Mechanism of Copper (I)-Catalyzed Cycloaddition of Azides to Terminal Alkynes: A Quantum Mechanical Investigation

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⬜ ABSTRACT ⬜

In this work, the mechanism for copper-catalyzed alkyne-azide cycloaddition (CuAAC) of benzyl-azide to Phenyl-acetylene was studied by quantum mechanical calculations. Clarification of the reaction mechanism will enable more control over the synthesis process and help to obtain tailor-made products with good yields with copper-catalyzed. The feasibility of the experimentally proposed reaction mechanism was investigated by modeling the profound intermediates and the transition state structures connecting them. The efficient theory level for the investigation of a click reaction is one of the main questions considered in quantum mechanical studies.

The DFT calculations with MN12-L functional with both basis sets Def2-TZVP for Cu and Def2-SVP for other elements, combination herein shows that the cycloaddition process of the proposed copper acetylide structures with azide requires facile energies within the proposed paths to triazole synthesis. The number of metal atoms involved in the click reaction is taken into consideration. In CuAAC reaction, a comparison of mononuclear and dinuclear paths shows that the barrier for dinuclear cases is lower than that of mononuclear for (HCN, NHC) Ligands. In contrast, the dinuclear pathway was higher in energy barrier than the mononuclear pathway with (PPh$_3$).

Keywords: Azide, 1-4 Triazole, Copper, Cycloaddition, Click Chemistry.

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التحقق الميكانيكي الكمومي لآلية تفاعل تحلق الأزيدات مع الألكينات الطرفية المحفزة بالنحاس

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□ ملخّص □

تم في هذا البحث دراسة آلية التحلق أزيد–ألكين المحفز بالنحاس (CuAAC) بوساطة الحسابات الميكانيكية الكمومية. سيتيح توضيح آلية التفاعل مزيدًا من التحكم في عملية الاصطناع ويساعد في الحصول على المنتجات المطلوبة بمردود جيد باستخدام النحاس المحفز. تم التحقيق في جدوى آلية التفاعل المقترحة تجريبياً من خلال نمذجة المركبات الوسطية المحتملة وهياكل الحالات الانتقالية المرتبطة بها. يعد المستوى النظري الفعال للتحقيق في تفاعل النقر أحد الأسئلة الرئيسية التي يتم أخذها في الاعتبار في دراسات الميكانيك الكمومي.

من خلال حسابات DFT باستخدام MN12-L الوظيفية مع كلتا المجموعتين الأساسيتين Def2-TZVP لـ Cu و Def2-SVP للعناصر الأخرى، تبين أن عملية cycloaddition لهياكل أسيتيل النحاس المقترحة مع الأزيد تتطلب طاقات سهلة داخل المسارات المقترحة لتخليق التريازول. يؤخذ في الاعتبار عدد ذرات المعدن المشاركة في تفاعل النقر، حيث تُظهر مقارنة المسارات أحادية وثنائية النوى أن حاجز الطاقة للحالات الانتقالية في المسار ثنائي النوى أقل مما هو عليه في المسار أحادي النوى عند استخدام المحفزات (NHC, HCN)، ونقيضاً لذلك أدى استخدام محفز (PPh₃) إلى أن المسار الأحادي هو السائد.

الكلمات المفتاحية: أزيد، 1–4 تريازول، نحاس، Cycloaddition، كيمياء النقر.

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Introduction:

The term relative regioselectivity when used in organic chemistry refers to the inclination and preference for one direction over all other directions that can be achieved for the formation or cleavage of chemical bonds. While the term Cycloaddition reaction is a process, in which two or more systems combine to form a stable cyclic molecule. In these interactions, sigma bonds form between the terminals of the systems without eliminating of any segment, but not always occur via a concerted mechanism [1].

The copper (I)-catalyzed azide-alkyne cycloaddition (CuAAC) constitutes the paradigm of the so-called click approaches enabling the expeditious and regiospecific preparation of triazoles [2-3]. A process that largely overcomes the minuses of the uncatalyzed classical Huisgen reaction [4]. Click interaction has general ease of execution, and smooth reaction conditions, and uses environmentally friendly aqueous media. Extensive applications of this methodology to the preparation of highly functionalized and complex molecules have also transformed Scientific Research areas such as materials and pharmaceuticals [5]. Although copper-free triazole syntheses via cycloadditions of azides with cycloalkynes have been developed [6], the metal-catalyzed reaction is still the favorite protocol to promote synthetically important and selective chemical ligation that is related to differences in distortion energies than the strain released [7]. Unfortunately, the literature describes a variety of mechanisms in order to interpret experimental observations, which often cannot be easily reconciled. The reaction pathway relates to the nature of the copper intermediates involved in the reaction, the numerous proposals suggest the formation of copper acetylides caused by the enhanced reactivity of terminal alkynes after proton abstraction. While other studies indicate the possibility of copper π-complexes as intermediates.

Transition metal catalysis is one of the most powerful means available to chemists to develop more sustainable and clean processes and reactions. Protecting the metal center or modulating its activity by using different ligand families is essential to advances in this field. In this context, N-heterocyclic carbenes (NHCs) have recently gained prominence in MAAC reactions due to their outstanding binding affinities to metal centers [8], of which have contributed to a plethora of organic transformations. Triphenylphosphine is the most versatile so far. Although other phosphorous ligands have shown to be effective in AAC reactions [9]. Hydrogen cyanide [HCN] is a well-known water-like solvent and although it is not favored in experimental organic and inorganic chemistry, it serves as a good model for CH3CN in quantum chemical studies [10-11].

In the initial Mononuclear Mechanism, the three required components of a CuAAC reaction are alkyne, azide, and Cu(I). Fokin, Sharpless, and co-workers proposed a mechanism (see **Figure 1**) [12] that started with the formation of a copper (I) acetylide (**AC_L**). In step (a) the coordination of the azide partner to Cu(I) at the alkylated nitrogen results in a complex of all three components (**RC**) (**Figure 1**), which transforms into a metallacycle (**IC**) upon forming the first C–N bond in step (b), where the copper center is formally oxidized from oxidation state 11 to 13. Ring contraction follows, in conjunction with the reduction of copper (III) to copper (I), to form triazolide (**P_CuL**) as in step (c). If there is no other proton source available, the cuprous triazolide has to acquire a proton from an alkyne molecule to complete the triazole formation as in step (d). Given the high pKa of an alkyne (in the 20s), the proton exchange between triazolide and alkyne is not an easy step.
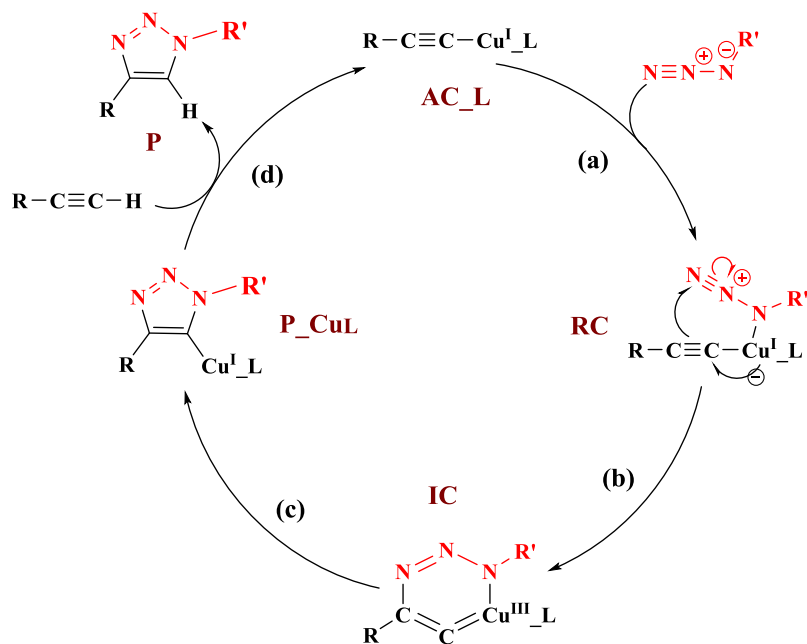
Figure 1. Suggested mononuclear catalytic cycle for Cu^I-catalyzed AAC reaction.

If there is a general base as a ligand (The "ligand" here refers to a deliberately added extra component rather than coordinating anions or solvents.) to assist with alkyne deprotonation, as depicted in (**Figure 2**) below, the kinetic burden of step (d) in (**Figure 1**) could be alleviated.
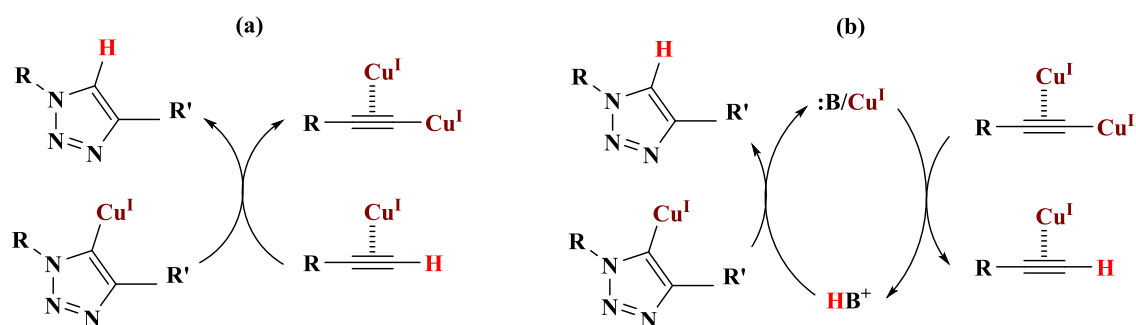

Figure 2. a) Proton transfer directly from alkyne to triazolide; b) general base-catalyzed proton transfer. B=NHC, HCN, PPh$_3$ ligand.

In the dinuclear Mechanism, **Figure 3** reflects the up-to-date understanding of the CuAAC reaction. The formation of the σ, π-di(Cu) acetylide (**Ac_L$_2$**) [13] initiates the reaction. The acetylide, which engages in both r and p bonding with Cu(I), picks up the azide in step (b) to form an azide/alkyne/copper(I) ternary complex (**RC**) [14]. Metallacycle (**IC**) formation in step (c) occurs, in which one Cu(I) is oxidized to Cu(III) [15-16]. Reductive ring contraction in step (d) follows to afford the Cu(I) triazolide (**P_L$_2$**) [17], which deprotonates an alkyne to complete the catalytic cycle in step (a). Among the four structures depicted in the catalytic cycle, both σ, π-di(Cu) acetylide (**Ac_L$_2$**) and the Cu(I) triazolide (**P_L$_2$**) have been fully characterized and verified as viable intermediates in the reaction pathway.
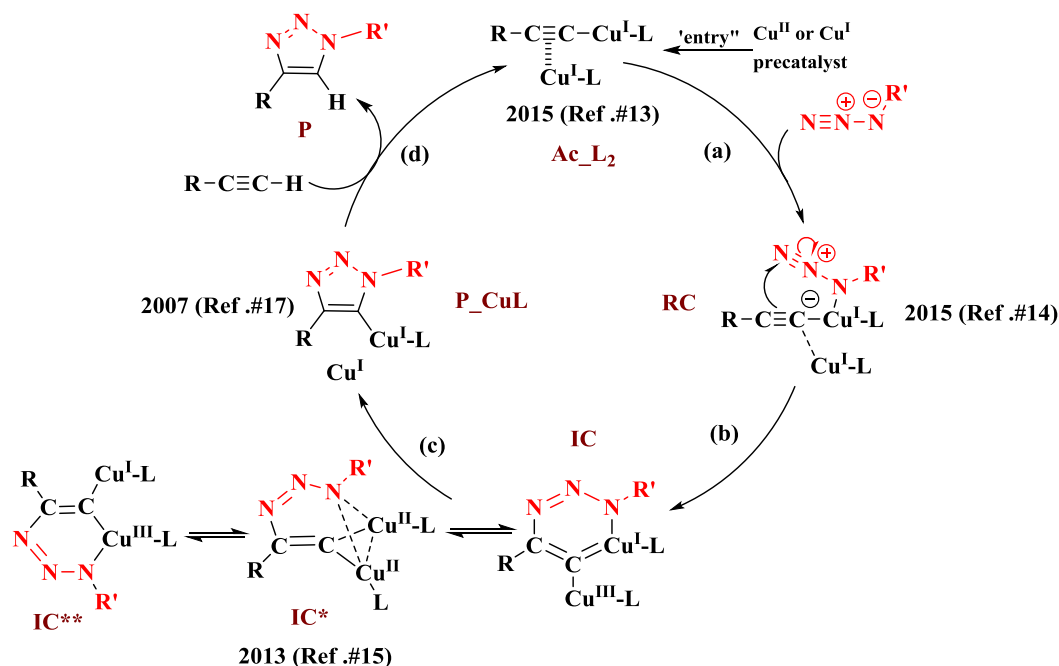
Figure 3. Suggested dinuclear catalytic cycle for Cu^I-catalyzed AAC reaction.

Computational details:

All geometries of intermediates and transition states optimized at DFT methods, exactly MN12L[18], functional with both basis sets Def2-TZVP [19] for Cu and Def2-SVP for other elements as applied in the Gaussian 16 package [20]. The MN12-L with def2-SVP (def2-TZVP for Cu) optimized geometries of all compounds and their energies (*Eo*), H*corr*, and G*corr* in the gas phase can be found in the (**supporting information**).

A preliminary benchmark calculation has been performed on a set of functionals (LC-wPBE, B3LYP, BPW91, wB97XD, MPWB1K, MPW1B95, MPW3LYP, MPWLYP1M, M05, M05-2X, M06, M06-2X, M06-L.) which have been used very frequently or reported to perform well, especially with transition metals. Even after the basis set and the functional were changed (6-31+G*, 6-31+G(d,p), LANL2DZ, LANL2TZ). It all failed to obtain optimized structures of the van der Waals complex (RC) and some transitional states for (NHC and PPh3) systems. Among them, MN12L functional has been found not only to perform well on the system of concern but also to have reasonable computational cost.

Results and Discussion:

To establish the effects of the catalysts, we studied the catalyzed CuAAC reactions of azide and alkyne based on the suggested mechanism shown in Figs 1-3, an alkyne is coordinated to the Copper in σ fashion via deprotonation of alkyne and forms a Copper (I) acetylide. After benzyl azide coordination to the metal center and the cycloaddition steps, the triazole compound has generated.

Mononuclear Mechanism:

First, the mononuclear mechanism that has been suggested in most literature was investigated, starting from Cu-acetylide with ligand (L= NHC, HCN, and PPh3) to form (**Ac_L$_1$**) (**Figure 1**). At the initial step, benzyl azide is coordinated to the silver metal (**RC**) while the terminal nitrogen atom attacks the more electropositive carbon on the alkyne to form a transitional state (**TS1**). The 6-membered metallacycle (**IC**) was formed in the

reaction pathway after the terminal carbon in the alkyne must undergo hybridization to allow the sp2-like structure to form a 6-membered metallacycle to form the triazolide complex (**P-L**) via transitional state (**TS2**) via a step-by-step fashion, that is, the related structures of the stepwise mechanism could be found (**Figure 1**). Figs. 4-6 show the optimized structures defined by the MN12-L/def2-SVP (def2-TZVP for Cu) level of theory. while Table 1 represents the selected bond lengths for the transition states computed at the same level.
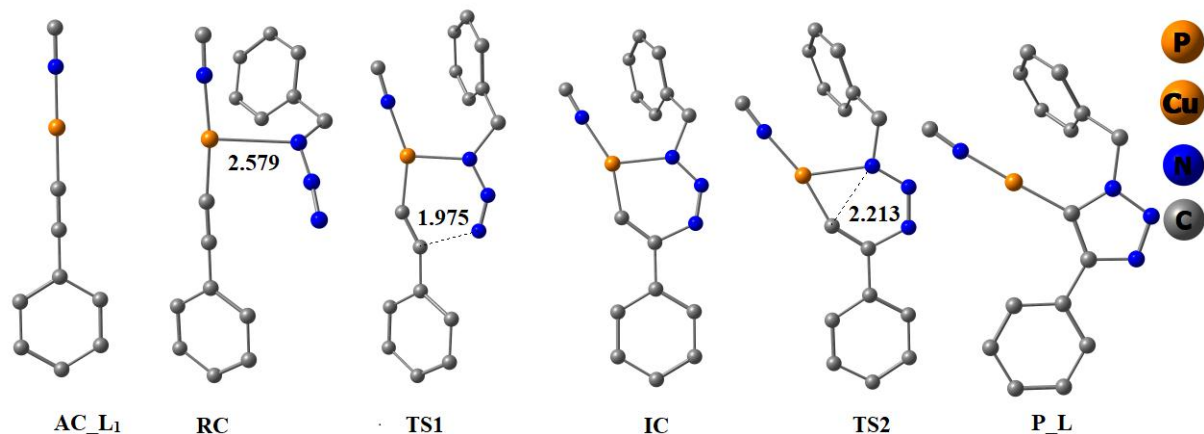

Fig. 4. MN12-L/def2-SVP (def2-TZVP for Cu) optimized structures of compounds associated with the mononuclear mechanism for (HCN) system, the hydrogen atoms are hidden to simplify the figures.
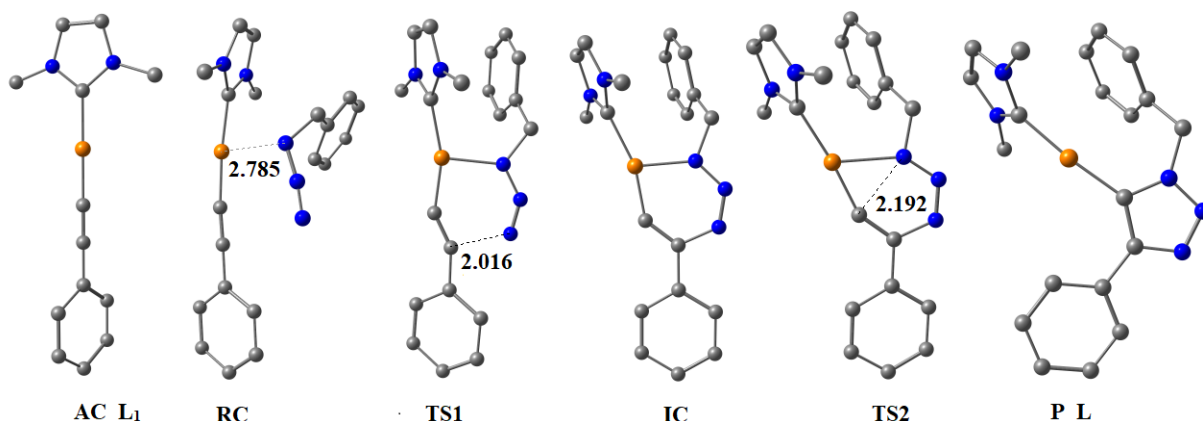

Fig. 5. MN12-L/def2-SVP (def2-TZVP for Cu) optimized structures of compounds associated with the mononuclear mechanism for (NHC) system.
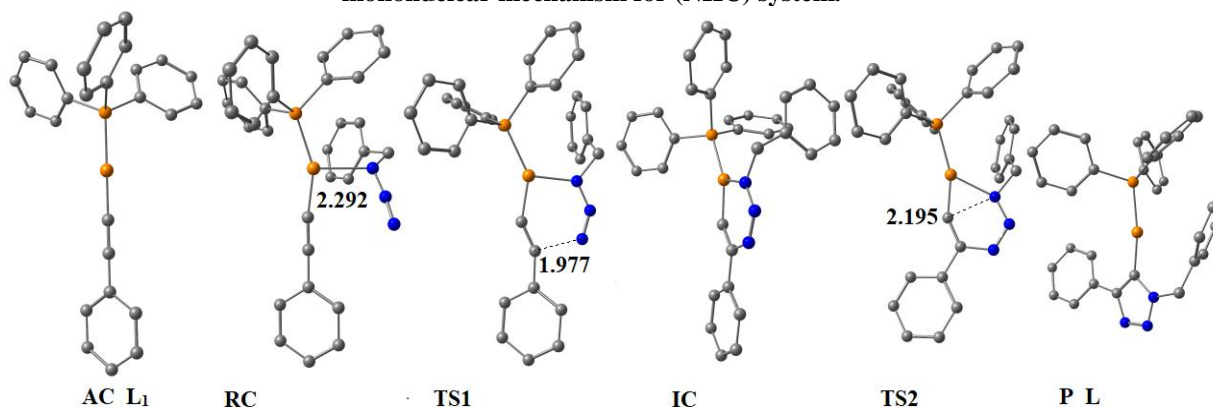

Fig. 6. MN12-L/def2-SVP (def2-TZVP for Cu) optimized structures of compounds associated with the mononuclear mechanism for (PPh₃) system.

Table 1 shows that the $C − N_{outer}$ and $Cu − N_{inerr}$ bond distance for the TS of the three systems were close to a difference of 0.03 Å for (HCN), 0.008 and 0.002 for (NHC) and (PPh$_3$), respectively, while the $C − N_{outer}$ distances in the three systems are close, reaching approximately 0.041 Å, and the $Cu − N_{inerr}$ distances, reach 0.033 Å. In addition, we noted that the MN12-L/def2-SVP (def2-TZVP for Cu) imaginary frequency value of TS (290.6i cm$^{−1}$) for (PPh$_3$) is higher than that for (HCN) and (NHC) (289.3i and 272i cm$^{−1}$) respectively.

Table 1 Selected C – N, and Cu – N distances (in Å) for transition states computed by the MN12-L/def2-SVP (def2-TZVP for Cu) level of theory and their imaginary frequency (in cm$^{−1}$) for Mononuclear Mechanism.

transition states	MN12L
TS- HCN (imag. freq.)	**289.3i**
$C − N_{outer}$	1.975
$Cu − N_{inerr}$	2.005
TS- NHC (imag. freq.)	**272i**
$C − N_{outer}$	2.016
$Cu − N_{inerr}$	2.008
TS- PPh$_3$ (imag. freq.)	**290i**
$C − N_{outer}$	1.977
$Cu − N_{inerr}$	1.975

We computed the free energy changes (ΔG298) along the reaction pathway for mechanisms of the three systems depicted in **Scheme 1**. MN12-L/def2-SVP (def2-TZVP for Cu) computational results indicate that the generation of (RC) requires Gibbs free energy of about -5.10 kcal/ mol for (PPh3) is lower than that for (HCN) and (NHC) (0.41 and 0.47 kcal/ mol) respectively.
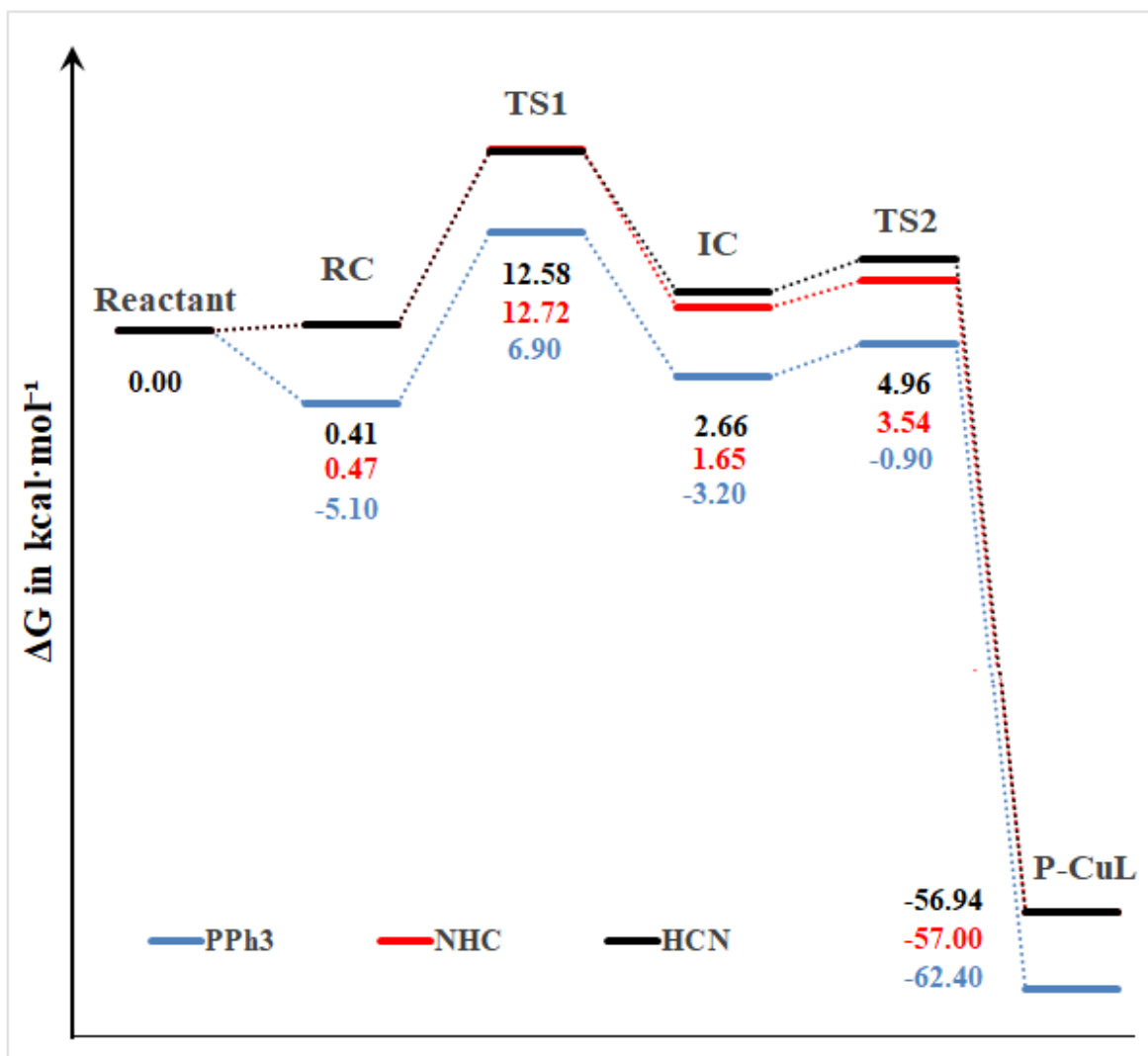
Scheme 1: Energy profile for the mononuclear CuAAC reaction path for three systems (HCN, NHC, and PPh₃) in the gas phase. By MN12-L/def2-SVP (def2-TZVP for Cu) level.

Among the transition state structures of the three systems, TS for (PPh$_3$) was the lowest in energy barrier at 6.90 kcal/mol, whereas the energy barriers of TS for (NHC) and (HCN) are very close (12.72 and 12.58 kcal/ mol) respectively. catalysts have not caused dramatic changes in structures, or charges, with a reduction in the energy barrier by the difference of 6 kcal/ mol when using phosphine catalysts.

Dinuclear Mechanism:

In this study, we were able to study the proposed dinuclear mechanism of Cu-AAC reactions based on the dinuclear mechanism of Cu-AAC copper-catalyzed reactions, starting with dinuclear Cu(I)-acetylides (**Ac_L$_2$**) as shown in **Figure 3**.

In our calculations, the Cu$_1$-Cu$_2$ distances in copper_acetylide (**Ac_L$_2$**) optimized structures defined by the MN12-L/def2-SVP (def2-TZVP for Cu) have been found as 2.519, 2.496, and 2.441 Å in (HCN, NHC, and PPh3) respectively, as shown in Figs 7-9. We also note that the Cu$_1$–Ninerr distances in the (**RC**) reactive complexes have been found as 2.104, 2.104, and 2.191 Å in (HCN, NHC, and PPh3) respectively. Which are shorter than the van der Waals radius for copper (2.8 Å) [21], and shorter than the Cu$_2$–

Ninerr distances with a difference of 2.234, 2.215, and 1.129 Å in (HCN, NHC, and PPh$_3$) respectively.
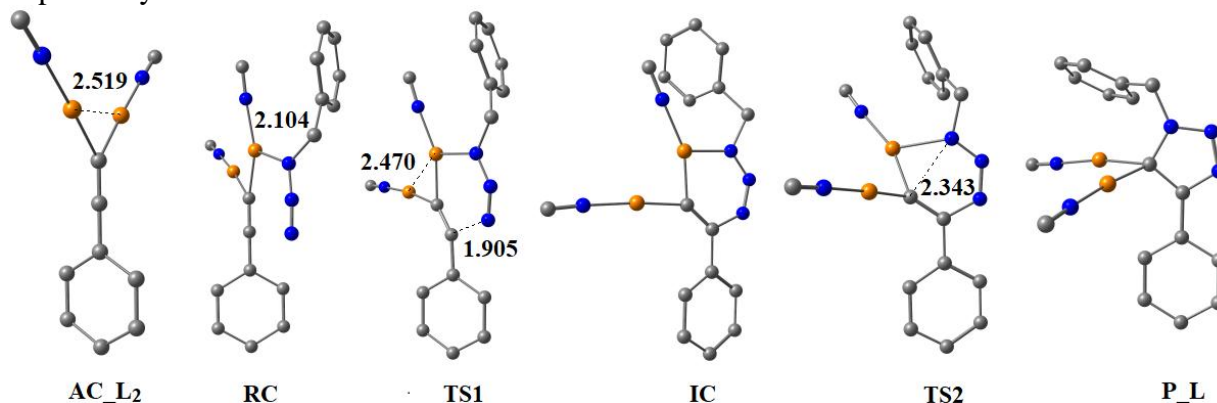

Fig. 7. MN12-L/def2-SVP (def2-TZVP for Cu) optimized structures of compounds associated with the dinuclear mechanism for (HCN) system.
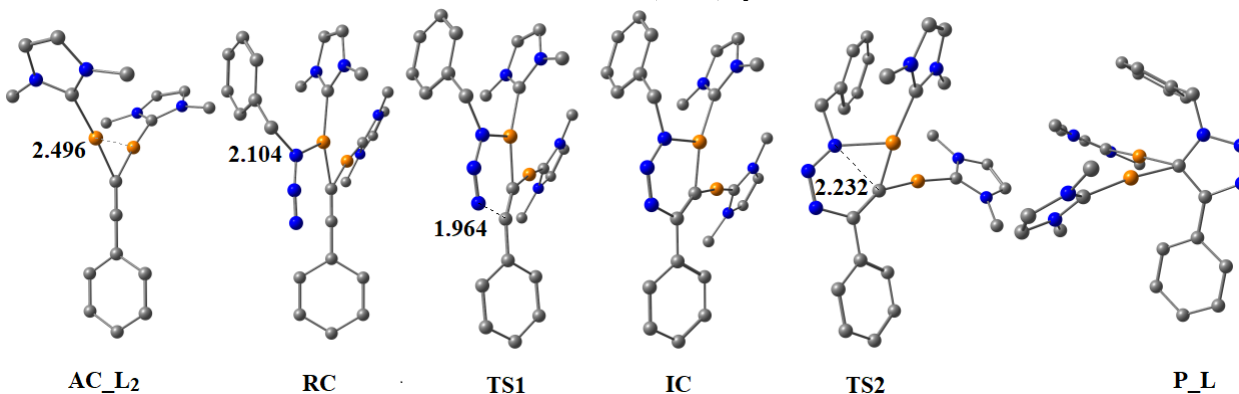

Fig. 8. MN12-L/def2-SVP (def2-TZVP for Cu) optimized structures of compounds associated with the dinuclear mechanism for (NHC) system.
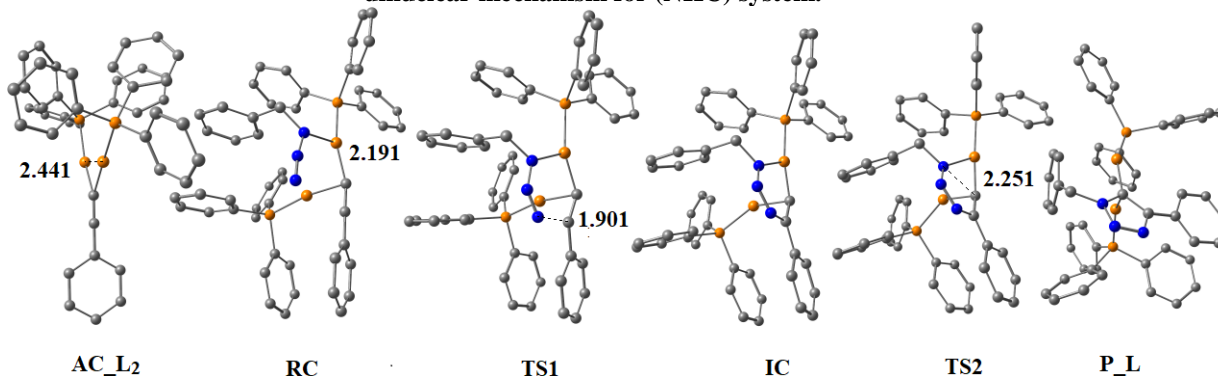

Fig. 9. MN12-L/def2-SVP (def2-TZVP for Cu) optimized structures of compounds associated with the dinuclear mechanism for (PPh3) system.

In Table 2 Cu$_1$–Cu$_2$, C–N, and Cu$_n$–N distances (in Å) of the transition states (**TSs**) have been listed, found that the C − N$_{outer}$ and Cu1 − N$_{inerr}$ bond distance for **TS** in the three systems were close to a difference of (0.07, 0.01, and 0.088 Å) for (HCN, NHC, and PPh3) respectively. While the C–N$_{outer}$ distances in the three systems are close and the highest value was 1.964 Å for (NHC). While the highest value of Cu$_1$− N$_{inerr}$ was 1.989 Å for (PPh3). Moreover, the MN12-L/def2-SVP (def2-TZVP for Cu) imaginary frequency value of TS (395.9**i** cm^{-1}) for (HCN) is higher than that for (NHC) and (PPh$_3$) (350.5**i** and 393.3**i** cm^{-1}) respectively.

Table 2 Selected C – N, and Cu – N distances (in Å) for transition states computed by the MN12-L/def2-SVP (def2-TZVP for Cu) level of theory and their imaginary frequency (in cm^{-1}). for dinuclear Mechanism.

transition states	MN12L
TS- HCN (imag. freq.)	**395.9i**
$C - N_{outer}$	1.905
$Cu_1 - N_{inerr}$	1.975
$Cu_2 - N_{inerr}$	4.209
$Cu_1 - Cu_2$	2.470
TS- NHC (imag. freq.)	**350.5i**
$C - N_{outer}$	1.964
$Cu_1 - N_{inerr}$	1.954
$Cu_2 - N_{inerr}$	4.169
$Cu_1 - Cu_2$	2.425
TS- PPh$_3$ (imag. freq.)	**393.2i**
$C - N_{outer}$	1.901
$Cu_1 - N_{inerr}$	1.989
$Cu_2 - N_{inerr}$	3.118
$Cu_1 - Cu_2$	2.639

The energy profiles of the reaction pathways associated with the CuAAC reactions are represented in **Scheme 2**. The species involved in the reaction paths have similar relative energies, indicating that the substitution of the coordinated ligands at the di-copper (I) produces a slight change. The first step of the dinuclear CuAAC consists of the formation of mononuclear Cu (I)-acetylide (**Ac-L$_1$**). Then subsequent coordination of the C-Cu carbon atom in (**Ac_L$_1$**) to a second copper (I) center yields (**Ac_L$_2$**) dinuclear. Thus, the coordination of benzyl azide to a copper (I) cation in (**Ac_L$_2$**) via its azide N-inert nitrogen atom permits the formation of the reactive **RC** complex. MN12-L/def2-SVP (def2-TZVP for Cu) computational results indicate that the generation of (**RC**) requires Gibbs free energy of about -9.01 kcal/ mol for (HCN) is lower than that for (NHC) and PPh$_3$ (-4.61 and -3.90 kcal/ mol) respectively. Among the transition state structures of the three systems, (TS) for (PPh$_3$) was the highest energy barrier at 14.50 kcal/mol, while the (TS) for (NHC) and (HCN) was an energy barrier at 7.86 and 7.33 kcal/mol respectively.
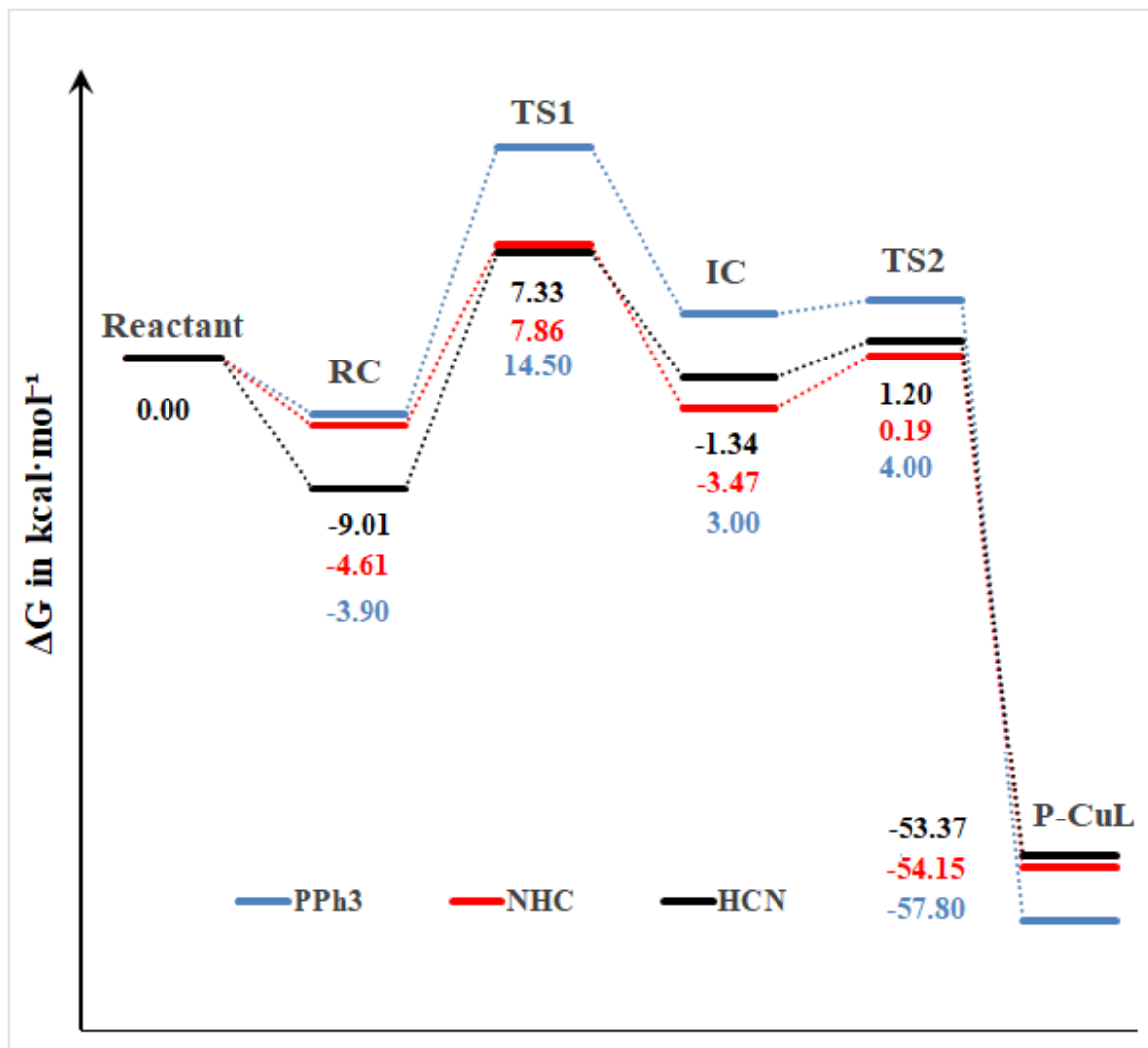
Scheme 2: Energy profile for the dinuclear CuAAC reaction path for three systems (HCN, NHC, and PPh₃) in the gas phase. By MN12-L/def2-SVP (def2-TZVP for Cu) level.

Conclusions and Recommendations:

In this work, the detailed mechanisms for copper-catalyzed alkyne-azide cycloaddition (CuAAC) of benzyl-azide to Phenyl-acetylene have been investigated for the first time with quantum mechanical calculations at DFT methods; exactly MN12-L functionals with def2-SVP (def2-TZVP for Cu) basis set in the gas phase (see Supporting Information). In quantum mechanical studies, the number of metal atoms involved in the click reaction is taken into consideration. Based on the experimental proposal and the general CuAAC pathway, we have studied the CuAAC mono and dinuclear paths. Generally, the cycloaddition process of the proposed copper acetylide structures with azide requires facile energies within the proposed paths. In CuAAC reaction, a comparison of mono and dinuclear paths shows that the energies barriers for dinuclear are lower than that of mononuclear by 4.86 and 5.25 kcal/mol with (NHC) and (HCN) respectively. In contrast, the dinuclear pathway was higher in energy barrier than the mononuclear pathway by 7.6 kcal/mol with (PPh₃).

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