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Impact of Lewis acid catalyst on the regioselectivity and kinetics of 1,3-dipolar cycloaddition reaction of azidobenzene with acrolein: a theoretical study using DFT

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ABSTRACT

In the present work, impact of Lewis acid (LA) catalysts BF_3, BCl_3, and BBr_3 on the kinetics and regioselectivity of 1,3-dipolar cycloaddition (1,3-DC) reaction between azidobenzene and acrolein was theoretically studied using B3LYP/6-31G* level. Our results indicate while the uncatalyzed 1,3-DC reaction under investigation takes place via a non-polar, non-regioselective, and low asynchronous process, the LA catalyzed 1,3-DC reaction takes place via a polar, regioselective, and high asynchronous process. In addition, the barrier height of the studied 1,3-DC reaction is considerably reduced in the presence of LA catalysts, and the catalytic activity of LAs in order to increase the electrophilicity character of acrolein and, consequently, to reduce barrier height of reaction, is increased with the increase of halogen atom size; $BBr_3 > BCl_3 > BF_3$. Regioselectivity in these LA catalyzed 1, 3-DC reactions appears to be controlled by steric repulsion effects between the LA catalyst and the azide phenyl substituent instead of the electronic effects.

Keywords: 1, 3-dipolar cycloaddition; Azidobenzene; Acrolein; regioselectivity; DFT reactivity indexes; Parr functions

INTRODUCTION

1, 3-dipolar cycloaddition (1, 3-DC) reactions play a key role in the syntheses of five-membered heterocyclic compounds which are widely used as important pharmacological agents [1]. 1, 3-DC reactions, due to their ability to present a high degree of regio- and/or stereoselectivity, have also been the aim of numerous experimental and theoretical investigations [2-4]. Since 1960 that Huisgen and co-workers introduced the concept of 1, 3-DC reactions [5], the mechanism of these reactions has been controversial among chemists [6]. Recent studies on stereochemistry and kinetics of 1, 3-DC reactions have proven that one-step mechanism is preferred over the stepwise one [7, 8]. The one-step mechanism has been specified with the following characterizations: single-step, five-center cycloaddition, and involves 4π electrons from the 1, 3-dipole and 2π electrons from the dipolarophile. In this mechanism, in agreement with the Woodward-Hoffmann rules [9], combination of three p_z orbitals of 1,3-

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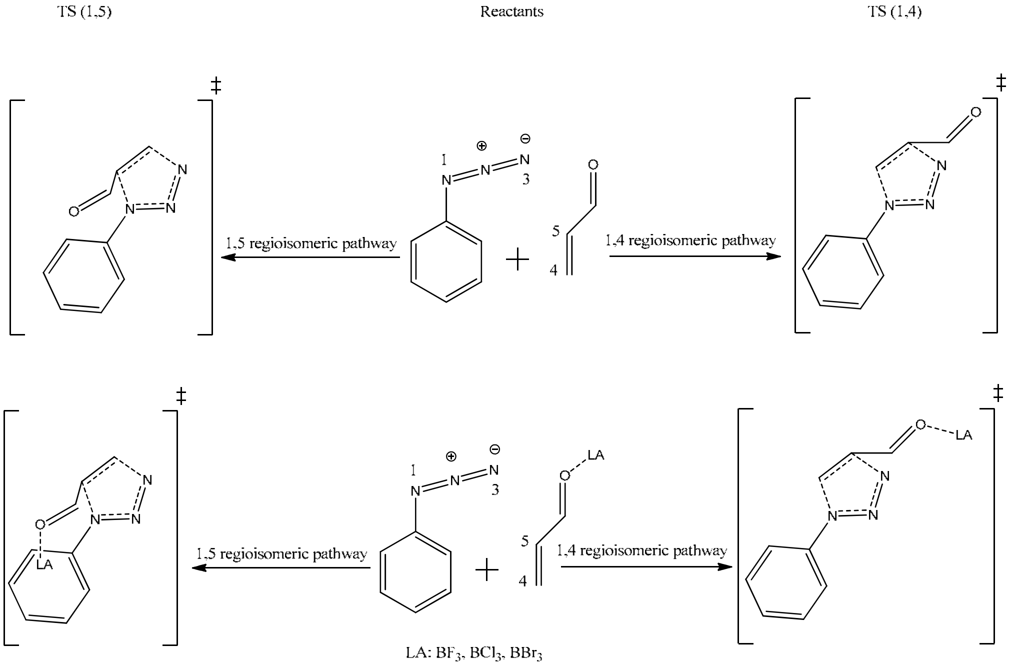
Corresponding author: s_emamian@iau-shahrood.ac.ir & saeedreza_em@yahoo.com dipole (containing 4π electrons) and two p_z orbitals of the dipolarophile (containing 2π electrons) takes place suprafacially and this is the reason why these reactions symbolized as $[{}_{\pi}4_s + {}_{\pi}2_s]$. The regio- and stereochemistry of 1, 3-DC reactions can considerably be affected either by substituents on the reactants or by using Lewis acid (LA) catalysts. The application of LA catalysts in cycloaddition reactions has been the subject of numerous studies within the last decades [10]. The chemistry of azides has attracted the attention of many chemists, since most of these compounds are used in rubber vulcanization, polymer crosslinking, dyes, tire cored adhesives, foaming of plastics, pharmaceuticals, pesticides and herbicides [11]. 1, 2, 3-triazole derivatives can be generated via 1, 3-DC reactions of azides with substituted ethylene or acetylene compounds [12, 13]. 1, 2, 3-triazoles has also received much attention due to their wide applicability as fungicides, herbicides, light stabilizers, fluorescent whiteners, optical brightening agents, and corrosion retardants [14, 15]. In the present work, impact of trifluoroborane (BF_3), trichloroborane (BCl_3), and tribromoborane (BBr_3) as LA catalysts on the regioselectivity of 1,3-DC reaction between azidobenzene as 1,3-dipole (D) and acrolein as dipolarophile (Dph) is theoretically studied at the B3LYP/6-31G level (scheme 1).

COMPUTATIONAL DETAILS

Previous theoretical studies devoted to the 1,3-DC reactions have confirmed that using DFT/B3LYP method together with the standard 6-31G* basis set is appropriate to obtain reliable geometries and energies [16,17]. Consequently, in the present work, geometries of all reactants (D, Dph, and Dph-LA complexes) and corresponding transition state structures (TSs) were fully optimized using density functional theory with the B3LYP [18] exchange correlation functional and 6-31G* basis set. To confirm the nature of



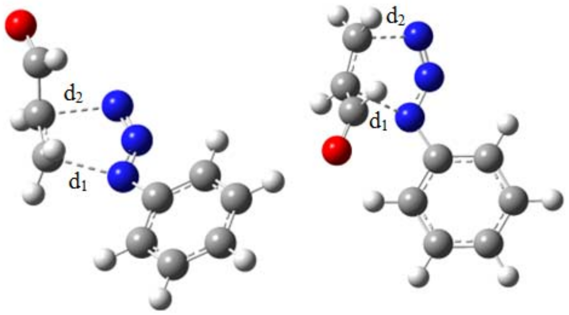
Scheme 1. 1,3-DC reaction between azidobenzene (D) and acrolein (Dph) in the absence of LA catalyst (top) and in the presence of LA catalyst (bottom) studied in this work.

stationary points located on the potential energy surface (PES) and evaluate the activation Gibbs free energies, frequency calculations were carried out at 298.15 K and 1.0 atm. For minimum state structures and for the TSs, only real frequency values and only a single imaginary frequency value were accepted, respectively. The normal modes corresponding to the imaginary frequencies in the transition state structures are related to the vibrations of new developing bonds. The stabilities of restricted wave functions toward unrestricted alternatives for reactants were verified using STABLE keyword [19] and instability was not found. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method [20]. The global electrophilicity index, introduced by Parr *et al.* [21], is given by the following expression, $\omega = (\mu^2/2\square)$, in terms of the electronic chemical potential μ and the chemical hardness $\square$. Following Koopman's theorem [22] allows to evaluate μ as $(\varepsilon_H + \varepsilon_L)/2$ and $\square$ as $(\varepsilon_L - \varepsilon_H)$ where ε_H and ε_L indicate the energy of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), respectively [16]. Recently, Domingo *et al.* [23] have introduced an empirical (relative) nucleophilicity index as $N = \varepsilon_{H(Nu)} - \varepsilon_{H(TCE)}$. In this index, the difference between HOMO energies of nucleophile (Nu) and tetracyanoethylene (TCE), as reference, is considered. This is worth to note that this definition always leads to positive value for nucleophilicity index because TCE presents lowest HOMO energy in a large series of molecule investigated in the context of polar cycloadditions. The electrophilic, P_k^+, and nucleophilic, P_k^-, Parr functions were obtained using methodology which has very recently been proposed by Domingo *et al.* [24]. With these values at hand, local electrophilicity index, ω_k, and local nucleophilicity index, N_k, can easily be obtained as $\omega_k = \omega P_k^+$ and $N_k = NP_k^-$ [24]. All calculations were carried out using Gaussian 09 computational program package [25].

RESULTS AND DISCUSSION

When an asymmetric 1,3-dipole and dipolarophile come into the reaction channel, depending on the direction of attack to each other, two regioisomeric cycloadducts associated with two different regioisomeric TSs can be generated. Considering this fact, two different TSs, TS (1, 4) and TS (1, 5), in the absence and presence of LA catalysts were located and characterized (see scheme 1 for more details and atom numbering). Relative Gibbs free energies for TS (1, 4) and TS (1, 5) associated with uncatalyzed 1,3-DC reaction between azidobenzene and acrolein are 30.05 and 30.35 kcal/mol, respectively. As can be seen, there is no significant difference between activation Gibbs free energies corresponded to two different regioisomeric pathways indicating that uncatalyzed 1, 3-DC reaction under study does not present any regioselectivity. In the other words, both cycloadducts can kinetically be generated in the approximately same rate. Optimized geometries of the two regioisomeric TSs involved in the uncatalyzed 1, 3-DC reaction are sketched in Fig. 1. Furthermore, the magnitude of the asynchronicity can be determined by considering the difference between the lengths of the two new single bonds which are being formed at the TSs; $\Delta d = d_1 - d_2$. The values of Δd for TS (1, 4) and TS (1,5) in the uncatalyzed 1,3-DC reaction are 0.16 and 0.26Å, respectively indicating low asynchronicity character of the process.

The polar nature of uncatalyzed 1, 3-DC reaction, in each regioisomeric pathway, can easily be clarified considering the global charge transferred (GCT) between two moieties at the corresponding TS. The net charges at the acrolein moiety are 0.01e and 0.02 at TS (1, 4) and TS (1, 5), respectively. These negligible CTs reveal a non-polar nature for the uncatalyzed 1,3-DC reaction between azidobenzene and acrolein. As outlined in the introduction, previous studies on the LA catalyzed 1,3-DC reactions have shown that the kinetic aspects of reaction, regioselectivity, mechanism, the polar nature of process, and asynchronicity of reaction can considerably be affected by the inclusion of LA catalysts. Relative Gibbs free energies for TS (1, 4) and TS (1,5) in the presence of various LA catalysts considered in this work are presented in Table 1.



d_1= 2.07Å, d_2= 2.23Å d_1= 2.24Å, d_2= 1.98Å

Fig. 1. Optimized geometries for regioisomeric TS (1,4), left, and TS (1,5), right, involved in the uncatalyzed 1,3-DC reaction between azidobenzene and acrolein including the lengths (d_1 and d_2) of the two new developing single bonds.

Table 1. Relative[a] Gibbs free energies for regioisomeric TSs involved in the LA catalyzed 1, 3-DC reaction between azidobenzene and acrolein

LA	[a]ΔG (kcal/mol)	
	TS (1,4)	TS (1,5)
BF_3	26.75	28.39
BCl_3	24.23	26.51
BBr_3	24.09	25.01

[a]: relative to azidobenzene + acrolein-LA complex.

As can be seen, in the presence of LA catalysts, the barrier height of reaction is significantly reduced and reaction presents a high degree of regioselectivity so that 1,4 cycloadduct, associated with TS (1,4), is kinetically favored in all catalyzed 1,3-DC reactions. A deep attention to the relative Gibbs free energies in the predominant pathway (1,4) clearly shows that the capability of LA in order to reduce activation height is increased with the increase of halogen atom size; that is, this capability is in order of: BBr_3> BCl_3> BF_3. In the other words, increasing the size of halogen atom leads to decrease its capability to share its lone pairs with boron atom via the formation of return π bonds. Consequently, the unfilled orbital of boron can better interact with the oxygen lone pairs of acrolein leading to further increase in the electrophilicity character of acrolein-LA which in turn will lead to further decrease in barrier height of reaction via a polar process. Optimized geometries of the two regioisomeric TSs involved in the catalyzed 1, 3-DC reaction between azidobenzene and acrolein are shown in Fig. 2.

Figure 2 also shows that the magnitude of asynchronicity, in both regioisomeric pathways, is noticeably increased in the presence of LA catalysts and this increment is in line with the increase of the LA capability in order to increase the electrophilicity character (activation) of acrolein; the stronger catalyst, the more asynchronous the reaction. The order of asynchronicity for both regioisomeric pathways in the presence of LA catalysts is: BBr_3> BCl_3> BF_3. The net charge at the acrolein-LA framework for LA catalyzed 1, 3-DC reaction between azidobenzene and acrolein is presented in Table 2.

Table 2. The net charge at the acrolein-LA framework for LA catalyzed 1, 3-DC reaction between azidobenzene and acrolein

LA	TS (1,4)	TS (1,5)
BF_3	0.13	0.11
BCl_3	0.19	0.18
BBr_3	0.21	0.20

Considering GCTs presented in Table 2, one can easily be concluded that the polar nature of studied 1, 3-DC reaction, especially in the predominant pathway (1, 4), is significantly increased in the presence of LA catalysts and, interestingly, the stronger catalyst leads to the more polar 1, 3-DC reaction. Parr functions can reliably be used to predict the regioselectivity in cycloaddition reactions. In order to reach to this purpose, global DFT reactivity indexes should be calculated. Frontier molecular orbital (FMO) energies, ε_H and ε_L, as well as electronic chemical potential, μ, chemical hardness, η, global electrophilicity, ω, and global nucleophilicity, N, for the ground state of azidobenzene, acrolein, and acrolein-LA complexes are displayed in Table 3.

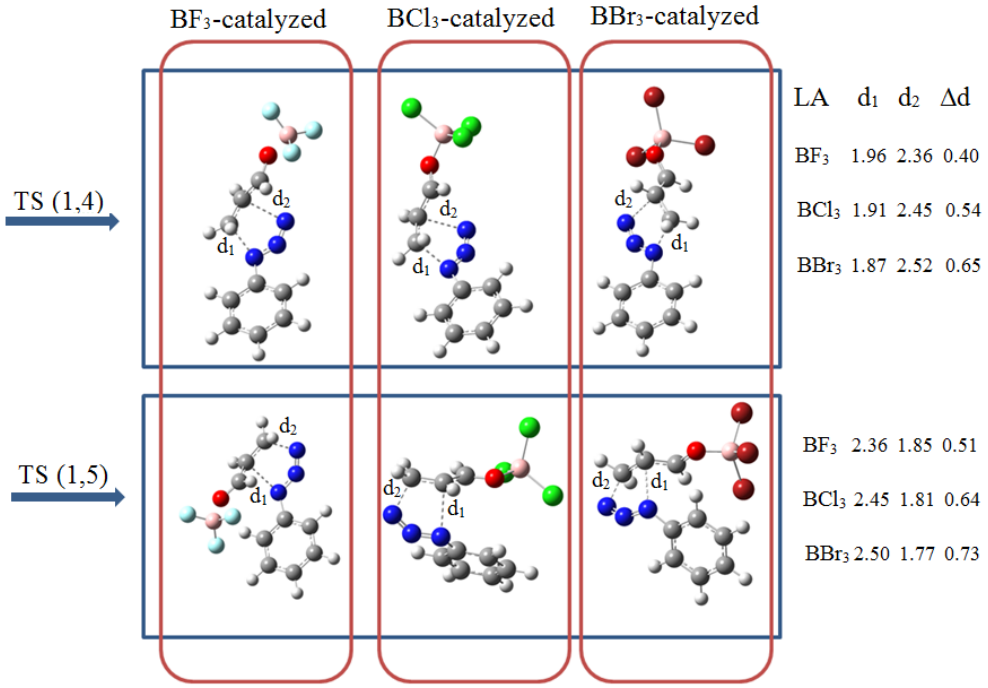


Fig. 2. Optimized geometries for regioisomeric TSs involved in the catalyzed 1,3-DC reaction between azidobenzene and acrolein including the lengths (d_1 and d_2 in Å) of the two new developing single bonds and the magnitude of the asynchronicity, Δd in Å.

Table 3. FMO energies (ε_H, ε_L), electronic chemical potential, μ, chemical hardness, η, global electrophilicity, ω, and global nucleophilicity, N, for the ground state of azidobenzene, acrolein, and acrolein-LA complexes

Compound	ε_H (a.u.)	ε_L (a.u.)	μ (a.u.)	η (a.u.)	ω (eV)	N^* (eV)
Azidobenzene	-0.22795	-0.03813	-0.13304	0.18982	1.26	2.92
Acrolein	-0.25714	-0.06503	-0.16108	0.19211	1.83	2.12
Acrolein-BF_3	-0.33526	-0.12060	-0.22793	0.21466	3.29	0.00
Acrolein-BCl_3	-0.27074	-0.14498	-0.20786	0.12576	4.67	1.75
Acrolein-BBr_3	-0.24305	-0.14540	-0.19422	0.09765	5.25	2.50

*: ε_H (TCE)= -0.33520 a.u.

The electronic chemical potential of azidobenzene, -0.13304, is higher than that of acrolein, -0.16108. Consequently, global charge transfer will take place from azidobenzene to acrolein via corresponding 1, 3-DC reaction. In the other words, azidobenzene acts as nucleophile and acrolein acts as electrophile. The global electrophilicity index for acrolein is ω= 1.83 eV allowing to be classified as strong electrophile considering the electrophilicity scale [26]. On the other hand, the global nucleophilicity index for azidobenzene is N= 2.92 eV, being classified as moderate nucleophile on the nucleophilicity scale [27]. The polar nature of a 1, 3-DC reaction can easily be foreseen using the electrophilicity difference of reaction pair, Δω [23]. The very small value, 0.57 eV, for Δω in uncatalyzed 1, 3-DC reaction between azidobenzene and acrolein indicates non-polar character for this cycloaddition which is in excellent agreement with the negligible GCTs in the corresponding 1, 3-DC reaction (see former). Coordination of LA catalysts to the oxygen atom of acrolein considerably increases the electrophilicity of acrolein-LA complexes. The Δω value between azidobenzene and acrolein-LA complex is increased with increase the size of halogen atom of LA catalyst: acrolein-BBr_3 (3.99 eV)> acrolein-BCl_3 (3.41 eV)> acrolein-BF_3 (2.03 eV) indicating the more polar nature for LA catalyzed 1, 3-DC reaction between azidobenzene and acrolein-LA complexes. The above trend for Δω is in complete agreement with that observed for GCTs in the corresponding LA catalyzed 1, 3-DC reaction (see Table 2). Since the uncatalyzed 1, 3-DC reaction between azidobenzene and acrolein does not present any regioselectivity, prediction of regioselectivity in just LA catalyzed 1, 3-DC reaction between azidobenzene and acrolein-LA complexes can be meaningful. Nucleophilic (P_k^-) Parr functions and corresponding local nucleophilicity indexes (N_k) for N1 and N3 nitrogen atoms of azidobenzene as well as electrophilic Parr functions (P_k^+) and corresponding local electrophilicity indexes (ω_k) for C4 and C5 carbon atoms of acrolein-LA complexes are calculated and collected in Table 4 (see scheme 1 for atom numbering).

Based on the values presented in Table 4, one can easily be concluded that the most nucleophilic center of azidobenzene is N3 nitrogen atom due to its higher N_k value than that of N1 nitrogen atom. On the other hand, the most electrophilic center of acrolein-LA complexes is C4 carbon atom. When local electrophilicity indexes for C4 and C5 carbon atoms in acrolein-LA complexes are compared with those calculated for acrolein (0.52 on C4 and 0.04 on C5), it is obvious that while C4 carbon atom is activated, C5 carbon atom is extremely deactivated due to negative values of ω_k for this center.

Table 4. Nucleophilic and electrophilic Parr functions as well as corresponding local nucleophilicity and local electrophilicity indexes for sites (atoms) directly involved in the LA catalyzed 1,3-DC reaction between azidobenzene and acrolein-LA complexes

Compound	P_k^-		N_k (eV)		P_k^+		ω_k (eV)	
	N1	N3	N1	N3	C4	C5	C4	C5
Azidobenzene	0.22	0.25	0.64	0.72	---	---	---	---
Acrolein-BF_3	---	---	---	---	0.55	-0.08	1.81	-0.27
Acrolein-BCl_3	---	---	---	---	0.56	-0.14	2.60	-0.66
Acrolein-BBr_3	---	---	---	---	0.56	-0.15	2.93	-0.80

Consequently, in LA catalyzed 1, 3-DC reaction between the nucleophilic azidobenzene and the electrophilic acrolein-LA complexes, the most favorable two-center interactions should occur between N3 nitrogen atom of azidobenzene and C4 carbon atom of acrolein-LA complexes leading to (1, 5) regioisomer as kinetically preferred regioisomer. Interestingly, regioselectivity predicted by local philicity indexes is against the regioselectivity obtained from kinetics studies. Indeed, while activation Gibbs free energies (Table 1) indicate (1, 4) regioisomer associated with TS (1, 4) is kinetically preferred regioisomer, local philicity indexes predict (1, 5) regioisomer associated with TS (1, 5) should be the preferred one. These unexpected results can be related to the low local nucleophilic discrimination between the N1 and the N3 centers in the azidobenzene, note that the corresponding nucleophilic Parr functions are 0.22 at N1 and 0.25 at N3, and to the steric repulsion effects that appears between the halogen atom of the LAs and phenyl ring of azidobenzene, which can be more important than poor nucleophilic activation of the N3 atom relative to the N1 one along the C-N single bond formation.

CONCLUSION

According to the computations carried out in this study, the following conclusions can be pointed out:

1- While uncatalyzed 1, 3-DC reaction between azidobenzene and acrolein takes place via non-polar, non-regioselective, and low asynchronous process, LA catalyzed 1, 3-DC reaction between azidobenzene and acrolein-LA complexes takes place via a polar, regioselective, and high asynchronous process.

2- Inclusion of LA catalyst extremely increases the electrophilicity character of acrolein-LA complex so that the barrier height of reaction is significantly reduced and (1,4) regioisomer, corresponded to TS (1,4), is allowed to be kinetically preferred regioisomer.

3- The most important point of this work is that in these LA catalyzed 1,3-DC reactions, the regioselectivity is controlled by steric repulsions that appears between the halogen atom of the LAs and the phenyl substituent of azidobenzene instead of the unequivocal local nucleophilic activation of the N3 nitrogen atom of azide.

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