Research Article

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Quantum chemistry study on the promoted reactivity of substituted cyclooctynes in bioorthogonal cycloaddition reactions

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Abstract: In the present research, we focus on the energetics and electronic aspects of enhanced reactivity in the regioselective bioorthogonal 1,3-dipolar cycloaddition reaction of various substituted cyclooctynes with methyl azide, applying quantum chemistry approaches. In this respect, we assessed the structural and energetic properties of regioisomeric products and their corresponded transition states and calculated the reaction electronic energy changes and energy barriers through the cycloaddition pathways. The obtained results revealed that the trifluoromethyl substitution and fluorination of cyclooctynes lead to improved reactivity, in conjunction with increased exothermicity and decreased activation energy values. On the other hand, quantum theory of atoms in molecules computations were performed on some key bond and ring critical points that demonstrated the stabilizing topological properties of electron density and its derivatives upon trifluoromethyl substitution and fluorination of propargylic carbon of cyclooctynes which can be regarded as the essential origin of enhanced reactivity.

Keywords: strain-promoted cycloadditions, enhanced reactivity, bioorthogonal reactions, density functional theory, quantum theory of atoms in molecules

1 Introduction

Cyclooctyne-based compounds have recently attracted much attention in the bioorthogonal chemistry field as

potential bioorthogonal reagents [1–3]. In recent decades, bioorthogonal reactions have been broadly applied in the metabolism of living systems without mixing with the main biological processes. Furthermore, bioorthogonal reactions are widely used in selective and rapid labeling of biomolecules for live-cell imaging, with no disruption of biological processes [4–10].

In this route, the bioorthogonal cycloaddition reaction of strained alkynes with common 1,3 dipoles such as azides has been investigated from the experimental and computational viewpoints [11–16].

Copper (Cu)-catalyzed azide–alkyne cycloaddition reactions introduced by Sharpless et al. [17] and Meldal et al. [18] independently lead to the regioselective and high-yield production 1,2,3-triazoles, with wide applications in organic synthesis, biochemical and drug discovery, chemical biology, and materials chemistry. However, due to the toxicity of copper that confines the application of Cu-catalyzed click reactions in biological scopes [19,20], the strain-promoted cycloaddition between cyclooctynes and azides were considered as a proper alternative process.

In this direction, many endeavors were allocated to interpret these cycloadditions-enhanced reactivities and selectivities quantitatively. From the biological point of view, it was shown that copper-free click cycloaddition of strained cycloalkynes with azides are fast enough for *in vivo* bioorthogonal labeling of biomolecules at physiological temperatures without the toxic side effects of copper [6,21–24]. Therefore, the researchers have concentrated on synthesizing highly strained cyclic alkynes, such as bicycle nonyne, azadibenzocyclooctyne, 4-dibenzocyclooctynol, difluorobenzocyclooctyne, and thiacycloheptyne [25–28].

On the other hand, to quantify the improved orthogonal reactivity of cycloalkynes, several computational investigations were performed on a series of cycloaddition reactions between 1,3-dipoles and cyclic alkynes as dipolarophiles using the distortion/interaction (D/I) model [29,30]. In this line, the enhancement of reactivity in cycloalkynes was modeled compared to unstrained alkynes, and it was shown that cycloalkynes require

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less distortion barrier to gain the transition-state structure, leading to both reducing the distortion energy and improving interaction energy.

In order to provide an accurate understanding of the effects of strain and electronics in reactivity, a series of cyclooctynes, benzocyclooctadienyne, dibenzo, and aza-analogues have been assessed via comparison with the calculated activation barriers [31], obtained by relative rate constants and D/I analysis using density functional theory (DFT) [32] methods.

In recent years, we have computationally focused on the energetic and electronic origins of regioselectivity in palladium- and ruthenium-catalyzed coupling reactions and azide-alkyne cycloadditions along the mechanical pathway [33,34] via DFT and quantum theory of atoms in molecules (QTAIM) [32,35,36] computations. Furthermore, we have investigated the stereoselective behavior of metal-free click synthesis of 1*H*-tetrazole-5-yl-acrylonitriles [37] from the mechanical and electronic viewpoints. With this in mind, we have presented a review article on the combined computational and experimental features of uncatalyzed Huisgen azide-alkyne cycloaddition, leading to the formation of 1,4 and 1,5-disubstituted 1,2,3-triazoles mixture [38,39].

In this context, in this research, we have focused on the probing of electronic aspects in cycloaddition of methyl azide with cyclooctyne and a range of substituted cyclooctynes at propargylic position to identify the stereoelectronic origin of strain-promoted rate enhancement in this type of 1,3-dipolar cycloadditions. To this goal, we comparatively assessed the structure and energetics of transition state barriers for the aforementioned concerted 1,3-dipolar cycloadditions and then analyzed the topological properties of electron density as the quantum mechanical observable quantity via QTAIM approach.

More clearly speaking, we concentrated on the topological analysis of electron density functions and their first (gradient) and second derivatives (Hessian), which revealed the zones of charge concentration and charge depletion for the newly formed bond critical points (BCPs) and ring critical points (RCPs) along the cycloaddition reaction path. In this line, we derived QTAIM quantified chemical information on the nature of strains and interactions in selectivity and reactivity of these types of azide-cyclooctyne cycloadditions.

2 Computational details

M08-HX functional methodology [40] in conjunction with 6-311+G** basis sets have been used to optimize the geometry of all reactants, products, and their corresponded

Figure 1: Schematic representation of cycloaddition reaction of various substituted cyclooctynes with methyl azide, leading to produce two regioisomeric 1,2,3 triazoles.

transition states, all in the C1 symmetry point group. Furthermore, harmonic frequency calculations were performed for all stationary points to demonstrate the local minima and saddle points. All DFT computations have been performed using GAMESS suite of programs [41].

On the other hand, the obtained M08-HX/6-311+G** wave functions for all optimized structures were used as input by AIM2000 [42] and were analyzed by QTAIM approach. In this route, electron density (ρ_b), its Laplacian ($\nabla^2\rho_b$), the electronic kinetic energy density ($G(r)$), the electronic potential energy density ($V(r)$), and the total electronic energy density ($H(r)$), were calculated on the key BCPs and RCPs to extract the relevant chemical features for the enhanced reactivity of azide-cyclooctyne (and their substituted fluoride analogues) cycloadditions.

Figure 2: Cycloaddition reaction pathway of methyl azide with cyclooctyne, in association with the optimized structure of triazole product and the corresponded transition state. We have reported the M08-HX/6-311+G** calculated values of activation energies and reaction electronic energies in the figure (note that the units are in kcal/mol).

Figure 3: Cycloaddition reaction pathway of methyl azide with propargylic substituted cyclooctyne by methyl, in association with the optimized structure of regioisomeric triazole products and the corresponded transition states. We have reported the M08-HX/6-311+G** calculated values of activation energies and reaction electronic energies in the figure (note that the units are in kcal/mol).

3 Results and discussion

3.1 Enhanced reactivity of fluorinated cyclooctynes in azide–cyclooctyne cycloaddition reaction: energetic aspect

As we discussed earlier, the main objective of this research is to investigate the stereoelectronic role of propargylic

substitution of cyclooctyne by methyl, trifluoromethyl, and fluoride on the enhancement of reactivity in strain-promoted azide–cyclooctyne cycloaddition reactions (as illustrated in Figure 1)

In this respect, we primarily obtained the optimized geometry of all reactants, regioisomeric 1,4 and 1,5-disubstituted triazole products (denoted as isomer1 and isomer2, respectively) and their corresponding regioisomeric transition states (denoted as TS1 and TS2, respectively), followed

Figure 4: Cycloaddition reaction pathway of methyl azide with propargylic two-substituted cyclooctyne by trifluoromethyl, in association with the optimized structure of regioisomeric triazole products and the corresponded transition states. We have reported the M08-HX/6-311+G** calculated values of activation energies and reaction electronic energies in the figure (note that the units are in kcal/mol).

Figure 5: Cycloaddition reaction pathway of methyl azide with propargylic mono-substituted cyclooctyne by fluoride, in association with the optimized structure of regioisomeric triazole products and the corresponded transition states. We have reported the M08-HX/6-311+G** calculated values of activation energies and reaction electronic energies in the figure (note that the units are in kcal/mol).

by determination of activation energy barriers and the reaction electronic energies. In Figures 2–6, we have displayed reaction paths of cyclooctyne, methyl-substituted cyclooctyne, trifluoromethyl-substituted cyclooctyne, and mono and difluorinated cyclooctyne with methyl azide, which lead to producing regioselective 1,4 and 1,5-disubstituted 1,2,3-triazoles together with M08-HX/6-311+G** optimized geometry of all species.

The M08-HX/6-311+G** calculated values of activation energies and the reaction electronic energies for 1,3-dipolar cycloaddition of cyclooctyne, methyl-substituted cyclooctyne, and mono and di-fluorinated cyclooctynes with methyl azide are reported in Figures 2–6.

The following three facts can be extracted from the comparative analysis of the reported result in Figures 2–6: (1) In all mentioned 1,3-dipolar cycloaddition reactions, the

Figure 6: Cycloaddition reaction pathway of methyl azide with propargylic two-substituted cyclooctyne by fluoride, in association with the optimized structure of regioisomeric triazole products and the corresponded transition states. We have reported the M08-HX/6-311+G** calculated values of activation energies and reaction electronic energies in the figure (note that the units are in kcal/mol).

Figure 7: Complete MGs of product-HH and TS-HH, obtained by QTAIM analysis of M08-HX/6-311+G** electron density. BCPs: blue circles; RCPs: red circles; and Bond Paths: black lines.

Figure 8: Complete MGs of isomer1-HMe, isomer2-HMe, TS1-HMe, and TS2-HMe, obtained by QTAIM analysis of M08-HX/6-311+G** electron density.

Figure 9: Complete MGs of isomer1-HCF₃, isomer2-HCF₃, TS1-HCF₃, and TS2-HCF₃, obtained by QTAIM analysis of M08-HX/6-311+G** electron density.

synthesis of both regioisomers is exothermic with the small difference between the calculated reaction electronic energy values (about 1–2 kcal/mol) and reveals the requisiteness for considering the energetics of transition states in two regioselective mechanistic reaction pathways. (2) Transition state barrier for the production of isomer2 is about 3 kcal/mol lower than the synthesis of isomer1, which may be rationally regarded as the energetic symptom for the regioselective behavior. (3) Fluorination adjacent to the triple bond of cyclooctyne increases the exothermicity and decreases the activation energy values which is in agreement with the reported rate enhancement computations and elucidations [13,14].

On the other hand, methyl and trifluoromethyl substitution at propargylic carbon of cyclooctyne show decrease in exothermicity, about 3 and 6 kcal/mol, respectively. While methyl substitution led to a rise in the barrier energy values, in an opposite trend, trifluoromethyl substitution

reduced the activation energy barriers. Clearly speaking, changing from non-substituted cyclooctyne to trifluoromethyl-substituted and monofluorinated cyclooctynes decreases the transition state barrier by about 2 kcal/mol, and in the case of difluorinated cyclooctyne, this substitution effect on reducing energy barriers is more intense by about 5 kcal/mol. Meanwhile, methyl substitution has no significant effect on the rate enhancement of these cycloaddition reactions. It should be noted that the regioselective behavior of the synthesis has been preserved via substituting cyclooctyne at a tertiary carbon α position.

3.2 QTAIM interpretations for the enhanced reactivity

In this section, we concentrated on QTAIM topological analysis of electron density and its derivatives [38,39]

Figure 10: Complete MGs of isomer1-HF, isomer2-HF, TS1-HF, and TS2-HF, obtained by QTAIM analysis of M08-HX/6-311+G** electron density.

via the quantum mechanical structures, which is the collection of BCPs and RCPs, respectively, and their associated bond paths, entitled as molecular graphs (MGs). In other words, the topological properties of electron density, ρ_b , along with its derivatives at critical points (CPs), are defined as useful tool to ascertain the concept of chemical bonding and the nature of interatomic interactions in molecular systems. Based on QTAIM formalism, chemical bonding is characterized by duo-gradient paths of charge density function that emanate from a BCP (where the gradient of charge density vanishes mathematically and the Hessian matrix of charge density has two negative and one positive eigenvalues) and end on the corresponding atomic nuclei. To present the more concise interpretation of the nature of bonding and interactions, Laplacian of electron density, $\nabla^2\rho_b$, is employed as an important indicator for the concentration or depletion of charge towards the interaction line. $\nabla^2\rho_b < 0$ leads to

the contraction of electron density perpendicular to the interaction line and lowers the potential energy, thereby creating attractive force and bond shared interaction. $\nabla^2\rho_b > 0$ implies that the interaction is dominated by contraction of electron density towards each nucleus with the net repulsion forces on the nuclei. Moreover, the characteristics of chemical interactions can be derived from the QTAIM energetic topological parameters, $G(r)$, $V(r)$, and $H(r)$, which are defined as the kinetic energy, the potential energy, and the total electron energy densities, respectively. More clearly, the balance between the kinetic electron energy density $G(r)$ and the potential electron energy density $V(r)$ is employed to classify and quantify the bonding interactions [43].

In this context, we investigated the topological analysis of electron density at some key BCPs and RCPs in regioisomeric products and their corresponded transition states via the cycloaddition of cyclooctyne, methyl- and

Figure 11: Complete MGs of isomer1-FF, isomer2-FF, TS1-FF, and TS2-FF, obtained by QTAIM analysis of M08-HX/6-311+G** electron density.

trifluoromethyl-substituted cyclooctynes, and mono and difluorinated cyclooctynes with methyl azide. In particular, we made a topological comparison of electron density and its derivatives at BCPs and RCPs to discern the electronic aspects of bonding and interactions in the enhancement of reactivity.

We have depicted the complete QTAIM molecular graphs of isomeric products and their corresponded transition states in Figures 7–11, for cycloaddition reaction of methyl azide with cyclooctyne, methyl- and trifluoromethyl-substituted cyclooctynes, and mono and difluorinated cyclooctynes, respectively. The QTAIM molecular graphs have been calculated at M08-HX/6-311+G** level of theory, which consist of all CPs of electron density and their associated bond paths.

In Tables 1–5, we have reported the calculated values of electron density, its Laplacian, kinetic and potential energy densities, and also the total electronic energy density at some key BCPs and RCPs of isomer1 and isomer2 products and their corresponded transition states for

cycloaddition reaction of methyl azide with cyclooctyne, methyl- and trifluoromethyl-substituted cyclooctynes, and mono and difluorinated cyclooctynes, respectively.

The comparative assessment on the calculated QTAIM results of BCPs comprehensively ascertains the following facts: (1) In all products and their corresponded transition states, the negative values of $\nabla^2\rho_b$ and also $H(r)$ at BCPs confirm the presence of covalent bonding and so charge concentration in the bonded region. (2) H–H intramolecular interactions with small positive (near zero) values of $\nabla^2\rho_b$ and $H(r)$ on the corresponded BCPs were obtained for product-HH, isomer1-HMe, isomer2-HMe, isomer2-HCF3, isomer1-HF, isomer2-HF, and isomer2-FF, while for isomer1-FF, isomer1-HCF3, isomer2-HCF3, and TS2-HCF3, H–F intramolecular BCPs were obtained. It is important to note that based on QTAIM calculations for transition states, there are no intramolecular BCPs in topological MGs, except for TS1-HCF3 and TS2-HCF3 species. In the case of TS1-HCF3 and TS2-HCF3, QTAIM MGs exhibit N–F intramolecular BCPs. (3) ρ_b calculated value of C=C bond

Table 1: Mathematical properties of some selected BCPs and RCPs of product-HH and TS-HH

	ρ_b	$\nabla^2\rho_b$	G_b	V_b	H_b
Product-HH					
BCPs					
N(2)–C(5)	0.280	–0.578	0.231	–0.607	–0.376
N(3)–C(4)	0.297	–0.799	0.174	–0.548	–0.374
C(4)–C(5)	0.308	–0.810	0.114	–0.431	–0.317
H(8)–H(21)	0.017	0.057	0.012	–0.009	0.002
H(17)–H(20)	0.019	0.068	0.015	–0.012	0.002
RCPs					
RCP1	0.053	0.492	0.097	–0.087	0.010
RCP2	0.011	0.047	0.009	–0.008	0.001
RCP3	0.011	0.053	0.011	–0.008	0.003
RCP4	0.010	0.049	0.009	–0.008	0.001
RCP5	0.014	0.068	0.014	–0.011	0.003
TS-HH					
BCPs					
N(9)–C(7)	0.049	0.090	0.028	–0.033	–0.005
N(8)–C(1)	0.060	0.088	0.031	–0.04	–0.009
C(1)–C(7)	0.399	–1.236	0.238	–0.806	–0.557
RCPs					
RCP1	0.023	0.149	0.031	–0.025	0.006
RCP2	0.009	0.038	0.008	–0.006	0.002

Note: These properties are obtained through QTAIM analysis at M08-HX/6-311+G** level of theory. The atoms are numbered according to Figure 7.

of eight-membered carbon ring in product-HH is smaller than the corresponded ρ_b value in TS-HH (0.308 in product-HH compared with 0.399 in the corresponding transition state, TS-HH) that demonstrates the increased elongation of triple C–C bond in cyclooctyne to react with azide reactant to form product-HH. It should be noticed that this comparative behavior was obtained for the calculated value of electron density on C=C bond in all regioisomeric products (isomer1-HMe, isomer2-HMe, isomer1-HCF3, isomer2-HCF3, isomer1-HF, isomer2-HF, isomer1-FF, and isomer2-FF) and their corresponded transition states. (4) In order to determine how the substitution of methyl, trifluoromethyl, and fluorine on propargylic carbon affects the reactivity of cyclooctyne with methyl azide, we comparatively assessed the electron density and its derivatives on C–C and C–N BCPs of triazole ring in all transition states. The QTAIM calculated results demonstrate no considerable difference between the electron density and its derivatives on C–C BCPs in triazole ring of all transition states, while ρ_b calculated values of triazolic C–N BCPs in TS-HCF3, TS-HF, and TS-FF MGs are relatively bigger than those calculated for TS-HH and TS-HMe (0.066 and 0.053 in TS1-HCF3 and TS2-HCF3, 0.060 and 0.051 in TS1-HF and TS2-HF, 0.064 and 0.049 in TS1-FF and TS2-FF,

Table 2: Mathematical properties of some selected BCPs and RCPs of isomer1-HMe, isomer2-HMe, TS1-HMe, and TS2-HMe

	ρ_b	$\nabla^2\rho_b$	G_b	V_b	H_b
Isomer1-HMe					
BCPs					
N(24)–C(23)	0.278	–0.566	0.231	–0.603	–0.372
N(30)–C(22)	0.297	–0.797	0.175	–0.549	–0.374
C(22)–C(23)	0.306	–0.801	0.114	–0.428	–0.314
H(9)–H(17)	0.009	0.030	0.006	–0.005	0.001
RCPs					
RCP1	0.053	0.428	0.097	–0.087	0.010
RCP2	0.008	0.034	0.007	–0.005	0.020
RCP3	0.008	0.034	0.007	–0.006	0.001
Isomer2-HMe					
BCPs					
N(25)–C(2)	0.277	–0.567	0.227	–0.597	–0.370
N(26)–C(1)	0.297	–0.798	0.172	–0.543	–0.371
N(25)–C(27)	0.246	–0.573	0.154	–0.451	–0.297
C(1)–C(2)	0.307	–0.805	0.115	–0.431	–0.316
H(9)–H(28)	0.005	0.017	0.004	–0.003	0.001
H(11)–H(21)	0.018	0.057	0.012	–0.010	0.002
RCPs					
RCP1	0.053	0.428	0.097	–0.087	0.010
RCP2	0.008	0.031	0.006	–0.005	0.001
RCP3	0.008	0.031	0.007	–0.005	0.002
RCP4	0.005	0.019	0.004	–0.003	0.001
TS1-HMe					
BCPs					
N(24)–C(1)	0.044	0.088	0.026	–0.029	–0.003
N(26)–C(2)	0.058	0.089	0.031	–0.039	–0.008
C(1)–C(2)	0.399	–1.239	0.249	–0.808	–0.559
RCPs					
RCP1	0.022	0.141	0.029	–0.023	0.006
RCP2	0.008	0.034	0.007	–0.005	0.002
TS2-HMe					
BCPs					
N(10)–C(1)	0.065	0.089	0.033	–0.044	–0.011
N(9)–C(2)	0.046	0.088	0.026	–0.030	–0.004
C(1)–C(2)	0.398	–1.238	0.246	–0.801	–0.555
RCPs					
RCP1	0.022	0.148	0.031	–0.025	0.006
RCP2	0.009	0.038	0.008	–0.006	0.002

Note: These properties are obtained through QTAIM analysis at M08-HX/6-311+G** level of theory. The atoms are numbered according to Figure 8.

compared with 0.049 in TS-HH, 0.044 and 0.065 in TS1-HMe and TS2-HMe, respectively) that can be attributed to the enhancement of reactivity for trifluoromethyl-substituted fluorinated cyclooctynes in cycloaddition reaction with methyl azide.

On the other hand, the more stringent analysis of RCPs on QTAIM MGs of regioisomeric products and their corresponded transition states (Figures 7–11) demonstrates the increased electronic stability of products in comparison

Table 3: Mathematical properties of some selected BCPs and RCPs of isomer1-HCF₃, isomer2-HCF₃, TS1-HCF₃, and TS2-HCF₃

	ρ_b	$\nabla^2\rho_b$	G_b	V_b	H_b
Isomer1-HCF₃					
BCP_s					
N(14)–C(2)	0.296	−0.791	0.166	−0.53	−0.364
N(13)–C(1)	0.279	−0.594	0.225	−0.599	−0.374
C(1)–C(2)	0.305	−0.797	0.114	−0.427	−0.313
H(26)–F(10)	0.031	0.143	0.033	−0.030	0.003
H(30)–F(11)	0.009	0.039	0.008	−0.007	0.001
H(30)–F(10)	0.009	0.039	0.009	−0.008	0.001
RCP_s					
RCP1	0.053	0.427	0.097	−0.087	0.010
RCP2	0.007	0.031	0.006	−0.005	0.001
RCP3	0.007	0.028	0.006	−0.005	0.001
RCP4	0.008	0.035	0.008	−0.006	0.002
RCP5	0.009	0.044	0.009	−0.008	0.001
RCP6	0.009	0.042	0.009	−0.007	0.002
Isomer2-HCF₃					
BCP_s					
N(14)–C(1)	0.279	−0.609	0.215	−0.582	−0.367
N(16)–C(2)	0.299	−0.815	0.174	−0.552	−0.378
C(1)–C(2)	0.304	−0.788	0.113	−0.423	−0.310
H(30)–F(11)	0.032	−0.147	0.034	−0.031	0.003
H(7)–H(22)	0.020	0.068	0.015	−0.013	0.002
RCP_s					
RCP1	0.053	0.428	0.097	−0.087	0.010
RCP2	0.009	0.050	0.010	−0.008	0.002
RCP3	0.011	0.054	0.011	−0.009	0.002
RCP4	0.008	0.041	0.008	−0.006	0.002
TS1-HCF₃					
BCP_s					
N(14)–C(1)	0.066	0.092	0.036	−0.049	−0.013
N(13)–C(2)	0.047	0.081	0.024	−0.028	−0.004
C(1)–C(2)	0.394	−1.206	0.244	−0.791	−0.547
N(13)–F(12)	0.010	0.045	0.009	−0.008	0.001
RCP_s					
RCP1	0.023	0.154	0.032	−0.026	0.006
RCP2	0.008	0.033	0.007	−0.005	0.002
RCP3	0.009	0.039	0.008	−0.007	0.001
TS2-HCF₃					
BCP_s					
N(10)–C(1)	0.053	0.089	0.029	−0.036	−0.007
N(9)–C(2)	0.062	0.088	0.032	−0.042	−0.010
C(1)–C(2)	0.399	−1.239	0.244	−0.799	−0.555
N(10)–F(19)	0.008	0.033	0.007	−0.006	0.001
F(19)–H(13)	0.008	0.037	0.008	−0.006	0.002
RCP_s					
RCP1	0.024	0.159	0.033	−0.027	0.006
RCP2	0.009	0.039	0.008	−0.006	0.002
RCP3	0.007	0.037	0.007	−0.006	0.001
RCP4	0.008	0.033	0.007	−0.006	0.001

Note: The atoms are numbered according to Figure 9.

with transition states from electron density topological viewpoints. Clearly speaking, due to the presence of H–H,

Table 4: Mathematical properties of some selected BCPs and RCPs of isomer1-HF, isomer2-HF, TS1-HF, and TS2-HF

	ρ_b	$\nabla^2\rho_b$	G_b	V_b	H_b
Isomer1-HF					
BCP_s					
N(9)–C(2)	0.299	−0.805	0.170	−0.542	−0.372
N(10)–C(1)	0.280	−0.588	0.227	−0.602	−0.375
C(2)–C(1)	0.305	−0.798	0.114	−0.428	−0.314
H(12)–H(21)	0.007	0.025	0.005	−0.004	0.0010
RCP_s					
RCP1	0.053	0.429	0.097	−0.087	0.010
RCP2	0.007	0.030	0.006	−0.005	0.001
RCP3	0.006	0.028	0.006	−0.005	0.001
RCP4	0.007	0.027	0.006	−0.004	0.002
Isomer2-HF					
BCP_s					
N(22)–C(2)	0.280	−0.581	0.230	−0.605	−0.375
N(21)–C(1)	0.300	−0.816	0.173	−0.551	−0.378
C(2)–C(1)	0.306	−0.801	0.114	−0.428	−0.314
H(12)–H(19)	0.019	−0.064	0.014	−0.012	0.0020
RCP_s					
RCP1	0.054	0.430	0.097	−0.087	0.010
RCP2	0.010	0.050	0.010	−0.008	0.002
RCP3	0.011	0.053	0.011	−0.009	0.002
RCP4	0.009	0.043	0.009	−0.007	0.002
TS1-HF					
BCP_s					
N(9)–C(2)	0.051	0.086	0.026	−0.032	−0.005
N(10)–C(1)	0.061	0.093	0.034	−0.044	−0.010
C(2)–C(1)	0.397	−1.218	0.247	−0.799	−0.552
RCP_s					
RCP1	0.023	0.156	0.033	−0.023	0.007
RCP2	0.009	0.035	0.007	−0.006	0.001
TS2-HF					
BCP_s					
N(21)–C(2)	0.060	0.090	0.032	−0.042	−0.010
N(22)–C(1)	0.054	0.085	0.028	−0.034	−0.006
C(2)–C(1)	0.398	−1.231	0.243	−0.793	−0.550
H(25)–F(20)	0.010	0.042	0.009	−0.008	0.001
RCP_s					
RCP1	0.024	0.161	0.034	−0.027	0.007
RCP2	0.009	0.036	0.007	−0.006	0.001
RCP3	0.008	0.039	0.008	−0.007	0.001

Note: The atoms are numbered according to Figure 10.

H–F, and F–C intramolecular semi-covalent semi-electrostatic interactions in regioisomeric products (with the small and positive $\nabla^2\rho_b$ and $H(r)$ values on the corresponding BCPs), two or three additional RCPs form in products leading to more electronic stability. Furthermore, a comparison of QTAIM MGs of regioisomeric transition states in TS-HF and TS-FF discloses that in addition to two RCPs on triazole and cyclooctyne rings in TS1 regioisomer, there is a new additional RCP (denoted as RCP3) in TS2 regioisomer which is owing to H–F intramolecular interaction occurred

Table 5: Mathematical properties of some selected BCPs and RCPs of isomer1-FF, isomer2-FF, TS1-FF, and TS2-FF

	ρ_b	$\nabla^2\rho_b$	G_b	V_b	H_b
Isomer1-FF					
BCP_s					
N(21)–C(2)	0.331	–0.886	0.248	–0.717	–0.469
N(22)–C(1)	0.309	–0.452	0.338	–0.789	–0.451
C(2)–C(1)	0.311	–0.832	0.117	–0.442	–0.325
RCP_s					
RCP1	0.059	0.474	0.109	–0.10	0.009
RCP2	0.006	0.027	0.005	–0.004	0.001
RCP3	0.006	0.028	0.006	–0.004	0.002
RCP4	0.007	0.033	0.007	–0.006	0.001
Isomer2-FF					
BCP_s					
N(22)–C(2)	0.281	–0.593	0.227	–0.602	–0.375
N(21)–C(1)	0.302	–0.828	0.172	–0.552	–0.379
C(2)–C(1)	0.306	–0.796	0.114	–0.426	–0.313
H(21)–H(19)	0.019	–0.064	0.014	–0.012	0.002
RCP_s					
RCP1	0.054	0.431	0.098	–0.087	0.010
RCP2	0.010	0.049	0.010	–0.008	0.002
RCP3	0.011	0.053	0.011	–0.009	0.003
RCP4	0.008	0.041	0.009	–0.007	0.002
TS1-FF					
BCP_s					
N(22)–C(1)	0.064	0.094	0.035	–0.046	–0.011
N(21)–C(2)	0.050	0.086	0.026	–0.031	–0.005
C(2)–C(1)	0.398	–1.222	0.251	–0.808	–0.557
RCP_s					
RCP1	0.024	0.159	0.033	–0.027	0.006
RCP2	0.009	0.035	0.007	–0.005	0.002
TS2-FF					
BCP_s					
N(9)–C(1)	0.049	0.083	0.025	–0.030	–0.005
N(8)–C(2)	0.066	0.094	0.036	–0.048	–0.012
C(2)–C(1)	0.399	–1.233	0.245	–0.799	–0.554
H(12)–F(16)	0.007	0.030	0.006	–0.005	0.001
RCP_s					
RCP1	0.024	0.160	0.034	–0.027	0.007
RCP2	0.009	0.037	0.007	–0.006	0.001
RCP3	0.007	0.032	0.007	–0.005	0.002

Note: The atoms are numbered according to Figure 11.

in TS2 regioisomer. In the case of TS-HCF3, besides two RCPs on triazole and cyclooctyne rings, there is a RCP in TS1 (denoted as RCP3), due to F–N intramolecular interaction, while an additional RCP can be seen in QTAIM molecular graph of TS2, arising from H–H interactions. This behavior can be mainly attributed to the origin of regioselectivity in cycloaddition reaction of trifluoromethyl-substituted and fluorinated cyclooctynes with methyl azide. Moreover, H–F and N–F intramolecular interactions occurred in trifluoromethyl-substituted and fluorinated transition states, and its

subsequent additional RCP leads to the more electronic stability of transition states and so can be ascribed to the promoted reactivity of trifluoromethyl-substituted and fluorinated cyclooctynes.

4 Conclusion

In this research, the effect of substitution at the propargylic position in cyclooctyne on the enhancement of reactivity in the strain-promoted azide–alkyne cycloadditions was assessed via the quantum chemistry calculations. We demonstrated how the QTAIM approach provides significant insight into the activity enhancement of strain-promoted azide–alkyne cycloadditions by methyl, trifluoromethyl, and fluorine substitution of propargylic position in cyclooctyne. In this respect, we primarily surveyed the energetic aspects in the mechanical pathway of cycloaddition reactions, considering the regioisomeric transition state structures and interpret the regioselectivity of reaction and methyl, trifluoromethyl, and fluorine substituent effects on the reactivity.

On the other hand, topological analysis of electron density was performed on some key BCPs and RCPs in regioisomeric products and their corresponded transition states along the cycloaddition of cyclooctyne, methyl- and trifluoromethyl-substituted cyclooctyne, and mono and difluorinated cyclooctynes with methyl azide. Based on the QTAIM calculated results, we have arrived at this insight that the enhanced cycloaddition reactivity of trifluoromethyl-substituted and fluorinated cycloalkynes can be substantially originated from the stabilizing topological properties of electron density and its derivatives upon trifluoromethyl substitution and fluorination and not just from the energetic aspects along the cycloaddition pathway.

In summary, our quantum chemistry investigation clearly proved that the promoted cycloaddition reaction of methyl azide with trifluoromethyl-substituted and fluorinated cyclooctynes benefited from both reduced activation energies and stabilized topological features of electron density.

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