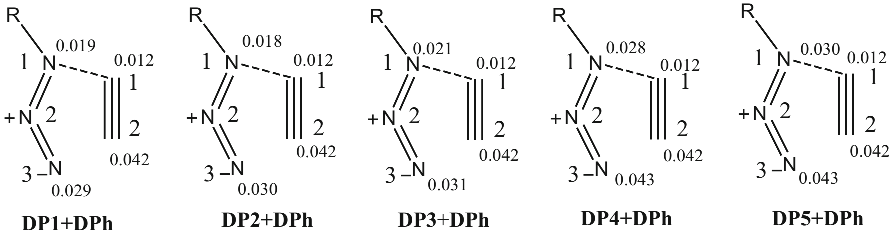


Fig. 7 Calculated local nucleophilicites, ω^{-}, for 13DPs 1–5, and local electrophilicites, ω^{+}, for DPh centres

and theoretical polarizabilities revealed 86 violations and suggested that the MPP is violated approximately two to three per cent of the time [59]. Moreover, Torrent-Sucarrat et al. carried out diagonalizations of the Hessian matrix of the polarizability to determine the molecular distortions with a more marked MPP or anti-MPP character and, subsequently, they could derive a set of simple rules that allow predicting a priori without calculations the existence of vibrational modes that break the MPP [60].

Conclusions

The mechanism, reactivity and regioselectivity of 13DC five aryl azides and an electron-deficient alkyne leading to two regioisomeric series (a) and (b) are studied at the B3LYP/6-31G(d,p) level of theory using different approaches (the maximum hardness principle, minimum polarizability principle, minimum electrophilicity principle, activation energies, FMO energies, Gazquez–Mendez rule and Chattaraj's polar model). All the 13DCs are high exoergic, have a NED character, $\mathrm{HOMO}_{13\mathrm{DP}}$–$\mathrm{LUMO}_{\mathrm{DPh}}$ interaction and are rather asynchronous. Except for polarizability values, the remaining methods predict the path (a) regioisomers as the major product. Interestingly, these finding are in good agreement with those experimentally reported for the titled reactions.

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