Original Research Article

Copper Catalyzed Cycloaddition Reaction of Azidomethyl Benzene With 2,2-Di(prop-2-yn-1-yl)propane-1,3-diol: DFT and QTAIM Investigation

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A B S T R A C T

In this study, the cycloaddition of azidomethyl benzene with 2,2-di(prop-2-yn-1-yl)propane-1,3-diol in the presence of copper catalyst was modeled electronically and thermodynamically in the gas and two solution phases, using quantum chemistry methods. In this line, we investigated some aspects of products and their related transition states through two plausible catalytic reaction pathways, leading to the unexpected synthesis of a statistical mixture of mono and bis-triazoles, from structural and energetic viewpoints. The obtained results revealed that production of mono and bis-triazole mixture can be essentially attributed to the balance of thermochemical and kinetical factors. Additionally, we analyzed topologically the electron density through quantum theory of atoms in molecules. In this line, electron density, its laplacian and electronic energy density properties were assessed on key bond and ring critical points to explicate more clearly the origins of electronic stability in triazole and bis-triazole products and their associated transition states.
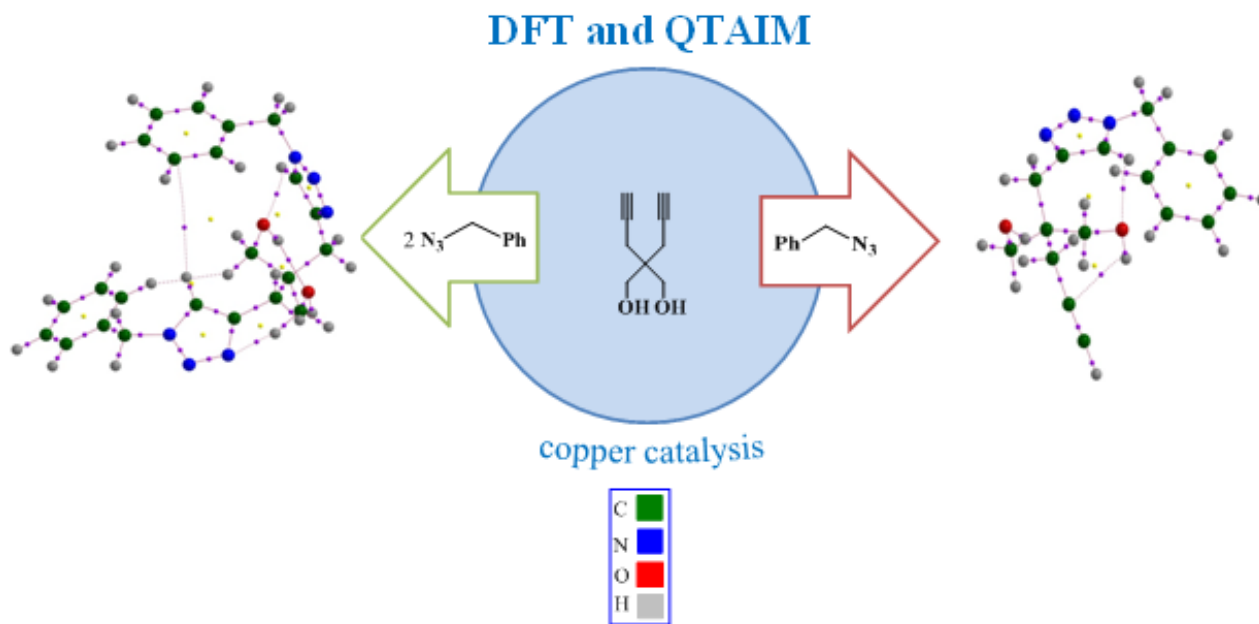
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G R A P H I C A L   A B S T R A C T

1. Introduction

1,2,3-Triazoles are present in the structure of many natural compounds, and due to their significant biological features, the synthesis of these compounds is of special importance in organic chemistry [1]. Among the important biological properties of 1,2,3-triazoles, we can point out antibacterial [2,3] and anti-fungal [4,5], anticancer [6-10], anti-HIV [11-14], anti-tuberculosis [15-20], anti-convulsant [21] and anti-inflammatory [22] activities.

1,2,3-Triazoles are an essential type of heterocyclic materials. Among applications of these compounds in the industry include dyes, fluorescents, polymer stabilizers, corrosion inhibitors, and photographic materials [23].

Currently, Cu(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC) is the most popular method for the preparation of triazoles and bis-triazoles, based on the click chemistry approach. Click chemistry is the best way for the synthesis of triazoles that was introduced firstly by Sharpless in 2001 and was expanded in 2002, inspired by Meldal's works [24,25]. With this in mind, in 1963

Huisgen introduced non-catalyzed azide-alkyne cycloaddition reaction, leading to the producing of 1,4 and 1,5-disubstituted 1,2,3-triazoles mixture [26, 27].

Due to the importance of click chemistry, Cu(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC) has been receiving the great attentions [28]. In subsequent years, the cycloaddition reaction between azides with di-alkynes has been investigating extensively for their application for production of bis-triazoles. Bis-triazoles have significant applications in pharmaceutical chemistry, organometallic chemistry, supramolecular chemistry and biological chemistry. There are three primary manners for the synthesis of bis-triazoles, but the most popular way is the CuAAC reaction of azides with terminal di-alkynes [29]. In this line, in 2012 Mohammed and coworkers applied D-mannitol to generate di-alkynes followed by CuAAC reaction for the synthesis of bis-triazoles with high yield. It should be noted that the deprotection of bis-triazole produces the surfactants [30] which have more than one hydrophilic head group

and hydrophobic tail group linked by a space rat the head groups or closed to them [31,32]. In the other studies, a groups of ester-linked di-alkynes has been produced from the propargyl alcohol and acid dichloride in the presence of 4-dimethylaminopyridine (DMAP) and then was used in CuAAC reaction for the production of bis-triazoles in high yield [33]. Moreover, copper catalyzed click reaction has been applied to synthesize phenanthroline bis-triazoles that is known as the potential G-quadruplex (G4) deoxyribonucleic acid (DNA) ligands with high selectivity over duplexed DNA [34]. From the computational viewpoints, the mechanistical aspects of di-alkyne-azide cycloadditions and di-azide-alkyne reactions have been assessed using density functional theory (DFT) approaches [35,36]. Furthermore, the computational design of several series of energetic bis-triazole onions has been performed by calculation of heat of formation, crystal density and impact sensitivity [37].

In the recent years, we have confined our attentions on computational investigation of regioselective behavior of metal catalyzed coupling and click reactions [38-41].

Moreover, we have carried out the combined experimental and computational researches on heterogeneous nanocatalysts through modeling of interactions between metal nanoparticles many different amine functionalized polymeric surfaces and silica bonded mesoporous supports [42-55].

Following our research trajectory, in this research, we investigated a computational study on the structural, energetic, and electronic aspects of cycloaddition reaction of azides with di-alkynes which leads to an unexpected statistical mixture of mono-triazole and bis-triazole (Fig.1). This unusual observed cyclodimerization has been reported by Rodinov and co-workers and have been explained by invoking to π complexation as a means of positioning substrates [56].

This context led us to investigate the mechanistical and thermodynamical properties of two reaction routes for the cycloaddition of azidomethyl benzene, as 1,3-dipolar azide, with 2,2-di(prop-2-yn-1-yl) propane-1,3-diol, as di-alkyne, in the presence of copper catalyst, applying DFT methods. It is worth mentioning that we have made a computational analysis on the formation of copper acetylide complexes through their significance in the kinetic of CuAAC reactions that has been approved via the various recent studies [57,58]. Clearly speaking, we surveyed the competitive thermodynamical and kinetical effects on the production of triazole and bis-triazole mixture by focusing on terminally-bound copper alkyne activation role toward cyclodimerization.

In the other hand, we employed quantum theory of atoms in molecules (QTAIM) approach [59] to assess the topological distribution of electron density, its laplacian and other electron density indices on critical points of some key bonds and rings. This topological analysis was performed to justify the electronic origins in the copper catalyzed cycloaddition of azides with di-alkynes.

2. Computational Methods

M06/6-31G* level of theory was applied to obtain the optimized structures of products and related transition states in the aforesaid copper catalyzed click reaction pathways. It is noteworthy to mention that in recent years M06 functional has been presented as a hybrid meta-GGA exchange correlation functional that was included both transition metals and nonmetals and was counseled for usage in organometallic and inorganometallic kinetic and Thermodynamic studies and noncovalent interactions [60]. Furthermore, we performed the harmonic frequency computations to acknowledge that the optimized structures at

M06/6-31G* level of theory related to a local minima or saddle point structure in conjunction with real and imaginary frequencies, respectively. In order to validate transition state (TS) computations, the intrinsic reaction coordinate (IRC) method that is based on the connection of reactants and products has not been applied. Alternatively, we used a popular approach in automated TS procedures through which the eigenvector corresponding to the imaginary frequency should have motion along at least one of the active bond stretching modes. Then, the obtained frequency values were employed to calculate the thermochemical corrections for free energies and enthalpies. Moreover, to investigate the effect of solvent on the thermochemistry of reactions, thermodynamic calculations using two different types of solvents (water and dimethyl sulfoxide (DMSO)) were performed at M06/6-311G** level of theory through the polarized continuum model (PCM) [61].

It should be emphasized that in the case of the copper atom, instead of using all electron basis set, the effective core potential (ECP)LANL2TZ, was applied to describe the valence electron density and its corresponding base set was used to core electrons [62]. All DFT calculations were carried out through GAMESS suite programs [63].

In the next stage, we topologically studied the electron density distribution on triazole and bis-triazole products and the correspondin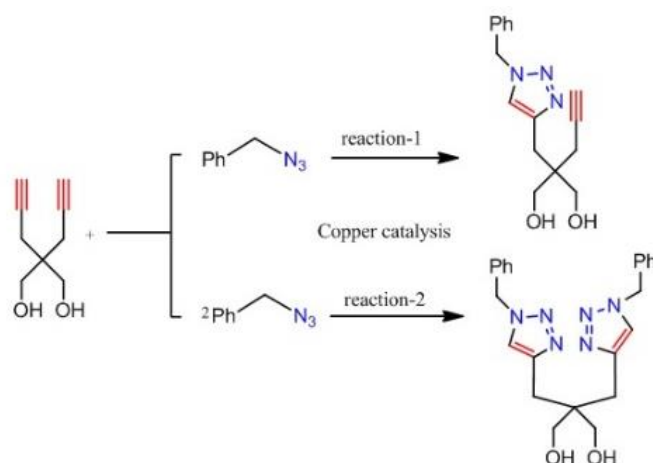g transition states based on QTAIM analysis. In this respect, we first configured the AIM2000 program input [64] based on the resulting M06/6-311G** wave function files to determine bond critical points (BCPs), ring critical points (RCPs) and bond paths. Then, to interpret the production of statistical mixture of triazole and bis-triazole, we analyzed the calculated values of electron density, ρb, laplacian of electron density, $\nabla^2 \rho b$, the electronic kinetic energy density, $G(r)$, the electronic potential energy density, $V(r)$, total electronic energy density, $H(r)$, and ratio $\frac{|Vb|}{Gb}$.
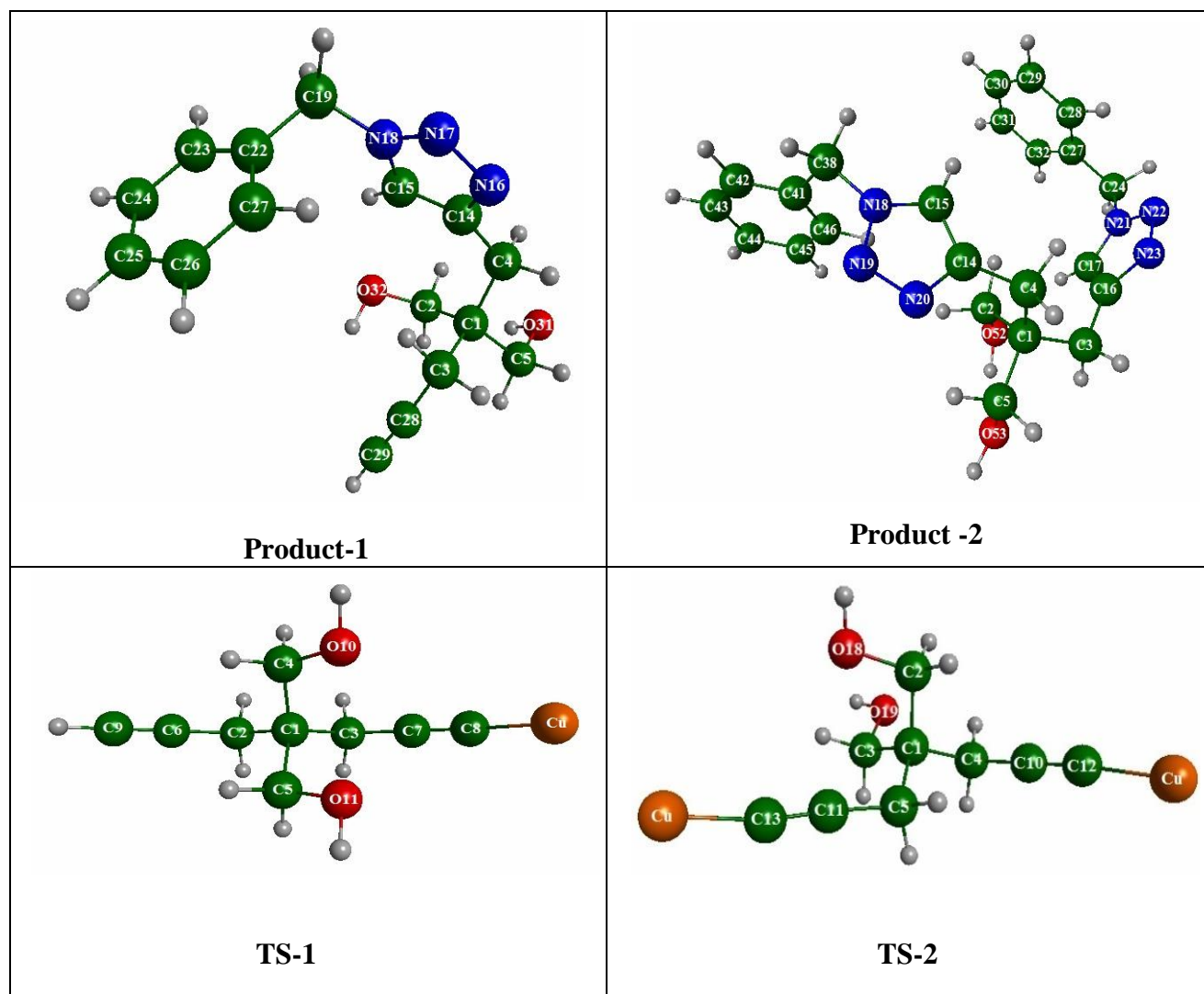
3. Results and Discussion

3.1. Structural and Energetic Aspects in Formation of Triazole and Bis-triazole Mixture

In the first step, the cycloaddition reaction between (azidomethyl) benzene, as azide, with 2,2-di(prop-2-yn-1-yl) propane-1,3-diol, as di-alkyne, was modeled in the presence of copper catalyst which results in production of a statistical mixture of (2-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-2-(prop-2-yn-1-yl) propane-1,3-diol), as mono-triazole product, and bis-triazole product (2,2-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)propane-1,3-diol), as bis-triazole product, (Figure 1).

At the rest of the article, for convenience, mono and bis-triazole products are called as product-1 and product-2, respectively. In Figure 2 M06/6-31G* optimized geometry of mono and bis-triazole products have been illustrated.

Fig.1. Copper-catalyzed azide-di-alkyne cycloaddition reaction pathways

Fig. 2. The optimized structures of product-1 and product-2 and the related transition states, TS-1 and TS-2, calculated at M06/6-31G* level of theory

Table 1. The thermochemical properties changes for reaction-1 in the gas and two solution phases at M06/6-311G** level of theory. ΔE,r is the reaction electronic energy. ΔE0,r is the reaction electronic energy containing zero-point correction, ΔHr is reaction enthalpy and ΔGr is Gibbs free energy (all energy units are kcal/mol)

	$\Delta E_{e,r}$	$\Delta E_{0,r}$	ΔH_r	ΔG_r
gas phase	-65.52	-59.63	-54.92	-40.14
Solution phase				
water	-66.35	-60.73	-55.75	-40.97
DMSO	-66.34	-60.72	-55.74	-40.96

Table 2. The thermochemical properties changes for reaction-2 in the gas and two solution phases at M06/6-311G** level of theory. The definition and units of quantities are the same as Table 1

	$\Delta E_{e,r}$	$\Delta E_{0,r}$	ΔH_r	ΔG_r
gas phase	-137.78	-124.87	-113.56	-83.73
Solution phase				
water	-139.50	-126.59	-115.28	-85.45
DMSO	-139.48	-126.57	-115.26	-85.43

By the comparison of the calculated thermochemical data which is reported in Tables 1 and 2, these primary results can be extracted: (i)the enthalpy and Gibbs free energy changes are negative in both reactions while the calculated Gibbs free energy change in the synthesis of bis-triazole is more negative about 40 kcal/mol, which reveals the more preference in production of bis-triazole from the thermochemical point of view, (ii)the calculated values of reaction Gibbs free energy changes are more positive i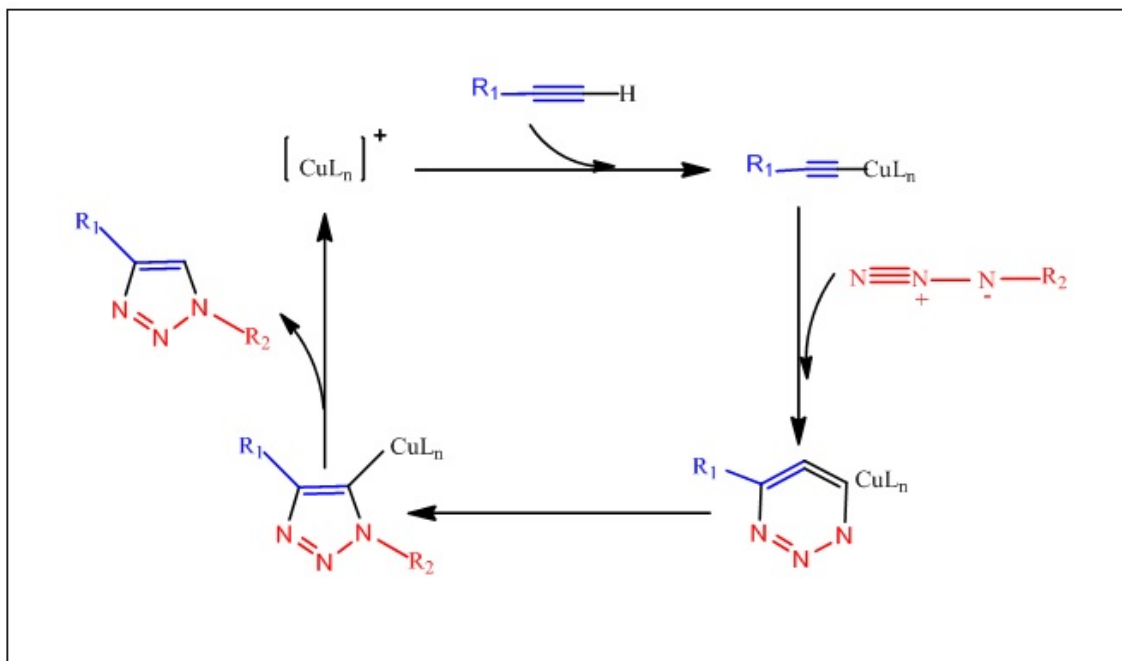n comparison with the reaction enthalpy changes which can be dedicated to the negative values of reaction entropy changes, (iii)Additionally, the changes of computed values related to the thermochemical aspect of the both reactions are very close in both solution phases, indicating that both water and DMSO are favorable solvents with no preference, in the synthesis reactions.

In the obtained thermochemical context with the considerable preference for the production of bis-triazole, it is necessary to assess the copper catalytic mechanistic route to present the quantitative insights for the observed

mixture of mono and bis-triazole in the aforementioned reaction. The kinetic studies and computations have shown that the copper catalyzed alkyne-azide cycloaddition reaction occurs through a stepwise mechanism, begins by producing of an active copper acetylide species via the π complex [56,57] that decreases the activation barrier relative to the uncatalyzed concerted process by as much as 11 kcal/mol.

In the next step, a copper acetylide-azide complex is generated through the azide replacement of a ligand in copper acetylide and then subsequent cyclization occurs by nucleophilic attack of acetylide carbon at nitrogen of the azide to produce copper metallocycle intermediate that is followed by transformation into triazole-copper derivative. Protonation of triazole-copper derivative leads to the triazole product and reproduce catalyst (The mechanistical pathway hasbeen represented schematically in Figure 3). Overall, it has been evidenced that the nature of copper acetylide complexes has a crucial mechanistical effect on the rate and success of catalysis [25, 56-58].

Fig. 3. The mechanistical steps of copper catalysis in azide-alkyne cycloaddition

In this line, we carried out computational modeling of copper acetylide transition states via π complexation, for two mentioned reactions (hereafter, called as TS-1 and TS-2) followed by saddle point computations at M06/6-31G* level of theory. The optimized structures of transition states, TS-1 and TS-2 have been represented in Fig. 2. In Tables3 and 4, we have reported the values of the activation electronic energy (without and with zero-point energy corrections), activation enthalpy and activation Gibbs free energy calculated at M06/6-311G** level of theory, in the gas and two solution phases for the synthesis of triazole and bis-triazole, respectively. The comparative assessment on the reported results of Tables 3 and 4 demonstrates the lower activation energy values (about 6 kcal/mol) for the production of triazole than bis-triazole, both in the gas and

solution phases and consequently, ascertains the kinetical preference in production of mono-triazole. In fig.4. we have demonstrated the energy profiles, corresponded to two reaction pathways of cycloaddition of azidomethyl benzene with 2,2-di(prop-2-yn-1-yl) propane-1,3-diol, displaying the M06/6-311G** calculated values of activation energies and reaction electronic energies in the gas and solution phases. In overall, based on the obtained energetic results on the mechanistical reaction pathway as well as focusing on the

formation of copper acetylide complexes due to their crucial role on the kinetic of the reactions, synthesis of a statistical mixture of both mono-triazole and bis-triazole products can be mainly attributed to the competitive effects of thermochemical and kinetical factors. More clearly speaking, the thermochemistry of reaction is in favor of the synthesis of bis-triazole, while in an inverse trend, the production of mono-triazole is more preferred with the lower activation barrier energy values.
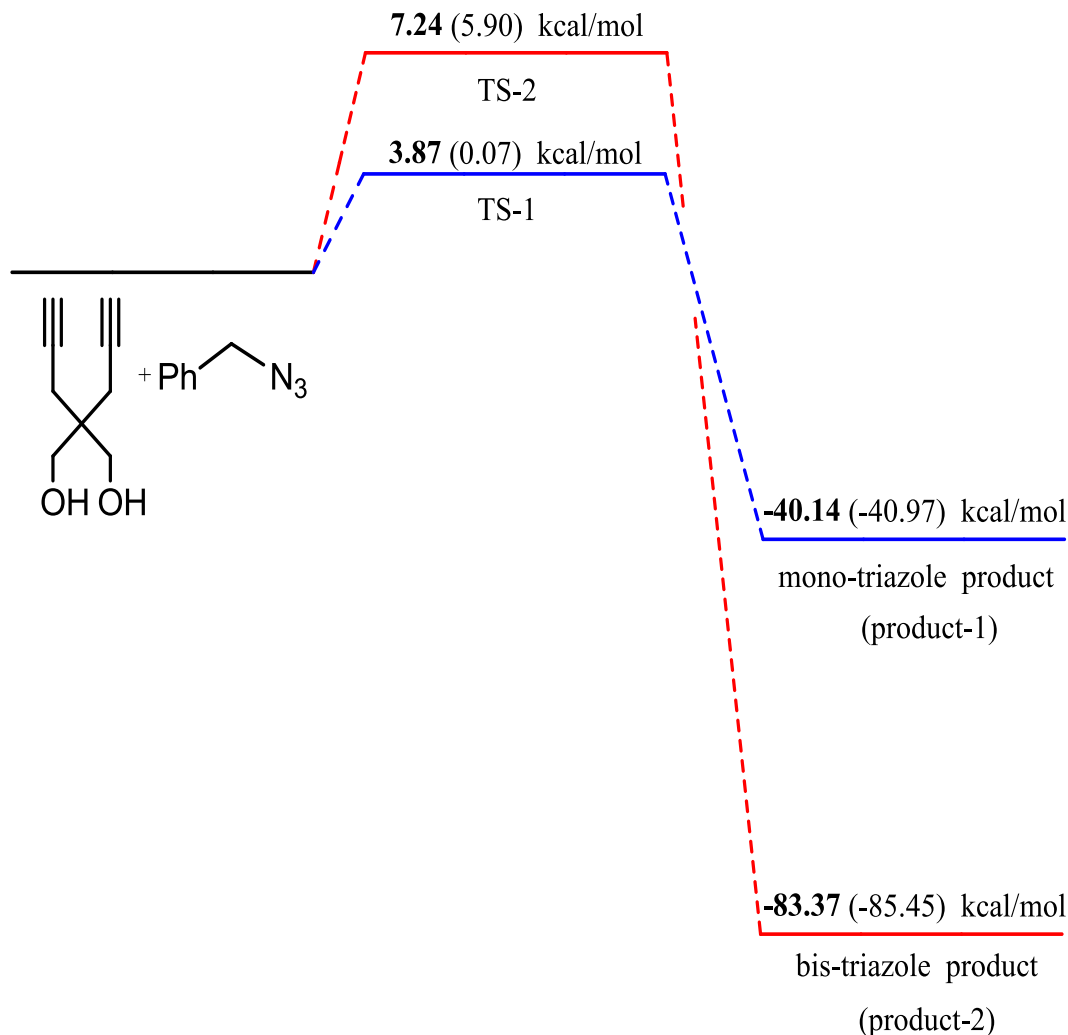
Table 3. The thermochemical properties of energy barrier for reaction-1 in the gas and two solution phases at M06/6-311G** level of theory. ΔEr is the electronic energy barrier. $\Delta E0,r$ is the electronic energy barrier including zero-point energy correction, ΔHr and ΔGr are enthalpy and Gibbs free energy barrier, respectively (all energy units are kcal/mol).

	$\Delta Ee,r$	$\Delta E0,r$	ΔHr	ΔGr
gas phase	14.80	10.67	7.49	7.24
Solution phase				
water	13.46	9.33	6.15	5.90
DMSO	13.47	9.34	6.16	5.91

Table 4. The thermochemical properties of energy barrier for reaction-2 in the gas and two solution phases at M06/6-311G** level of theory. The definition and units of quantities are the same as Table 3.

	$\Delta Ee,r$	$\Delta E0,r$	ΔHr	ΔGr
gas phase	20.79	11.76	4.34	3.87
Solution phase				
water	16.99	7.96	0.54	0.07
DMSO	17.04	8.01	0.59	0.12

Fig. 4. The energy profiles for two reaction routes of cycloaddition of azidomethyl benzene with 2,2-di(prop-2-yn-1-yl) propane-1,3-diol. The M06/6-311G** activation energies and the reaction electronic energies in the gas (and solution phase in the parenthesis) have been reported.

3.2. QTAIM Topological Analysis of Electron Density

In this segment, the analysis of electron density distribution on mono and bis-triazole materials and their related transition states based on QTAIM method have been investigated from the topological viewpoint.

The starting point of QTAIM theory is the assessment of electron charge distribution at critical points where the electron density gradient vanishes, $\nabla \rho(r) = 0$. The electron density pathway, which starts at the bond critical point (BCP) and ends at each nucleus, is known as the bond path; thus, the molecular shape is a network of bonding pathways that is often identical to a network of chemical bonds in molecular equilibrium geometry. Moreover, the laplacian of electron density, $\nabla^2 \rho(r)$, has a particular importance in determining the nature of chemical bonds. In this line, $\nabla^2 \rho(r) <$ 0 conveys the electron density enhancement in inter-nuclei region, assigned as a covalent

interaction and in contrast, $\nabla^2\rho(r)$ > 0 at the critical point indicates a decrease in electron density at the interaction region between the two nuclei, called as closed-shell interactions. Moreover, for identifying interatomic interactions nature the electronic energy parameters such as kinetic energy G(r), potential energy V(r) and the total electronic energy densities H(r), have been applied as topological indicators.

In this research, for gaining a clearer elaboration on the electronic features of the aforementioned copper catalyzed azide-di-alkyne cycloaddition, we have carried out QTAIM computations on triazole and bis-triazole products and their related copper alkyne transition states. The QTAIM molecular graphs, including bond critical points (BCPs), ring critical points (RCPs) and bond paths for triazole and bis-triazole products and the corresponded transition states have been depicted in Figure 5, respectively. The M06/6-311G** calculated values of electron density, laplacian of electron density, the electronic kinetic energy density, G(r), the electronic potential energy density, V(r), the total energy density, H(r), and $\frac{|Vb|}{Gb}$ ratios on some key BCPs and RCPs have been listed in Tables 5 and 6 for products and their related transition states, respectively. Based on the reported results of Tables 5 and 6, we can deduce the following results:
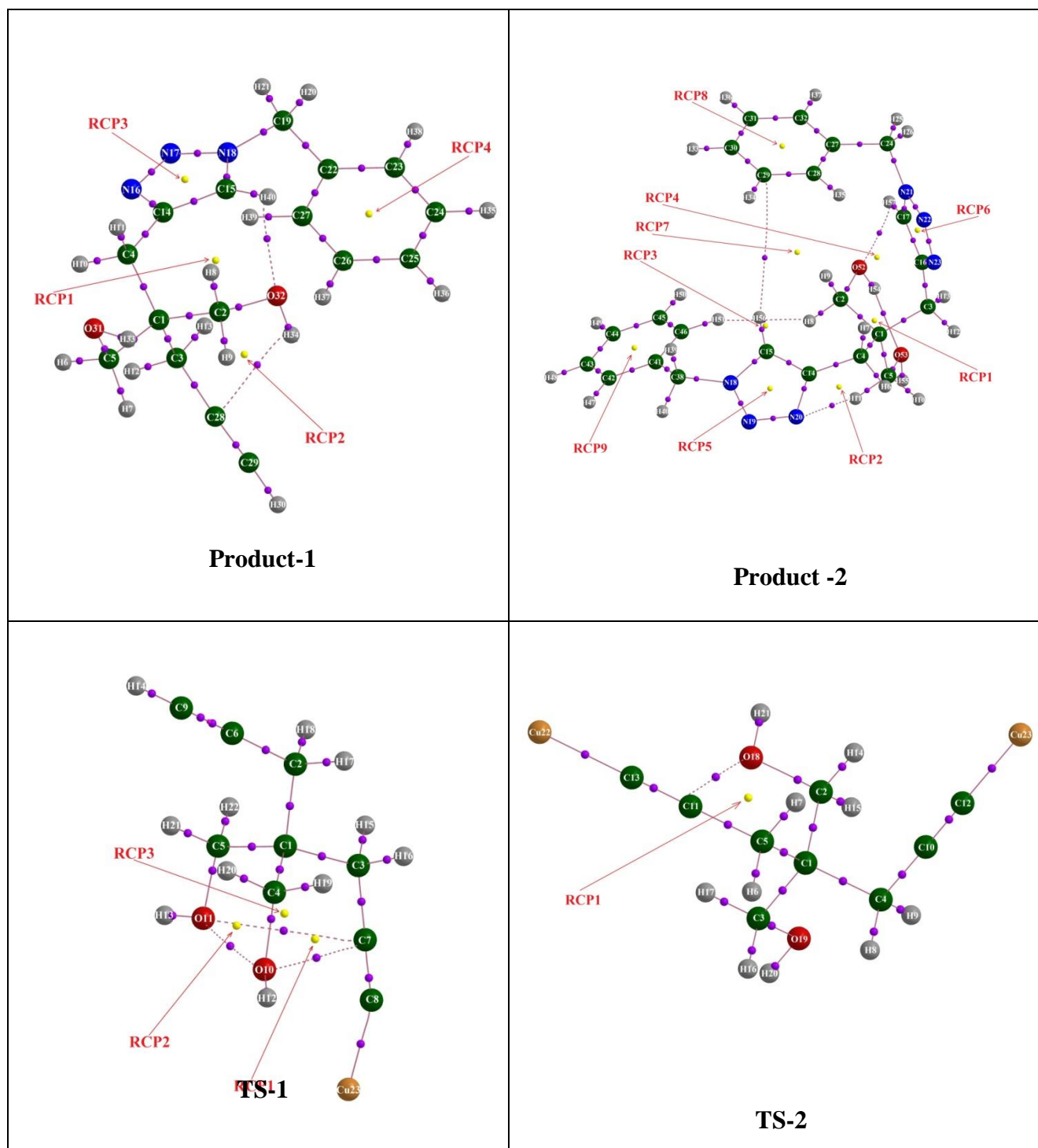
I) the negative amounts of $\nabla^2\rho_b$ and H(r) and values of $\frac{|v_b|}{G_b} > 2$ at triazole ring BCPs in product-1 and product-2 can be assigned to the covalent character of all bond critical points and in consequent, stable charge concentration in the newly formed triazole rings,

II) QTAIM molecular graphs of product-1 and product-2 demonstrate that in addition to phenyl and triazole ring critical points, there are 2 and 5 new RCPs in product-1 and product-2, respectively, which have been generated mainly through the presence of H...H, O...H and C...H intramolecular interactions, leading to the more electronic stability of bis-triazole products,

III) on the key BCP between copper and terminal alkyne carbon in the transition states structures, the calculated values of electron density, its laplacian, all electronic energy density indices and ratio $\frac{|Vb|}{Gb}$ indicates the semi-electrostatic and semi-covalent character. The calculated value of ratio $\frac{|Vb|}{Gb}$ on Cu-C8 BCP is 1.534 in TS-1 and on BCPs Cu-C12 and Cu-C13 in TS-2 equal to 1.574 and 1.588, respectively,

IV) as it was extracted from the QTAIM molecular graphs of transition states, 3 and 1 RCPs have been formed in TS-1 and TS-2, respectively which is assigned to the intramolecular interactions O...O and O...C in TS-1 and O...C in TS-2 and can be regarded as the main electronic origins of more stability in TS-1 in comparison with TS-2.

Fig. 5. Complete molecular graphs (MGs) of product-1, product-2, TS-1 and TS-2, performed by QTAIM methods of M06/6-311G** electron density functions. Bond Critical Points: purple circles, Ring Critical Points: yellow circles and Bond Paths: purple lines.

Table 5. Calculated properties related to some selected BCPs and RCPs of product-1 and product-2. These properties are assessed through QTAIM methods at M06/6-311G** level of theory. The atoms are numbered according to Fig. 5.

	ρ_b	$\nabla^2\rho_b$	H_b	$|V_b|/G_b$
Product-1				
BCPs				
C14-C15	0.317	-0.859	-0.328	3.884
C28-H34	0.011	0.040	0.001	0.830
O32-H40	0.016	0.059	0.000	0.931
RCPs				
RCP1	0.006	0.032	0.001	0.785
RCP2	0.011	0.053	0.002	0.793
Product-2				
BCPs				
H8-H51	0.003	0.012	0.000	0.638
H11-N20	0.011	0.039	0.001	0.875
C14-C15	0.319	-0.870	-0.333	3.881
RCPs				
RCP1	0.014	0.077	0.002	0.849
RCP2	0.009	0.043	0.002	0.762
RCP3	0.003	0.010	0.000	0.697
RCP4	0.008	0.039	0.001	0.790
RCP7	0.000	0.000	0.000	0.370

Table 6. Calculated properties related to some selected BCPs and RCPs of TS-1 and TS-2. These properties are studied through QTAIM methods at M06/6-311G** level of theory. The atoms are numbered according to Fig. 5.

	ρ_b	$\nabla^2\rho_b$	H_b	$|V_b|/G_b$
TS-1				
BCPs				
C5-O11	0.249	-0.473	-0.345	2.522
C7-O10	0.009	0.035	0.000	0.905
C7-O11	0.010	0.035	0.000	0.905
O10-O11	0.010	0.038	0.0001	0.985
C8-Cu23	0.170	0.371	-0.106	1.534
RCPs				
RCP1	0.009	0.041	0.001	0.839
RCP2	0.009	0.045	0.001	0.877
RCP3	0.009	0.041	0.001	0.838
TS-2				
BCPs				
C5-C11	0.264	-0.660	-0.233	4.401
C11-O18	0.022	0.088	0.001	0.923
C12-Cu23	0.120	0.210	-0.071	1.574
C13-Cu22	0.121	0.201	-0.071	1.588
RCPs				
RCP1	0.015	0.086	0.003	0.812

4. Conclusion

In this research, we carried out the thermochemical and electronic origins of production of mono-triazole and bis-triazole mixture in copper catalyzed cycloaddition of azides and di-alkynes using computational quantum chemistry methods. In this respect, we first investigated the energetic and thermochemical properties along the cycloaddition reaction path using DFT methods in the gas and two solution phases. The obtained thermochemical results revealed the thermodynamic preference in production of bis-triazole in comparison with mono-triazole, which is associated with the more negative reaction Gibbs free energy values. Furthermore, the

negative values of reaction entropy changes were deduced for both cycloadditions which were assigned to the more positive values of calculated reaction Gibbs free energy changes compared to the reaction enthalpy changes.

In another hand, the comparative analysis of transition states structures and energy barriers for two cycloaddition reaction pathways demonstrated that the production of triazoles are more desirable with the corresponded less activation barrier Gibbs free energy. The overall assessment on the obtained energetic and thermochemical results indicated obviously the competition between kinetical and thermochemical controls in the synthesis of triazole and bis-triazole which work in the opposite direction and lead to the production of mixture.

In the final stage, we topologically assessed the electron density of triazole and bis-triazole products and their related transition states using QTAIM calculations. In this respect, electron density and its laplacian, as well as electron energy density properties were calculated on key bond and ring critical points of triazole and bis-triazole products and their related transition states. The QTAIM obtained results affirms the covalent nature of the newly formed bonds in the triazole rings, regarding the negative amounts of $\nabla^2\rho_b$ and H(r) and values of $\frac{|V_b|}{G_b} > 2$. Moreover, the presence of H...H, O...H and C...H intramolecular interactions results to the formation of 2 and 5 additional RCPs in triazole and bis-triazole products, respectively, and shows the more electronic stability of bis-triazole. Finally, the topological analysis on QTAIM molecular graphs of the corresponding transition states represented the semi-electrostatic and semi-covalent nature of the interaction between copper and terminal alkyne carbon. Moreover, it was shown that there are 3 and 1 RCPs in TS-1 and TS-2, respectively, leading to the more electronic stability of TS-1

compared to TS-2 and consequently, the more kinetical preference in the synthesis of triazole. In overall, we can claim that synthesis of a statistical mixture of both mono-triazole and bis-triazole products can be mainly originated to the balancing competition between the thermochemical and kinetical effects.

Acknowledgements

Supplementary Information

The electron density distribution on triazole and bis-triazole products and the corresponded transition states was studied based on QTAIM approach. In this line, we first used the AIM2000 program input according to the resulting M06/6-311G** wave function files to determine bond critical points (BCPs), ring critical points (RCPs) and bond paths. Then, we carried out the calculated values of electron density, ρb, laplacian of electron density, ∇2ρb, the electronic kinetic energy density, G(r), the electronic potential energy density, V(r), total electronic energy density, H(r),and ratio $\frac{|V_b|}{G_b}$ that have been reported in Tables S1-S4.

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