The mechanism of copper-catalyzed azide–alkyne cycloaddition reaction: A quantum mechanical investigation

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ABSTRACT

In this study, the mechanism of CuAAC reaction and the structure of copper acetylides have been investigated with quantum mechanical methods, namely B3LYP/6-311 + G(d,p). A series of possible copper-acetylide species which contain up to four copper atoms and solvent molecules as ligand has been evaluated and a four-copper containing copper-acetylide, **M1A**, was proposed more likely to form based on its thermodynamic stability. The reaction has been modeled with a representative simple alkyne and a simple azide to concentrate solely on the electronic effects of the mechanism. Later, the devised mechanism has been applied to a real system, namely to the reaction of 2-azido-1,1,1-trifluoroethane and ethynylbenzene in the presence of copper. The copper catalyst transforms the concerted uncatalyzed reaction to a stepwise process and lowers the activation barrier. The pre-reactive complexation of the negatively charged secondary nitrogen of azide and the positively charged copper of copper-acetylide brings the azide and the alkyne to a suitable geometry for cycloaddition to take place. The calculated activation barrier difference between the catalyzed and the uncatalyzed reactions is consistent with faster and the regioselective synthesis of triazole product.

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1. Introduction

1,2,3-Triazole derivatives are pharmacologically very important class of compounds and have received considerable attention due to their ability to mimic peptide bonds and work as precursor for a number of important compounds. They are chemically stable, inert to severe hydrolytic, oxidizing and reducing conditions even at high temperatures. Their derivatives show anti-HIV [1,2], anti-bacterial [3], anti-histamine [4–6] and anti-tumor [7–9] activity. Besides their pharmacological features, they are used in agro chemistry, dye industry and anti-corrosion agent [10].

Formerly, 1,2,3-triazoles were synthesized by heat. However; this process required high temperature, showed slow rate and low regioselectivity. In 2001, Sharpless and Meldal independently devised processes in which azide and alkyne have produced triazole in the presence of copper catalyst at room temperature (Fig. 1) [11,12]. This methodology provided faster (about 10^7 times) [13] and regioselective (1,4 disubstituted 1,2,3-triazole) synthesis under benign reaction conditions. The reaction can take place in organic solvents or on solid support regardless of the reaction conditions, as long as Cu(I) is present in the medium.

The most well-known click reaction, copper catalyzed azide–alkyne cycloaddition reaction (CuAAC), has been the subject of many synthetic and application studies [14–18]. Although the area of click chemistry ranges from the fuel cells to polymers, there are still some uncertain points in the mechanism of CuAAC reaction. Generally copper salts are used as catalyst and the catalytically active form of the copper is known to be +1. The catalytic activity of copper (I) has been explained by its ability to have σ and π-interactions with the alkynes and to exchange alkyne and other ligands in its coordination sphere, especially in aqueous conditions. In the proposed mechanism of CuAAC (Fig. 2), first, copper coordinates to π electrons of the alkyne compound. After deprotonation by base or solvent, copper-acetylide molecule is formed. Formation of copper-acetylide has been verified by the reaction being possible only by the terminal alkynes. The deprotonation is expected to be very efficient since the reaction takes place even in highly acidic conditions [19]. Experimentally, a decrease in pK_a has also been observed as evidence to deprotonation. Coordination of the azide to copper-acetylide is followed by the cyclization to produce the triazole ring. Finally, protonation releases the free triazole molecule [20].

The first DFT-based mechanistic study was carried out by the Sharpless group [21]. In their study, the mechanism advances with mononuclear copper-acetylide species in step-wise manner. Soon after this study, the kinetic study, done by the same group, showed that the reaction is second order with respect to copper,

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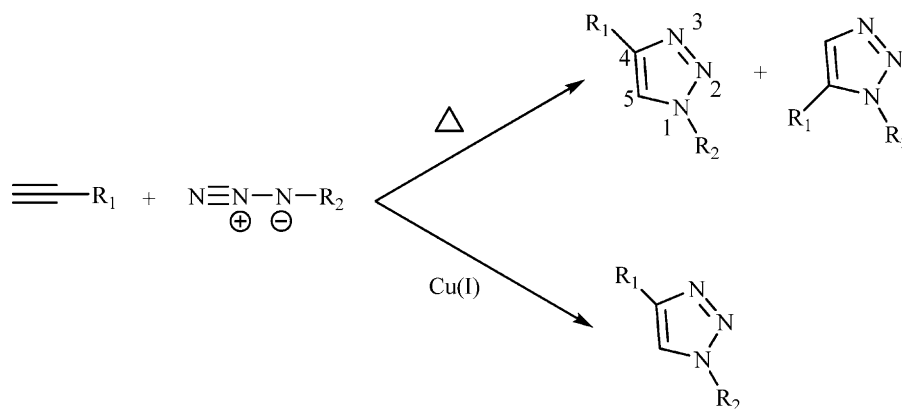 *E-mail address:* nurcant@itu.edu.tr (N.Ş. Tüzün).

Fig. 1. Thermal and copper catalyzed azide alkyne cycloaddition reactions and product distribution.

indicating the presence of multinuclear copper-acetylides in the reaction media [22]. The results of the kinetic work led to other computational studies where the mechanism has been modeled via various copper-acetylide species. In those mechanistic studies, the presence of dinuclear and tetranuclear copper acetylide complexes have been considered in model reactions where copper has been mostly treated by the LACVP basis at the B3LYP level of theory. In the work of Straub [23], tetranuclear copper acetylides were proposed to be the catalyst resting states while Cantillo et al. have proposed two-metal centered species based on their computed reaction barriers [24].

In this paper, the mechanism of CuAAC reaction will be investigated in detail based on previously proposed mechanism [21], by the quantum mechanical calculations to account on the differences observed in earlier studies. The nature of copper acetylide and how it participates in the reaction will be elucidated by considering the possible types of multinuclear copper-acetylide species with full basis set for copper, in contrast to some earlier computational studies. Although the history of the copper-acetylide species is very old, their nature is not well-known due to their tendency to form polymeric structures [25]. Understanding the interaction of copper and alkynes is the key factor to explain the copper-acetylides. The reaction with a representative simple alkyne and a simple azide will be modeled first with full basis set to concentrate solely on the electronic effects of the mechanism. Later, the devised mechanism will be applied to an experimentally worked system [26], namely to the reaction of 2-azido-1,1,1-trifluoroethane and ethynylbenzene in the presence of copper.

2. Computational methods

In most of the previous computational studies mentioned so far, effective core potential has been used. In a previous computational study on the copper-acetylide complexes, it is stated that the LACVP calculations did not reproduce the cuprophilic interactions [23], which are reported to be important interactions for dimeric and tetrameric Cu (I) complexes [27]. The DFT methodology with B3LYP [28,29] hybrid functional and $6-311+G(d,p)$ basis set has been carried out for optimizations of all atoms in gaseous phase at 298 K to provide sufficient accuracy and to refine the

energetics. So far, mechanistic studies about CuAAC have been generally carried out with LACVP pseudopotential, however; it is known that this ECP overestimates cuprophilic interactions [27]. B3LYP has been reported to give accurate results with transition metals [30–33] and in our previous studies on copper [34,35], it had shown satisfactory performance. Additionally, in the literature, this functional has been successfully used for the mechanisms of copper catalyzed azide–alkyne cycloaddition reactions [23,24,36,37]. The stationary points were analyzed by vibrational frequency calculations. All transition states were verified to be saddle points by one imaginary frequency belonging to the reaction coordinate. For all transition state structures, the intrinsic reaction coordinate (IRC) [38,39] was followed to validate the expected reactants and products. Charge analysis has been performed with Natural Bond Orbital (NBO) [40–44] calculations. Throughout the investigation, all structures and mechanisms have been interpreted by means of relative Gibbs free energy, unless otherwise stated. The effect of solvent was considered for the reactions in real world system by single-point SCRF calculations with the IEF-PCM [45,46] method at the B3LYP/6-$311+G(d,p)$ level. The free energies in acetonitrile and water were obtained by using the frequencies from the gas-phase results. These calculations, submitted in Scheme S1 in Supporting information, have revealed no significant change in trends. Gaussian 03 computational chemistry software was utilized for all calculations [47].

3. Results and discussion

The reaction of azide with alkyne is assumed to start with π coordination of the alkyne to copper, followed by deprotonation of the alkyne and formation of a copper-acetylide species. To understand the nature of copper acetylides first a model system, then an experimentally worked system has been modeled with full basis set calculations. For this purpose one, two, three and four-copper-membered possibilities of copper-acetylide species for model reaction have been evaluated computationally. Even though polynuclear copper-acetylide structures may form, it is not possible in CuAAC reactions since it will be hindered by both azide and amine ligands [25]. Although three-copper-membered acetylide species have been proposed [48], it was later reported to be unfavourable and additionally no experimental evidence existed
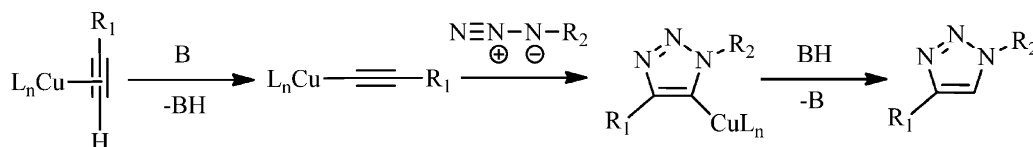

Fig. 2. The basic mechanism of copper-catalyzed azide–alkyne reaction.

Table 1
The relative Gibbs free energy (G_{rel}) values of the most stable six copper-acetylide species with acetonitrile ligand as solvent (the relative energies are calculated by adding the energies of smaller units so as to keep the number of atoms equal). A table including all optimized structures, their 3D geometries and their energy data is presented in Supporting information.

Structure	G_{rel} (kcal/mol)
M1A(4 Cu)	0.0
M1B(4 Cu)	4.0
M1C(2 Cu)	35.4
M1D(2 Cu)	42.7
M1E(3 Cu)	45.1
M1F(1 Cu)	46.7

Table 2
The relative Gibbs free energy (G_{rel}) values of the most stable six copper-acetylide species with water ligand as solvent. (The relative energies are calculated by adding the energies of smaller units so as to keep the number of atoms equal). A table including all optimized structures, their 3D geometries and their energy data is presented in Supporting information.

Structure	G_{rel} (kcal/mol)
M1A(4 Cu)	0.0
LW_A(3 Cu)	36.6
LW_B(2 Cu)	50.8
LW_C(2 Cu)	51.7
LW_D(3 Cu)	74.4
LW_E(1 Cu)	76.3

[25]. Solvent molecules are known to act as ligand and high alkyne concentration was reported to affect the binding of azide in CuAAC reactions [21]. The presence of ligands increases the rate of reaction however, they are not mandatory for the fate of the reaction and as stated by Finn et al., the ligand-free process is a good starting point for mechanistic study [22]. In our effort to rationalize the structure of copper-acetylide species, besides the number of copper, the number of alkyne has been modified and the possibility of binding one or more acetonitrile and water molecules has been considered. The calculations have showed that while acetonitrile molecules can bind to copper in two- and three copper-membered copper-acetylide species, no four-copper-membered copper-acetylide structure could be optimized with acetonitrile or water. Moreover, in our calculations, many copper-acetylide structures with acetonitrile as ligand could be located, in contrast to the ones with water. This is in accordance with the literature findings that acetonitrile is a more effective ligand than water [49,50]. According to our results, four-copper-membered structures are much more stable than the others, consistent with the literature [23] (Tables 1 and 2). The copper-acetylide with two copper atoms and acetonitrile (**M1C**) as ligand has been found to be the lowest energy dicopper species.

The relative energies and the three-dimensional structures of all optimized copper-acetylides are presented in Scheme S1 in Supporting information. In Fig. 3, the most stable structures of the four

membered copper species are shown. For four membered copper-acetylide species, two different structures, **M1A** and **M1B** will be considered. Coordination of copper to π electrons in **M1B** has distorted the planarity by 30° although **M1A** has a perfectly planar structure. The electronic and Gibbs free energies show the opposite trends, such that the free energy of **M1A** is lower than **M1B** by 4.0 kcal/mol and the electronic energy of **M1B** is lower than **M1A** by 4.0 kcal/mol. Cataldo et al. reported similar Cu-polynide structures based on their FT-IR spectra, which may serve as an experimental basis for the modeled **M1B** structure [51]. **M1B** is also similar to the propeller-like structure of the 2,4,6-triisopropylphenylcopper compound, a tetranuclear organocopper species with unsymmetrical bridging of σ—π bonded aryl ligands in the solid state [52]. The tetranuclear species **M1A** and **M1B** also resemble the X-ray structures of organocopper compounds of the type [Cu₄R₄] [27].

After formation of copper-acetylide, azide molecule attacks to the copper atom in **M1A**. The approach of azide forces the **M1A** conformer to turn into **M1B** structure in the forming van der Waals complex, **M2** (Fig. 4). Energetically, the coordination of α-nitrogen to copper is considerably endergonic. The terminal nitrogen in **M2** attacks to the alkyne carbon atom to constitute the six-membered metallocyclic structure. According to NBO charges, π interaction with alkynes causes a small increase in the charge of the two copper atoms in **M1B** structure compared to that of **M1A**. When the azide molecule approaches to the copper through α-N, the charge
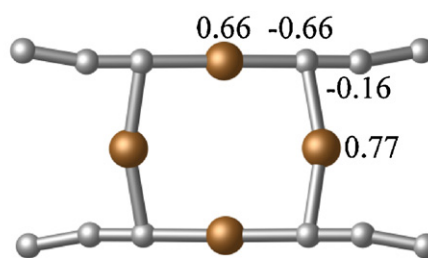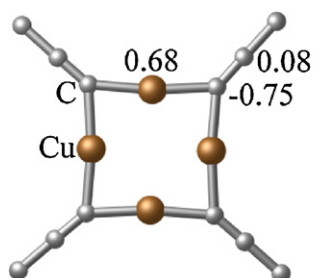
Fig. 3. 3D representations of **M1A**, **M1B** and NBO charges.
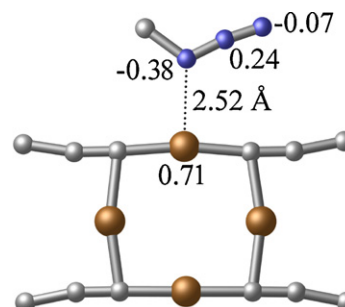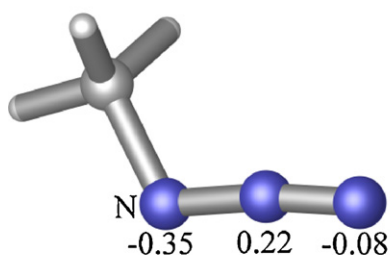
Fig. 4. 3D representations of the azide, **M2** and NBO charges.
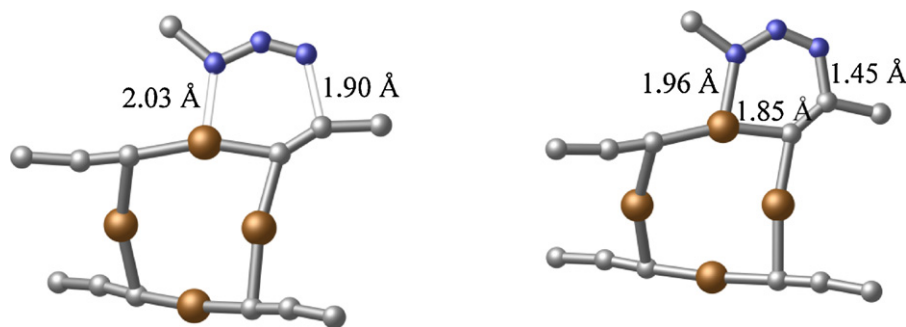
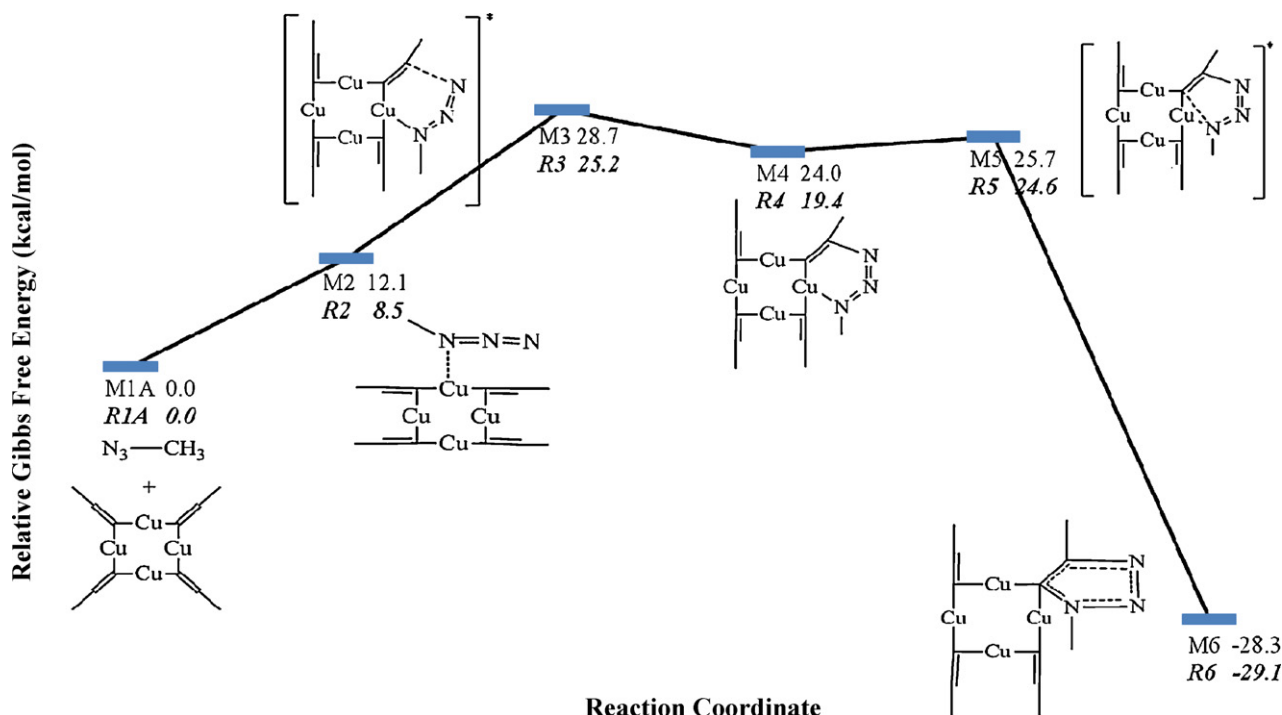**Fig. 5.** 3D representations of **M3** and **M4**.

of interacted copper is increased from 0.66 to 0.71. As the reactants engage to undergo cyclization reaction, a small electronic interaction between copper and α-N takes place to enable 1,4-product to form. The azide coordination brings the substrates to proper position and suitable electronic states for cyclization to take place through transition state **M3** (Fig. 5) which requires a barrier of 16.6 kcal/mol (Scheme 1). After formation of six-membered metallocyclic structure **M4** with a relative 24.0 kcal/mol free energy, α-N starts to detach from copper atom to bind to carbon atom, leading to 1,4-triazole molecule with a small barrier of 1.7 kcal/mol (**M5**). The catalyst associated 1,4-triazole structure **M6** is formed as a result of the exergonic process. In the literature, a similar stucture of **M6**, with steric substituents and single-copper as catalyst was isolated and identified by NMR [53]. The forming triazole can be regenarated by protonation of **M6** structure.

In this mechanism, formation of **M3**, is the rate-determining step and the highest point on the Gibbs free energy diagram. This result is in accordance with a recent IR study which states that the rate determining step is the preproduct formation from the azide–alkyne complex [54]. The B3LYP/6-311 + G(d,p) calculations in this study predict a stepwise reaction contrary to computational studies in the literature, all performed at the B3LYP level of theory with LANL2DZ on copper. The second transition state, **M5** (Fig. 6)

from a short-lived complex **M4**, takes place via a very small energy barrier but at a relatively high energy point on the reaction profile. Analogous metallacyclic intermediate **M4** has been suggested for dinuclear paths in the literature, but not for the tetranuclear path [23,24].

The possibility of 1,5-disubstituted triazole formation has also been investigated in the context of this study. It was found to undergo a concerted mechanism contrary to 1,4-disubstituted triazole formation. The transition state for 1,5-product, **M7**, is 9.0 kcal/mol higher in energy than **M3**, as expected (Fig. 7). The bigger barrier for 1,5-triazole formation is stemming from the unfavorable electronic interaction between the terminal nitrogen and the positively charged copper atom. Additionally, while in **M6** two copper atoms coordinate to the triazole's carbon atom, in **M8**, the product of **M7**, one copper atom coordinates to nitrogen and the other one coordinates to the carbon atom, which makes it harder for the triazole molecule to detach and regenerate the catalyst.

At the final stage of the study, the model mechanism was tested with an experimentally reported system. For this purpose, a convenient example in terms of computational cost has been searched among the many CuAAC reactions that have been reported in literature. The experimental results of Wu et al. have been chosen

Scheme 1. Reaction mechanism of copper-catalyzed azide–alkyne cycloaddition reaction (M refers to model system, R refers to real system).
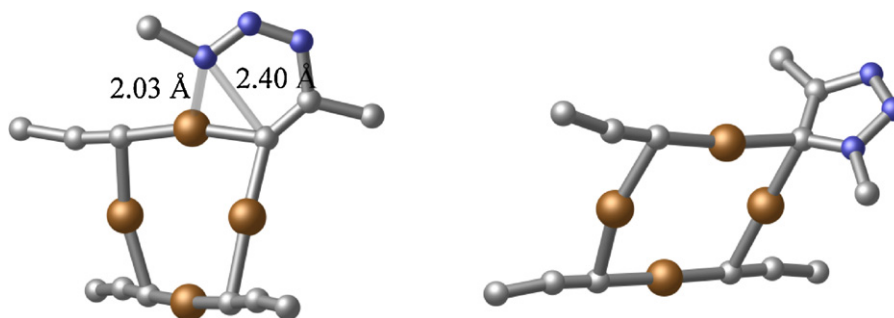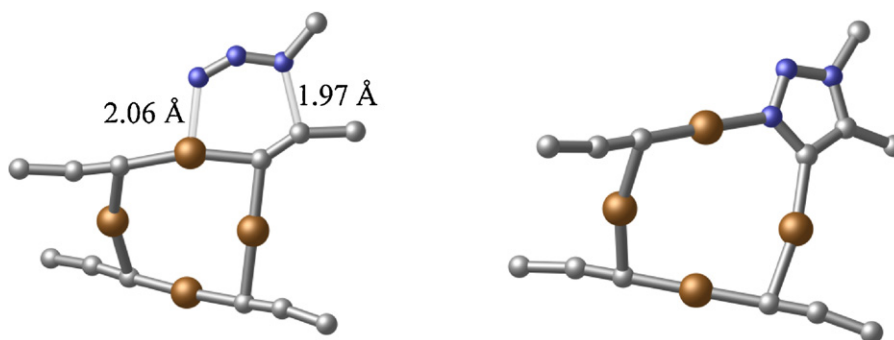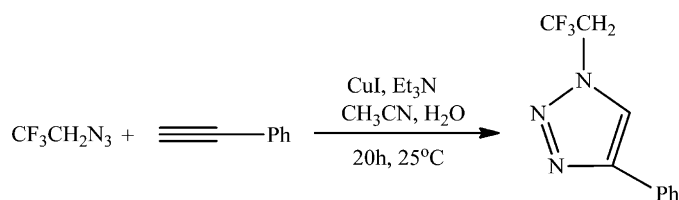
Fig. 6. 3D representations of **M5** and **M6**.

Fig. 7. 3D representations of **M7** and **M8**.

Fig. 8. Reaction scheme of Wu et al.

in which 2-azido-1,1,1-trifluoroethane reacts with ethynylbenzene in the presence of copper catalyst (Figs. 8 and 9) [26]. Among the vast of triazole derivatives, CF_3 containing scaffolds have increasing attention due to their biological features [55–57].

The substituents on the real system did not show a change in the reaction mechanism of the model (Scheme 1) in production of the triazole product **R6** (Fig. 9). The barriers are slightly lower than the model system. The electron-withdrawing substituent on the alkyne has enabled easier complexation of the copper-acetylide with the azide as compared to the model compound (12.1 kcal/mol for **M2**

and 8.5 kcal/mol for **R2**). This is consistent with the experiments where electron-withdrawing groups on the alkyne were reported to accelerate the CuAAC reaction rate [12,58].

While the energy barrier for transition from **M4** to **M5** is 1.7 kcal/mol, this value is increased to 5.2 kcal/mol in the real system, although other barriers have decreased slightly as compared to the model system. Thus, depending on the substitutents, the second transition state may become more distinctive and reach to a relative energy comparable to the highest point on the free energy diagram.

The effect of solvent has been investigated for the real system with two solvents that are most frequently used: acetonitrile and water. It has been observed that solvents increase the barriers by 0.4–3.7 kcal/mol. The barrier of the rate determining step has increased by 3.7 kcal/mol in acetonitrile (3.4 kcal/mol in water) since the stabilization in the bimolecular starting step of reaction is higher than in the unimolecular **R3** step.

The calculated energy barrier for the uncatalyzed process of 1,4-disubtituted triazole formation is 34.0 kcal/mol in the gas phase (36.0 kcal/mol in acetonitrile) (Fig. 10). The difference in barriers of
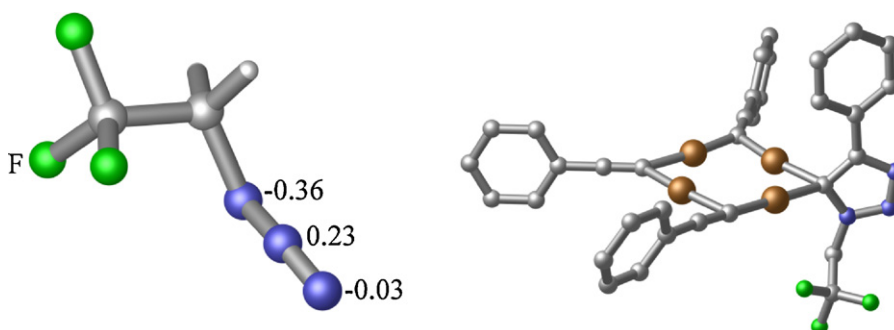
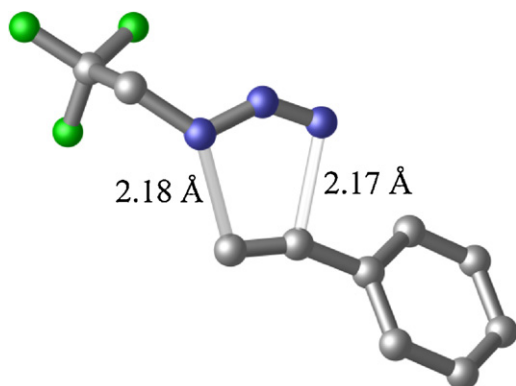**Fig. 9.** 3D representation of 2-azido-1,1,1-trifluoroethane and **R6**.

Fig. 10. 3D representation of the transition state for the uncatalyzed real system.

catalyzed and uncatalyzed reactions (8.8 kcal/mol in the gas phase and 7.4 kcal/mol in acetonitrile) has exhibited great acceleration of the reaction in the presence of copper catalyst.

In a recent paper on CuAAC reaction mechanism, the authors consider the reaction barrier from the polynuclear copper species without considering the stability of these copper-acetylides and conclude that the CuAA reaction proceeds via di-copper acetylide structures, based on their calculated barriers [24]. Our calculations show that formation of a 4-membered acetylide is much more facile as compared to that of dicopper acetylide species both in the gas phase and in solvent (35.4 kcal/mol in the gas phase and 18.2 kcal/mol in acetonitrile). Following the reaction from **M1C** (Fig. 11) and azide, the highest point on the energy path corresponds to the first transition structure (**M3**) at a relative free energy of 23.6 kcal/mole and the azide coordinated complex is 8.0 kcal/mol higher than the uncoordinated reactants. A direct comparison of the reaction barriers of four and two centered species shows that once the azide-copper acetylide complex is formed, the reaction through the dicopper species **M1C** is slightly more facile then the tetracopper species (16.6 kcal/mol for tetracopper and 15.6 kcal/mol for the dicopper acetylides, in the gas phase, and 17.9 kcal/mol for tetracopper and 16.1 kcal/mol for dicopper in acetonitrile). The corresponding barriers in the aforementioned study were 18.0 kcal/mol and 16.0 kcal/mol for the tetracopper and dicopper acetylides, respectively and the dicopper species involved odd number of electrons, indicating that the species had a charged nature [24]. Additionally, the IRC calculations following the dicopper transition state structure with full basis set in this study predict a complex and separated reactants contrary to the results of Cantillo et al. [24].
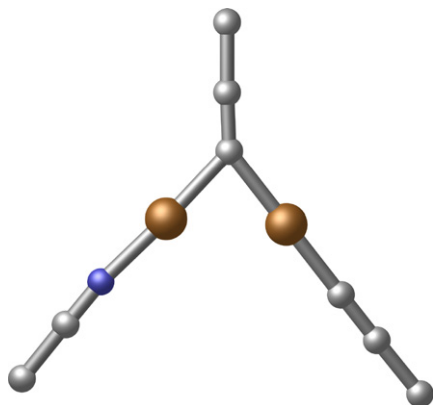

Fig. 11. 3D representation of **M1C**.

4. Conclusion

In this study, the mechanism of CuAAC reaction and the copper acetylides have been investigated with quantum mechanical methods, namely B3LYP/6-311 + G(d,p). A series of possible copper-acetylide species which contain up to four copper atoms and solvent molecules as ligand, has been evaluated and a four-copper containing copper-acetylide, **M1A**, was proposed more likely to form based on its thermodynamic stability.

Applying the earlier proposed mechanism to a model then to an experimentally worked system with tetracopper acetylide have mechanistically revealed similar results. The copper catalyst transforms a concerted uncatalyzed reaction to a stepwise process, thereby lowers the activation barrier. The negatively charged site of the azide and the positively charged site of the copper enable a favorable complexation and bring the azide and the alkyne to a suitable geometry for the attack to take place. In a recent study, the activation energy for the uncatalyzed dipolar cycloaddition was found to be correlated with the energy to distort the reactants into transition geometry [59]. Hence, the copper catalyst is helping the substrates to overcome this difficulty by bringing them closer with the help of electronic effects.

For 1,5-triazole to form, the terminal nitrogen should be complexed with the copper of the acetylides. However, this is electronically not preferred and the concerted reaction requires high activation barrier, thus, leads to a regioselective synthesis, as shown by the calculations.

Solvents calculations in acetonitrile and water have shown slightly higher barriers for both the catalyzed and the uncatalyzed reactions, however, the acceleration of reaction as compared to that of uncatalyzed is almost the same in both solvents, consistent with the reaction taking place in a variety of solvents.

The kinetic studies being secondary with respect to copper indicates the presence of multinuclear species and the dynamic nature of the reaction rather than the strict nature of acetylide species containing two coppers. The barriers being facile with both tetra and dicopper acetylide species may enable the reaction to start with 4-centered acetylide species and proceed with two-centered species when the alkyne concentration decreases.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jmgm.2011.12.012.

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