Computational Study of the Regioselective 1,3-Dipolar Cycloaddition of 3-Methylpyridinium Methylide and Acetylenic Dipolarophile using DFT based Reactivity Descriptors

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Abstract

1,3-Dipolar cycloaddition of *N*-(2-ethoxy-2-oxoethyl)-3-methylpyridinium ylide to $-C\equiv C$ -bonds of dipolarophiles such as functionalized acetylene derivatives has been investigated at the B3LYP/6-31+G* level of DFT. Location of transition state along a concerted but asynchronous reaction pathway suggests that the reaction is HOMO_(dipole) controlled and is not much affected by the presence of methyl substituent in pyridine ring. In case of unsymmetrically substituted dipolarophile, the experimentally observed regioselectivity is supported by the calculated values of reactivity indices such as, Fukui function, local electrophilicity index and local nucleophilicity index.

Keywords: 1,3-Dipolar cycloaddition, Fukui function, Local hardness, Reactivity descriptors, Regioselectivity.

Introduction

1,3-Dipolar cycloaddition is a well known pericyclic reaction that has proven to be one of the most versatile synthetic routes for the preparation of five membered heterocyclic ring systems (Yavari et. al., 2016; Ren et. al., 2019; Li et. al., 2015). Since their discovery in 1960 by Rolf Huisgen (Huisgen, 1963), these cycloaddition reactions have been extensively utilized in organic synthetic chemistry, as they are atom economical and allow researchers to activate conjugated π -systems for the synthesis of stereochemically diverse cyclic products and lately have found applications in diverse fields of material sciences (Zhu et. al., 2008) and drug discovery (Krasinski et. al., 2005) as well. 1,3-Dipolar cycloaddition is a thermally allowed process according to the Woodward-Hoffmann rules (Woodward and Hoffmann, 1970), and involve suprafacial interaction of three p orbit als of 1,3-dipole (possessing 4π electrons) with two p_{a} orbitals of the dipolarophile (possessing 2π electrons) in a concerted man ner. Another important aspect of cycloaddition reactions is their regioselectivity in cases when unsymmetrically substituted dipole and dipolarophiles are involved. Although, transition state theory remains the most widely used approach for the regiochemical analysis and mechanistic studies of these reactions, the localization of transition states may be difficult and time consuming when bulky substituents are present in the substrate. Lately, modern physical organic chemistry has witnessed successful implementation of density functional theory (DFT) (Parr and Yang, 1989) for the study of chemical reactivity. DFT based global reactivity descriptors, such as

electronic chemical potential (µ) (Parret. al., 1978), chemical hardness (η) (Parr and Pearson, 1983) and global electrophilicity index (ω) (Parr et. al., 1999; Chattaraj et. al., 2006) have proven to be quite successful in explaining the reactivity of different chemical species involved in a chemical reaction in context with the Pearson's hard-soft acid-base (HSAB) principle (Pearson, 1963). Similarly, local reactivity descriptors, such as Fukui function (Parr and Yang, 1984), local electrophilicity and local nucleophilicity (Pérez et. al., 2009) developed on the basis of DFT, have been extensively utilized for prediction of site selectivity and regioselectivity (Gupta et. al., 2007). Several reports are available in the literature presenting theoretical investigation of the observed regioselectivity in 1,3-dipolar cycloaddition reactions (McIntosh et. al., 2012; Moeinpour et. al., 2012). Nevertheless, it has been observed in such studies that any single criterion is not sufficiently able to explain the experimental evidences accumulated in cycloaddition processes. Recently, we have investigated 1,3-dipolar cycloaddition reaction of unsymmetrically substituted 3-methylpyridinium ylides 1 with symmetric and unsymmetric acetylenecarboxylates 2 experimentally (Agarwal and Gupta, 2020), when it was observed that unsymmetrical substitution in dipolarophile leads to its regioselective addition at the ylidic moiety, but presence of unsymmetrical substitution in the pyridine ring does not influence much the related regioselectivity aspect (Scheme 1).





Scheme 1

In the present investigation, an attempt has been made to study regioselective aspects of 1,3-dipolar cycloaddition reaction between 3-methylpyridinium ylide and differently substituted acetylenic dipolarophiles using computational tools and compare the results with the experimental observations. For this purpose, Density Functional Theory (DFT) based reactivity descriptors have been calculated and correlated with observed regioselectivity in two Model reactions - **A** and **B**. Model reaction **A** between *N*-(2-ethoxy-2-oxoethyl)-3-methylpyridinium ylide **3** and dimethyl acetylenedicarboxylate (DMAD) **4** (Scheme 2) has been investigated to study the effect of substitution in the pyridine ring of the 1,3-dipole.



Scheme 2

Second Model reaction (Reaction B) i.e., 1,3-dipolar addition of methyl propiolate 5 on *N*-(2-ethoxy-2-oxoethyl)-3-methylpyridinium ylide 3 has been chosen to study the effect of unsymmetrical substitution in the dipolarophile (Scheme 3).





Material and Methods

In the past couple of decades, the DFT based theoretical calculations have proven to be computationally more efficient and promising alternative to traditional *ab initio* methods for the study of structure and reactivity of organic molecules. Thus, in the present investigation, all calculations were performed at B3LYP level of Density Functional Theory (Parr and Yang, 1989) by applying Becke's nonlocal three parameter hybrid functional (Dickson and Becke, 1993) in combination with Lee, Yang and Parr correlation potential (Lee *et. al*, 1998) using Gaussian 09 quantum chemistry package (Frisch *et. al*, 2010). The geometries of the reactants as well as products were optimized at B3LYP/6-31+G* level using standard convergence criteria. Zero point energy (ZPE) correction values for all optimized structures were obtained from frequency calculations at the same level. Transition state (TS) calculations corresponding to different regioisomeric pathways were also performed at the same level. Wiberg Bond indices (Wiberg, 1968) were computed from natural bond orbital (NBO) calculations. Various global and local reactivity descriptors used in the present work are described below.

The global electrophilicity index (ω), was calculated following the expression, $\omega = (\mu^2/2\eta)$, where μ is the electronic chemical potential and η is chemical hardness. Both these descriptors were derived from the energies of HOMO ($E_{\rm H}$) and LUMO ($E_{\rm L}$) of the reactants as: $\mu = (E_{\rm H}+E_{\rm L})/2$ and $\eta = (E_{\rm L}-E_{\rm H})$. The global nucleophilicity (N) was calculated with reference to tetracyanoethylene (TCE) as suggested by Domingo *et. al.* (2008); $N_{\rm (Nu)} = E_{\rm HOMO(Nu)} - E_{\rm HOMO(TCE)}$. Local electrophilicity ($\omega_{\rm k}$) and nucleophilicity ($N_{\rm k}$) were evaluated by following the expressions: $\omega_{\rm k} = \omega f_{\rm k}^+$ and $N_{\rm k} = N f_{\rm k}^-$ where $f_{\rm k}^+$ and $f_{\rm k}^-$ are the Fukui functions for a nucleophilic and electrophilic attack, respectively and calculated as follows-

$$f_k^+ = [\rho_k(N+1) - \rho_k(N)]$$
$$f_k^- = [\rho_k(N) - \rho_k(N-1)]$$

Here, the $\rho_k(N)$, $\rho_k(N+1)$, $\rho_k(N-1)$ represent the condensed electronic population on the atom "k" calculated for the neutral, anionic and cationic species, respectively.

Results and Discussion

As mentioned above, [3+2]cycloaddition reaction of unsymmetrically substituted pyridinium ylide 3 with symmetrical dipolarophile, dimethyl acetylendicarboxylate(DMAD) 4 may take place at two regioisomeric positions in the dipole, thereby leading to the formation of two possible cycloadducts CDI & CDII(Scheme 2). Similarly, the reaction of 3 with asymmetrically substituted dipolarophile 5 (i.e. methyl propiolate) may further take place via two different orientations of dipolarophile approaching the ylidic moiety leading to the formation of two additional cycloadducts; i.e. a total four isomeric cycloadducts CDI-CDIV (Scheme 3). The analysis of regioisomeric product distribution in these two reactions has been done on the basis of activation energies, geometries, bond orders and by considering the DFT reactivity descriptors in the following manner.

Activation energies, geometries and bond ordersTran-

sition states corresponding to each reaction pathway in both model reactions - **A** and **B** could be located (Fig. 1) and verified by the presence of one and only one imaginary frequency (NImag = 1) corresponding to cycload-dition. The total energies of the reactants, cycloadducts and the corresponding transition states alongwith the activation energies (ΔE_{a}) and the energies of reaction (ΔE_{rxn}) calculated at B3LYP/6-311+G**//B3LYP/6-31+G* level compiled in Table 1 reveals that the total energy of the cycloadduct in all cases, is less than the total energies of the corresponding reactants (dipole and dipolarophile)

making 1,3-dipolar cycloaddition exothermic. For model reaction A, the calculated activation barrier of two transition states TSIIA (3.45 Kcal mol⁻¹) and TSIA (3.47 Kcal mol⁻¹) is almost similar, indicating to the equal probability and formation of both cycloadducts, CDIIA and **CDIA** in conformity with the experimental observation (Agarwal and Gupta, 2020). However, in case of model reaction **B**, the activation energy barrier for **TSIIIB** and TSIVB (10.19 and 9.48 Kcal mol⁻¹, respectively) is quite high as compared to that for TSIB and TSIIB (2.48 and 2.50 Kcal mol⁻¹, respectively) indicating the preferential formation of cycloadducts CDIB and CDIIB over CDIIIB and CDIVB. Similar values of activation barrier for **TSIB** and **TSIIB** again imply that the substitution at 3-position of pyridine ring does not affect the regiselectivity of cycloaddition.

Table 1. Total energies (a.u.) and relative energies (Kcal mol⁻¹) calculated for reactants, cycloadducts and transition states of model reactions A & B

Total Energy	a	Relative Energy
3	-594.010000	
4	-533.123435	27
5	-305.226255	- T .1
TSIA	-1127.127892	3.47 ^b
TSIIA	-1127.127933	3.45 ^b
TSIB	-899.232305	2.48 ^b
TSIIB	-899.232270	2.50 ^b
TSIIIB	-899.220008	10.19 ^b
TSIVB	-899.221148	9.48 ^b
CDIA	-1127.153110	-12.35 ^c
CDIIA	-1127.149923	-10.35 ^c
CDIB	-899.251008	-9.26 ^c
CDIIB	-899.253120	-10.58 ^c
CDIIIB	-899.256730	-12.85 ^c
CDIVB	-899.258489	-13.95°

^aSum of calculated Energy at B3LYP/6-311+G** level & ZPE at B3LYP/6-31+G* level; ^bActivation Energy ΔE_a ; ^cReaction Energy ΔE_{rxm}

Values of the bond lengths and bond orders (in parentheses) of the two newly forming bonds in the respective transition states of two Model reactions shown in Fig.1, indicate that the formation of transition state in all cases involve an asynchronous process. The degree of asynchronicity (Δ d) calculated from the difference of C-C bond lengths of the two newly forming bonds for IISU different transition states of the two model reactions **A** and **B** is given in Table 2. From the comparison of the Δd values, transition state of 1,3-dipolar cycloaddition reaction of ylide3 with methyl propiolate 5 appears to be more asynchronous in comparison to its reaction with DMAD 4 due to the unsymmetrical presence of EWG in the dipolarophile. The concept of bond order (Wiberg bond indices) can be utilized to obtain a deeper analysis of the extent of bond formation or bond breaking along a reaction pathway. For the two regioisomeric pathways in reaction **A**, bond order of the forming C3-C4 bond is considerably higher than C1-C5 bond (Fig 1), thereby, indicating that the reaction is initiated by donation of ylidic charge from C3 of dipole to the C4 in dipolarophile, leading to more advanced bond formation processes

at C3–C4 as compared to C1–C5. For model reaction **B**, Wiberg bond indices of the two newly forming bonds in transition states **TSIB** and **TSIIB**, reveal that the transition state is asynchronous with advanced C3–C4 bond formation at the unsubstituted end of the dipolarophile. This may be attributed to the initiation of the reaction by donation of electronic charge from ylidic carbon of the dipole to acetylenic end of methyl propiolate which is having net positive charge due to –M effect of ester group. Optimized transition states **TSIIIB** and **TSIVB** on *path c* and *path d* (Scheme 2), having higher activation barriers show smaller extent of asynchronicity and probably in the absence of the driving force the formation of corresponding cycloadducts is not observed experimentally (Agarwal and Gupta, 2020).



Fig. 1. Bond length and bond orders of newly forming bonds in B3LYP/6-31+G*level optimized geometries of tran - sition states



Table 2. Degree of asynchronicity (Δd) in TS of model reactions A and B

Entry	B1ª	B2 ^b	Δd^{c}
TSIA	2.08	2.71	0.63
TSIIA	2.10	2.73	0.63
TSIB	2.05	2.86	0.81
TSIIB	2.07	2.87	0.80
TSIIIB	2.39	2.12	0.27
TSIVB	2.42	2.12	0.30

^aB1 = C3-C4 bond length (Å)

^bB2 = C1-C5 bond length (Å)

 $^{c}\Delta d$ = difference between B1 & B2

DFT based reactivity indices Energies of HOMO and LUMO of pyridinium ylide **3**, DMAD **4** and methyl propiolate **5** computed at B3LYP/6-31+G* DFT level and global descriptors calculated from these values (Table 3) reveal that the energy gap Δ E1 (3.34eV, 3.56eV) corresponding to the interaction between HOMO_(dipole) **3** and LUMO_(dipolarophile) (**4**/**5**) is lower than Δ E2 (6.06eV, 6.09eV) for interaction of HOMO_(dipolarophile) and LUMO_(dipole) (Fig. 2). Therefore, it is justified that the reactions under investigation fall under Sustmann type I reaction (McGarrity, 1979) and according to the Normal Electron Demand (NED) the flow of electrons in transition state would be from dipole (**3**) to dipolarophile (**4** or **5**).



Fig. 2. Visualization of HOMO and LUMO of reactants for model reactions A & B

Table 3. Energies of frontier molecular orbitals and calculated global properties of pyridinium methylide 3, DMAD 4 and methyl propiolate 5

_	Еномо* (а.ц.)	ELUMO* (a.u.)	ΔE1 ^h (eV)	ΔE2° (eV)	μ	η	ω* (eV)	N* (eV)
3	-0.195	-0.072			-0.133	0.123	1.956	3.815
4	-0.305	-0.072	3.34	6.06	-0.188	0.233	2.063	0.820
5	-0.296	-0.064	3.56	6.09	-0.180	0.232	1.900	1.065

 $\label{eq:acomputed at B3LYP/6-31+G* DFT level} \ ^{b}\Delta E1 = HOMO_{dipole(3)} - LUMO_{dipolarophile(4/5)} \ ^{c}\Delta E2 = HOMO_{dipolarophile(4/5)} - LUMO_{dipolarophile(4/5)} \ ^{c}\Delta E1 = HOMO_{dipolarophile(4/5)} \ ^{c}\Delta E2 = HOMO_{dipolarophile(4/5)}$

As the electronic chemical potential (μ) describes the charge transfer (CT) in a species occurring in its ground state, in present case, it depicts the direction of the electronic flux during the cycloaddition. In accordance with the NED reaction, larger electronic chemical potential of the ylide 3 as compared to that of dipolarophile (4 / 5) (Table 3) further supports the charge transfer from dipole

to the dipolarophile. On the other hand, the resistance to this electronic charge flow during the cycloaddition may be estimated by the chemical hardness. Smaller value of global hardness for N-ylide (0.123) as compared to the dipolarophile (0.233, 0.232 for 4 & 5, respectively) indicate that the charge transfer from N-ylide is easier. As the reaction under investigation involves regioselective preferences, the local philicity indices (ω_{ν} , N_{ν}) seem to be a reliable tool for the prediction of most favored interaction. Therefore, taking into account the flow of electrons from the dipole to dipolarophiles in the transition state, the nu cleophilic Fukui function (f_k) for the dipolar species and electrophilic Fukui function (f_k^+) for the dipolarophiles have been calculated using Mulliken and natural population analysis. From the calculated Fukui function values, local nucleophilicity index (N_{μ}) for reactive sites of ylide (3) and local electrophilicity index (ω_{ν}) for reactive sites of dipolarophile (4/5) have been computed and summarized in Table 4. The local nucleophilicity (N_{μ}) and local electrophilicity (ω_{i}) indices so obtained also support the observed regioselectivity in the 1,3-dipolar cycloaddition reaction under investigation as shown in Fig. 3.

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Table 4. Condensed Fukui functions $f(k \otimes f_k)$, Local electrophilicity (ω_k) and nucleophilicity (N_k) indices calculated for reactive sites of ylide (3) and dipolaro phile (4,5)

	site	f_k	f_k^+	$\omega_k (eV)$	N _k (eV)
3	C-1'	0.07206		-	0.27
	C-1	0.07663		-	0.29
	C-3	0.33287		-	1.26
4	C-4	144 144	0.13605	0.28	120
	C-5		0.13569	0.28	-
5	C-4		0.39066	• .74	177
	C-5		0.05182	0.09	240

According to the HSAB principle, more electrophilic site of one reactant is directed to the more nucleophilic site of other reactant. In pyridinium ylide **3**, ylidic carbon C3 has higher local nucleophilicity index than either of the C1 or C1', therefore C3 is the preferred site of attack for the dipolarophile. At the same time, nucleophilicity index of both C1 and C1' are comparable and do not affect the regioselective addition at either of the pyridinic carbons. As C3 is the preferred site for electrophilic attack, in the model reaction **B**, the unsubstituted end of **5** interacts with it by virtue of having much larger local electrophilicity index (0.74) as compared to the substituted end (0.09) and substituted end may interact with either C1 or C1' leading to the formation of two regioisomers, **CDIB** and **CDIIB**.

Conclusion

Experimentally observed regioselectivity in 1,3-dipolar cycloaddition reaction of 3-methylpyridinium ylide with acetylenic dipolarophiles has been rationalized with the help of DFT based global and local reactivity descriptors. FMO approach confirmed the NED character of the reaction and the concerted mechanism involving an asynchronous transition state. In case of the reaction with unsymmetrical dipolarophile having EWG at one end, formation of the preferred cycloadduct has been rationalized by the application of Pearson's HSAB principle according to the attack of more nucleophilic site in one component to the more electrophilic site in the second component.

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