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THEORETICAL STUDY OF 1, 3-DIPOLAR CYCLOADDITIONS REGIOSELECTIVITY OF BENZYL AZIDE WITH GLYCOSYL-O-ACETYLENE USING DENSITY FUNCTIONAL THEORY (DFT)

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Abstract: A theoretical study of 1, 3 cycloaddition has been carried out using density functional theory (DFT) methods at the B3LYP/6-31G* level. The regioselectivity of the reaction have been clarified through different theoretical approaches: Case of a Two-Center Process (domingo approach), HSAB principle (Gazquez and Mendez approach), and the activation energy calculations. The analysis of results shows that the reaction takes place along concerted asynchronous mechanism and the isomer meta is favored, in agreement with the experiment results.

Keyword: 1, 3-dipolar cycloadditions; 1,2,3-Triazole; regioselectivity; DFT calculations; Parr Functions.

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1. Introduction

Cycloaddition reactions are one of the most important synthetic processes, with both synthetic and mechanistic interest in organic chemistry. Among them, 1,3-dipolar cycloadditions (13DCs) [1], that have a tremendously successful history of building five-membered heterocycles. Now they are utilized in almost every area of chemistry, including, materials chemistry [2], drug discovery [3], and chemical biology [4].The general concept of 1,3-dipolar cycloadditions was introduced by Huisgen and co-workers in the early 1960s[5]. Huisgen's work stated the basis for the understanding of the mechanism of concerted cycloaddition reactions. The formation of triazoline from Azides and olefins was first reported by Wolff [6]. Subsequently, many theoretical studies have been devoted to study the regionselectivity of the reaction between triazole and alkyls [7-8]. In this context molecular orbitals frontier (FMO) seemed to be able to explain the regioselectivity and reactivity differences [9], over the last decades, reactivity descriptors, as Parr function indices, local electrophilicity and local softness, derived from density functional theory were widely used for the interpretation of the regioselectivity [10].

Our work is aimed to study the regio-selectivity of 1,3DC between benzyl azide and glycosyl-o-acetylene (Figure1) by using three different approaches: Case of a Two-Center Process (domingo approach), HSAB principle (Gazquez and Mendez approach), and the activation energy calculations, these approaches are successfully allowed us predict the favored stereoisomer, and it is according to the experimental results [11].

2. Theory and computational details

All energies and geometries of the reactants, transition states (TSs) and cycloaddition

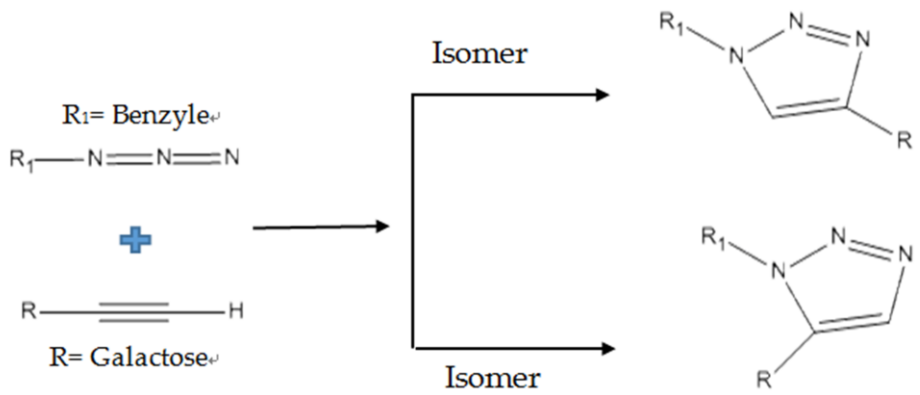


Figure 1: 1,3-Dipolar cycloaddition reaction.

products (CAs) presented in this study are computed by DFT method at the B3LYP/6-31G* level of theory carried out with Gaussian G09 [12, 13]. The frequency calculations were carried out to characterize stationary points to ensure that minima and transition states have zero and one imaginary Frequency [14]. The global reactivity indices (electronic chemical potential μ, chemical hardness η, global electrophilicity ω, global nucleophilicity N) were estimated according to the equations recommended by Parr [15,16] and Domingo [17,18]. In particular, the electronic chemical potentials and chemical hardnesses of the reactants studied here were evaluated in terms of the one-electron energies of the frontier molecular orbitals using the following equations:

$$\mu \approx (E_{HOMO} + E_{LOMO})/2, \quad (1)$$

$$\eta \approx (\varepsilon L - \varepsilon H), \quad (2)$$

The values of μ and η were then used to calculate ω according to the formula:

$$\omega = (\mu^2/2\eta), \quad (3)$$

Nucleophilicity index N has been recently introduced on the basis of the HOMO energies [19]:

$$N = E_{HOMO}\text{ (nucleophile)} - E_{HOMO}\text{ (TCE)}, \quad (4)$$

The tetracyanoethylene (TCE) is taken as a reference because of its lower HOMO energy in a large series of molecules [20,21].

The chemical softness S was introduced as the inverse of the chemical hardness [22]:

$$S \approx 1/\eta, \quad (5)$$

In case an amount equivalent to one electron is transferred, the nucleophile becomes a radical cation, while the electrophile becomes a radical anion. Interestingly, analysis of the atomic spin density (ASD) at the radical cation and the radical anion gives a picture of the distribution of the electron density in the electrophile and the nucleophile when they

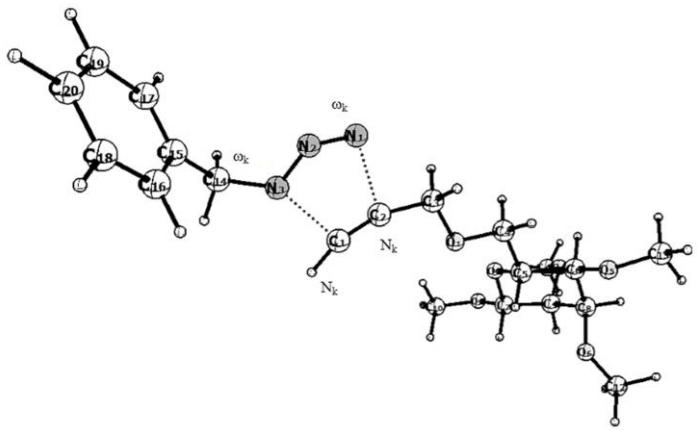


Figure 2: Prediction of the favored interactions between dipole and dipolarophile.

approach each other along the reaction progress.

Based on these observations, in 2014, Domingo proposed the Parr functions P(r) [17, 18], which are given by the following equations:

$$P^{-}(r) = \rho_s^{rc}(r) \text{ for electrophilic attacks} \quad (6)$$

And

$$P^{+}(r) = \rho_s^{ra}(r) \text{ for nucleophilic attacks} \quad (7)$$

Where $\rho_s^{rc}(r)$ is the ASD at the r atom of the radical cation of a considered molecule and $\rho_s^{ra}(r)$ is the ASD at the r atom of the radical anion. Each ASD gathered at different atoms of the radical cation and the radical anion of a molecule provides the local nucleophilic P_k^- and electrophilic P_k^+ parr functions of the neutral molecule.

With these electrophilic and nucleophilic Parr functions at hand, we can redefine the local electrophilicity ω_k, and the local nucleophilicity N_k *i*ndices as follows:

$$\boldsymbol{\omega_{k=}} \omega P_k^+, \quad (8)$$

$$N_{k=} N P_k^-, \quad (9)$$

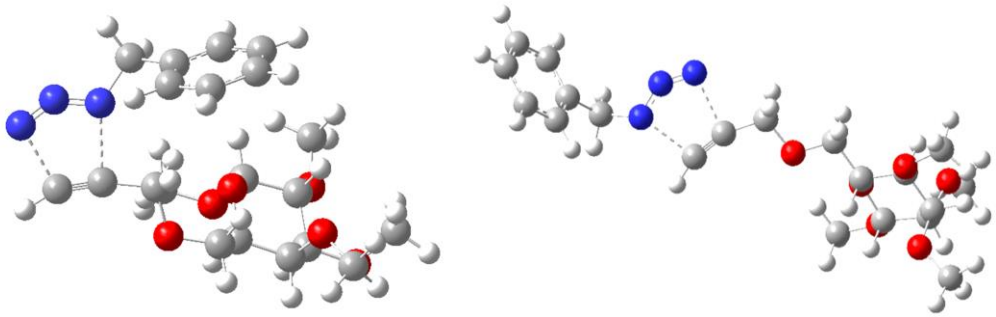
where ω and N are obtained from equations (3) and (4), respectively.

3. RESULTS AND DISCUSSION

3.1 The Global properties

To determine static global properties: electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω), and nucleophilicity (N), softness (S) of reagent we used equations (1), (2), (3), (4), (5), respectively **Table 1**.

The chemical potential μ and nucleophilicity N of dipole (-4.113ev, 2.41ev respectively) are lower than those of dipolarophile (-3.327ev, 2.75ev respectively). The value of electrophilicity indice (ω) indicates that dipole (1.48ev) behave like an acceptor of electrons



Ortho cyclization Meta cyclization

Figure 3: The two possible cyclization modes.

(electrophile), and dipolarophile (0.85ev) as donor of electrons (nucleophile) for the reaction (inverse electronic demand). These results are in agreement with the global electron density transfer performed on the TSs (see later).

3.2 Prediction of regiochemistry

To predict the favored isomer, an approach of two-Center Process proposed by Domingo, and Criteria for Four-Center Reactions approach were performed.

The approach Domingo in 2002 proposed that the formation of first bond is due to the interaction between the most electrophilic site of the dipolarophile (characterized by a biggest value of ωk) and the most nucleophile site (characterized by the biggest value of Nk)[23,24]. The prediction of the first bond formed is sufficient to predict the favored isomer formed.

The values of local electrophilicities ωk and nucleophilicities Nk listed in **table2**, allow us to characterize the most favorable two-center interaction along an asynchronous bond-formation process, the more favorable interaction of two polar sites in this reaction takes place between C1(the more nucleophile site) and N3(the more electrophile site) shown in Figure3. Which indicate that 1,4 isomer (isomer1) is favorable. Moreover, this is in concordance with the experiment results. The analysis based on local electrophilicity ωk, nucleophilicity Nk of both Mk (Merz–Kollman) and NPA (natural population analyses) charges allow us to predict the favorable isomer for the reaction.

3.3 Regioselectivity Criteria for Four-Center Reactions

Table1: Frontier orbital energies (eV) for the different compounds at B3LYP/6-31G* theoretical level

Compound	*Global properties*				
	$\mu(ev)$	$\eta(ev)$	$S(a.u)$	$\omega(ev)$	$N(ev)$
Dipole	-4.113	5.68	4.79	1.48	2.41
Dipolarophile	-3.327	6.53	4.16	0.85	2.75

Table2: Local properties of dipole and dipolarophile, k define the site in the molecule where the property evaluated.

Compounds		P^+		P^-		S^+		S^-		ω_K(ev)		N_k(ev)	
		MK	NPA	MK	NPA	MK	NPA	MK	NPA	MK	NPA	MK	NPA
Dipole (R=CH_2Ph)	**N1**	0.03	0.11	0.11	0.05	0.14	0.52	0.52	0.24	0.04	0.16	0.28	0.14
	N3	0.21	0.28	0.07	0.09	1.00	1.34	0.34	0.43	0.32	0.41	0.18	0.23
Dipolarophile(R_1H)	**C1**	0.05	0.13	0.05	0.08	0.23	0.54	0.21	0.33	0.04	0.11	0.14	0.22
(R_2=Galactose)	**C2**	0.13	0.06	0.02	0.01	0.54	0.25	0.08	0.04	0.11	0.05	0.05	0.03

Gazquez and Mendez [25] proposed a local version of the well-known HSAB principle, which essentially indicates that the interaction between A and B is favoured when it occurs through those atoms having approximately equal softness values. For explaining this regioselectivity, the two reactants are classified as nucleophile or electrophile and then the local HSAB principle has been applied. Starting from the idea that the softnesses of the interacting atoms should be as close as possible, a quantity has been defined for the regioselectivity that could be a measure of predominance of one approach over the other. When atoms i and j of molecule A (say electrophilic) are involved in the formation of a cycloaddition with atoms k and l of another molecule B (say nucleophilic), one can defined equation (5) as a measure of regioselectivity [26, 27].

$$\Delta_{ij}^{K1} = (S_i^- - S_k^+)^2 + (S_i^- - S_l^+)^2, \tag{10}$$

where i and j are the atoms of molecule A involved in the formation of a cycloaddition with atoms k and l of molecule B, $S_{i,j}$ are the appropriate type of atomic softnesses (if S_i and S_j are electrophilic then S_k and S_l are obviously nucleophile) [28,29].

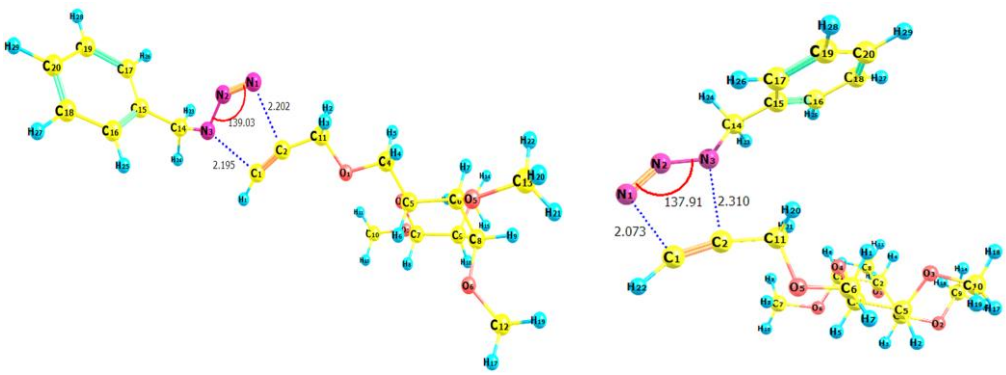
The application of the Gazquez–Mendez rule is reduced to the calculation of the quantities Sortho and Smeta corresponding to the ortho and meta cycloaddition channels. These quantities are expressed in equation (6):

$$S_{ortho} = (S_{N3}^- - S_{C2}^-)^2 + (S_{N1}^- - S_{C1}^+)^2,$$
$$S_{meta} = (S_{N3}^- - S_{C1}^+)^2 + (S_{N1}^- - S_{C2}^+)^2, \tag{11}$$

The formation of the regioisomer meta is favored if $S_{meta} < S_{ortho}$.

Table 3: Values of Sortho and Smeta quantities calculated with NPA

	$S_{isomer2(ortho)}$	$S_{isomer1(meta)}$
Reaction	0.124	0.012



1,4-regiochemistry (Isomer meta), 1,5-regiochemistry (Isomer Ortho)

Figure 4: Optimized transition structures of the two isomer for reaction.

Table 3 results shows that the favored isomer to be formed of the reaction is isomer meta (isomere1) (S1=0.012<S2=0.124). Therefore, Gazquez–Mendez rule based on electrostatic charges is able to predict the right regioselectivity.

3.4 Activation Energy of reaction:

The reaction was calculated by DFT at B3LYP/6-31G*(d) level. Our calculations gave, as expected, analogous energy barriers for the 1,4- and 1,5-regiochemistries (Figure6), resulting in 15.18 and 18.76 kcal mol-1, respectively. This energy deference explains that isomer meta is the favorable isomer to be formed, and this prediction is supported by experiment. The optimized transition-state structures are shown in **Figure5**. In addition, an analysis of the geometries at the TS is given in **table 4** and **5**.

Table 4: Transition state proprieties of the two possible isomers.

Propriety	Isomer ortho (TS)	Isomer meta(TS)
Energy (a.u)	-1394.96872234	-1394.97443455
Frequency (cm^{-1})	-378.95	-364.54
the global electron density transfer (GEDT)	0.08	0.02

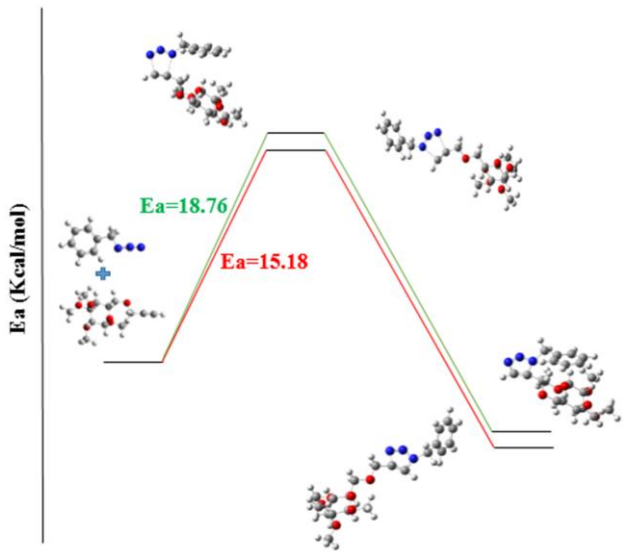


Figure 5: Relationship between activation, distortion, and interaction energies for cycloaddition of a benzyl azide with glycosyl-o-acetylene.

- Global electron density transfer (GEDT):

The analysis of the natural population (NPA) allows us to evaluate the global electron density transfer (GEDT**)** along the cycloaddition processes. For the reaction between benzyl azide and glycosyl-o-acetylene, the global electron density transfer in the TS1 and TS2 from the glycosyl-o-acetylene to the benzyl azide is 0.08, 0.02 respectively, for both 1,4 and 1,5 isomers. These results indicate that this cycloaddition reaction has a low polar character.

- Asynchronicity extension :

The extension of the asynchronicity can be measured by the difference between the lengths r of the two links formed in the cycloaddition [Dr = [d (N1-C2) -d (N3-C1)]. Therefore, the asynchronicity of TS1 is 0.007 and 0.237 for the TS2. This result shows that TS1 is more synchronous than TS2.

4. CONCLUSION

The DFT calculations at the B3LYP/6-31G* level of theory, using Domingo approach, Gazquez and Mendez approach, and the activation energy confirmed the favored regioisomere obtained experimentally (isomere meta). The caractere IED of the reaction was descriped by the analysis chemical potentials and global electrophilicity.

The analysis based on local electrophilicity ω_k, nucleophilicity N_k using parr function,

Table 5: Optimized geometry parameters for the TSortho and TSmeta in concerted mechanism for reaction

Variable	Isomere1	Isomere2
N1-N2-N3	139.03	137.91
C14-N3-N2	119.55	119.69
C1-C2-C11	159.99	159.683
N1-N2	1.17	1,17
N2-N3	1.26	1,25
N1-C2	2.20	-
N3-C1	2.19	-
N1-C1	-	2.07
N3-C2	-	2.31
C1-C2	1.23	1,23

*Angles are in degrees and distances in angstroms.

and activation energy calculated could predict successfully the experimental regioselectivity.

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