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Reaction Mechanisms of Transition-Metal-Catalyzed
Azide-Alkyne Cycloaddition “Click” Reactions: A DFT
Investigation

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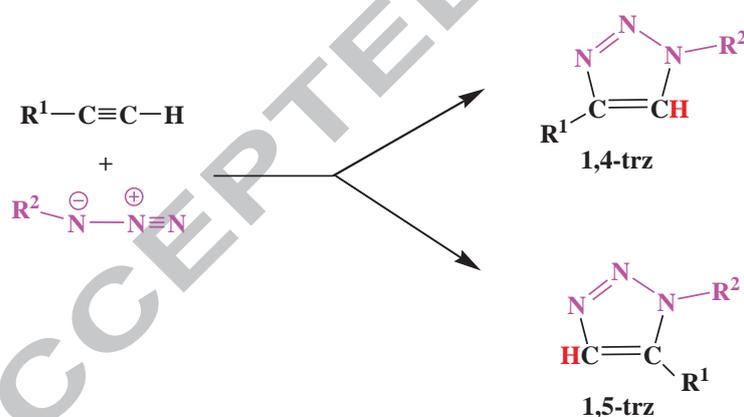
Abstract

DFT calculations at the PBE0/LANL2DZ level have been performed on model compounds to investigate the reaction mechanism of two recently reported metal-catalyzed alkyne azide cycloaddition (MAAC). The first one, that involves a $[\text{Cu}(\text{tren})]^+\text{Br}^-$ catalyst, is shown not to proceed through a metal alkynyl intermediate, but, after precomplexation of the alkyne in an η^2 -mode, directly to the 1,4-disubstituted 1,2,3-triazole product, through a metallacyclic transition state. The other system, involving a rare-earth $\text{Ln}[\text{N}(\text{SiMe}_3)_2]_3$ complex, is found to proceed through an alkynyl-azide complex which produces an η^2 -coordinated heterocyclic ligand before protonation by an incoming alkyne molecule. Our results are discussed with respect to other computational data from the literature.

1. Introduction

Sharpless' concept of "click" chemistry involving facile and sustainable bond linkage between molecular fragments has considerably enriched molecular chemistry. [1] The most common click reaction is the copper-catalyzed alkyne azide cycloaddition (AAC) discovered by both the Sharpless-Fokin [2] and the Meldal group [3] in 2002. This useful reaction is a mild, catalytic and selective version of the Huisgen reaction. [4]. Whereas the Huisgen AAC reaction produces 1,4-disubstituted 1,2,3-triazoles (trz) and their 1,5 isomers (Scheme 1), the Cu-catalyzed AAC (CuAAC) selectively forms the 1,4 isomer [2, 3, 5, 6]. Later, the Fokin group has reported Ru catalysis of the AAC reaction (RuAAC) of the formation of the 1,5 isomer [7]. Then some copper complexes with *N*-heterocyclic carbene ligands were shown by Nolan's group to also catalyze the formation of the 1,5 disubstituted isomer [8]. Finally catalysis of the AAC reactions was conducted using various other metals such as Ir [9], Ag [10, 11], Au [12], Zn [12, 13, 14], and lanthanides [15].

Owing to the huge impact of the MAAC reactions in molecular engineering and organic synthesis, the elucidation of their mechanisms is of primary importance and from this point of view the contribution of theoretical investigations has been particularly fruitful [16-27]. In this paper we owe to contribute, with the help of density functional theory (DFT) calculations, to the understanding of some MAAC reaction mechanisms that had been postulated and compare the conclusions with some earlier results on related systems.



Scheme 1: Huisgen's AAC reaction

2. Computational details

DFT calculations were carried out with the Gaussian 09 program [28], using the PBE0 functional [29-31] and the LANL2DZ basis set [32-35] for all atoms. This basis set was augmented by the corresponding Ahlrichs-type polarization functions except for yttrium. In the case of yttrium we used another Ahlrich-type polarization function taken from the EMSL Basis Set Exchange Library [36]. In order to save computational efforts, the investigated system was simplified in considering the

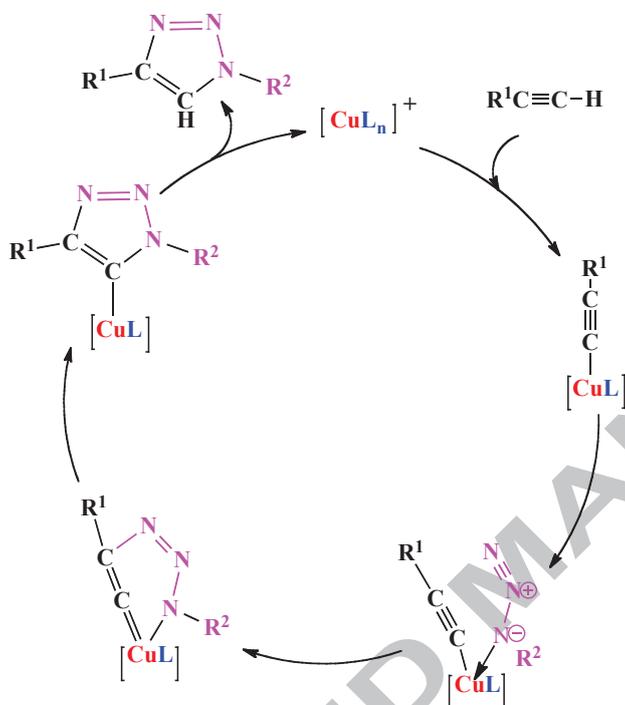
substituents on the azide and alkyne reactants to be hydrogen, unless specified in the text. Whereas this approximation lowers the quantitative level of the computed numbers, it does not prevent full quantitative comparison between different mechanisms, and it allows investigating large numbers of spatial configurations with full geometry optimizations and associated (harmonic) vibrational frequency calculations to ascertain the nature of the stationary points on the energy hypersurface. Solvation effects and dispersion forces were not considered in our calculations since they are likely to be different from that of the real compounds. However, from the literature covering the theoretical aspects of MAAC click mechanisms, one can reasonably assume that these effects are not crucial parameters for such very general reactions [17, 27, 29] which experimentally work for families of reacting compounds. Nevertheless, we have performed PCM [37] test calculations of solvation effects (with water as solvent) on the mechanism in Figure 1. The inclusion of solvent effect was found to lower the activation energy by less than 1 kcal/mol. The default convergence cutoffs were considered in all the calculations. The Synchronous Transit-Guided Quasi-Newton (STQN) method [38, 39] was used with the QST2 option for the search of transition states and intrinsic reaction coordinate (IRC) calculations [40, 41] were performed to ascertain that each computed transition state connects with the proper reactants and products. Reported free energies refer to reactions at 298.15 K and 1 atm. Natural population analysis (NPA) were performed with the NBO 5.0 program [42].

3. Results and discussion

The mechanism of the CuAAC reaction when catalyzed by classical Sharpless-type catalysts (Cu(I) in the presence of water and nitrogenous ligands) has been extensively investigated, both experimentally and theoretically [2,3,5,6,16-21]. The usually admitted general mononuclear mechanism [16] is sketched in Scheme 2. It involves the formation of an alkynyl complex, followed by azide coordination and subsequent formation of a 6-membered metallacycle. Subsequent investigations [18,19, 43] have shown that this mechanism involves a second metal center that lowers the activation energies in coordinating the carbon-carbon bond all along the metallacycle formation.

Recently, one of us developed the new [Cu(hexabenzyl)tren][Br] (tren = tris(2-aminoethyl)amine) catalyst [44, 45], that is easy to synthesize, soluble and extremely efficient, even in part-per-million amounts when it is used together with a catalytic amount of a dendritic unimolecular micelle [46]. Experimental evidences for a monometallic process, due to the bulky environment of the catalyst at the center of a large dendrimer have been established. Two different mechanisms were originally suggested [44], one corresponding to a “classical” attack of the azide on the metal prior to the metallacycle formation (as in Scheme 2) and the other one involving a direct attack of the azide on the α -alkynyl carbon. Both hypothetical mechanisms are given in Figure 1. We have theoretically investigated these mechanisms through DFT

calculations on the simplified system composed of acetylene, hydrogen azide and $[\text{Cu}(\text{tren})]^+$ with $\text{tren} = \text{N}(\text{N}-\text{CH}_2-\text{CH}_2-\text{NH}_2)_3$.



Scheme 2: General reaction mechanism of the reaction CuAAC (adapted from ref. 42).

The computed energy profiles of the two mechanisms of Figure 1 are shown in Figure 2. The one involving a direct attack of the azide on the α -alkynyl carbon is shown in black color. The optimized geometries of the transition states are shown in Figure 3. The starting $[\text{Cu}(\text{tren})]^+$ catalyst is a strained tetracoordinated 18-electron species [46, 47], with two fairly different computed N-H bond distances (2.107 Å (equatorial) and 2.228 Å (axial)). It spontaneously coordinates to the alkyne with concomitant decoordination of one of the equatorial nitrogen atoms, leading to an η^2 -alkyne complex. No transition state could be identified for its formation which proceeds through a very flat energy surface. This alkyne complex **R** is chosen as the starting reactant in Figure 2. The next step is a concerted exchange of Cu-N bonds leading to the **I1** isomer in which one equatorial nitrogen atom is decoordinated to the profit of the axial one. The formation of the key alkynyl intermediate **I2** by the transfer of a proton on the decoordinated nitrogen atom requires moderate activation energy (14.1 kcal/mol above **R**), through a transition state lying almost at the same energy that **I2**. It is noteworthy that the proton does not go onto the central nitrogen of the tren ligand, as initially suggested [44] (see Figure 1), but onto one of the terminal nitrogen atoms that are more negatively charged (-0.99 vs. -0.64; from natural

population analysis). As a matter of fact, proton addition onto the central tren nitrogen atom would require a free energy barrier of 32.4 kcal/mol above the reactants. The rate-determining step is computed to have a free energy barrier of 36.7 kcal/mol above the reactants, corresponding to the attack of the azide on the α -alkynyl carbon and the formation of the heterocyclic complex intermediate **I3**. The last step (proton transfer onto the heterocycle and decoordination of the 1,4-trz) is found to have a transition state (**TS3**) energy calculated to be slightly lower than its **I3** reactant. Such an unphysical result is an artifact due to computational accuracy limits, likely those related to the harmonic approximation in vibrational frequency calculations. It is characteristic of a strongly exothermic reaction with extremely low activation barrier [48].

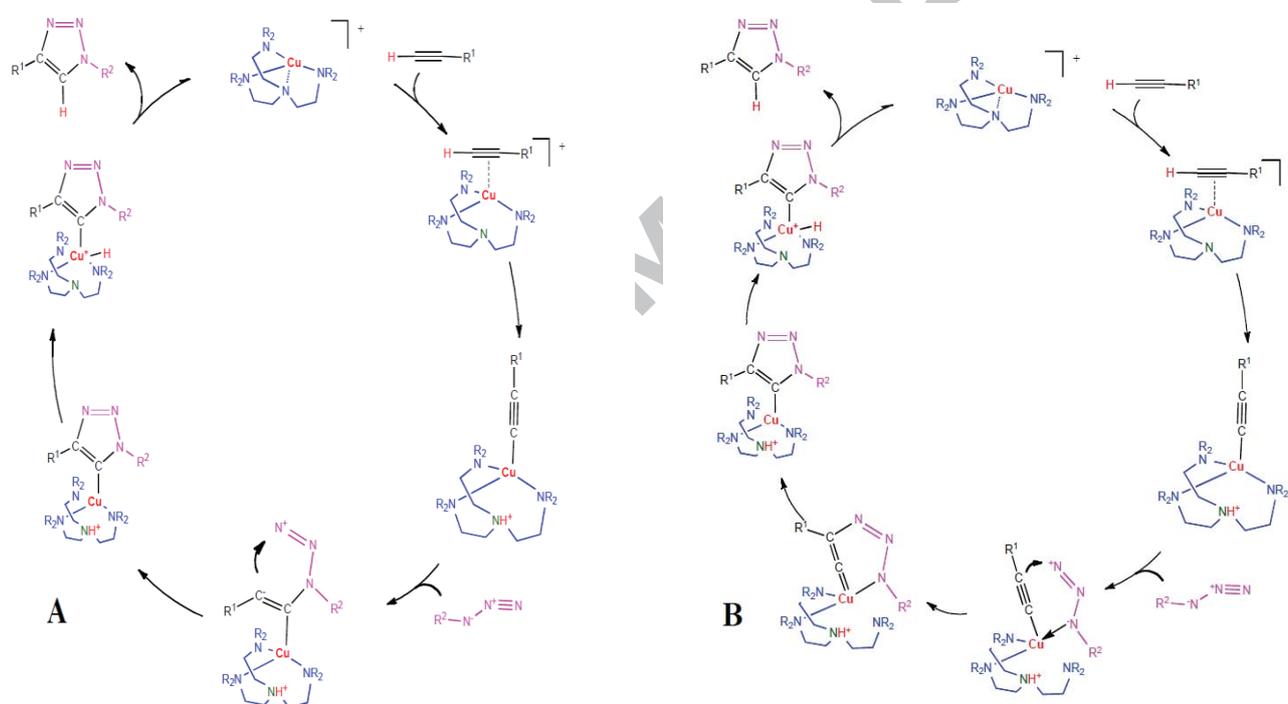


Figure 1. The two possible mechanisms that were suggested in ref. 42, for CuAAC reactions catalyzed by [Cu(tren)]⁺. A: Direct attack of the azide on the α -alkynyl carbon. B: Azide attack on the metal (Fokin-type mechanism).

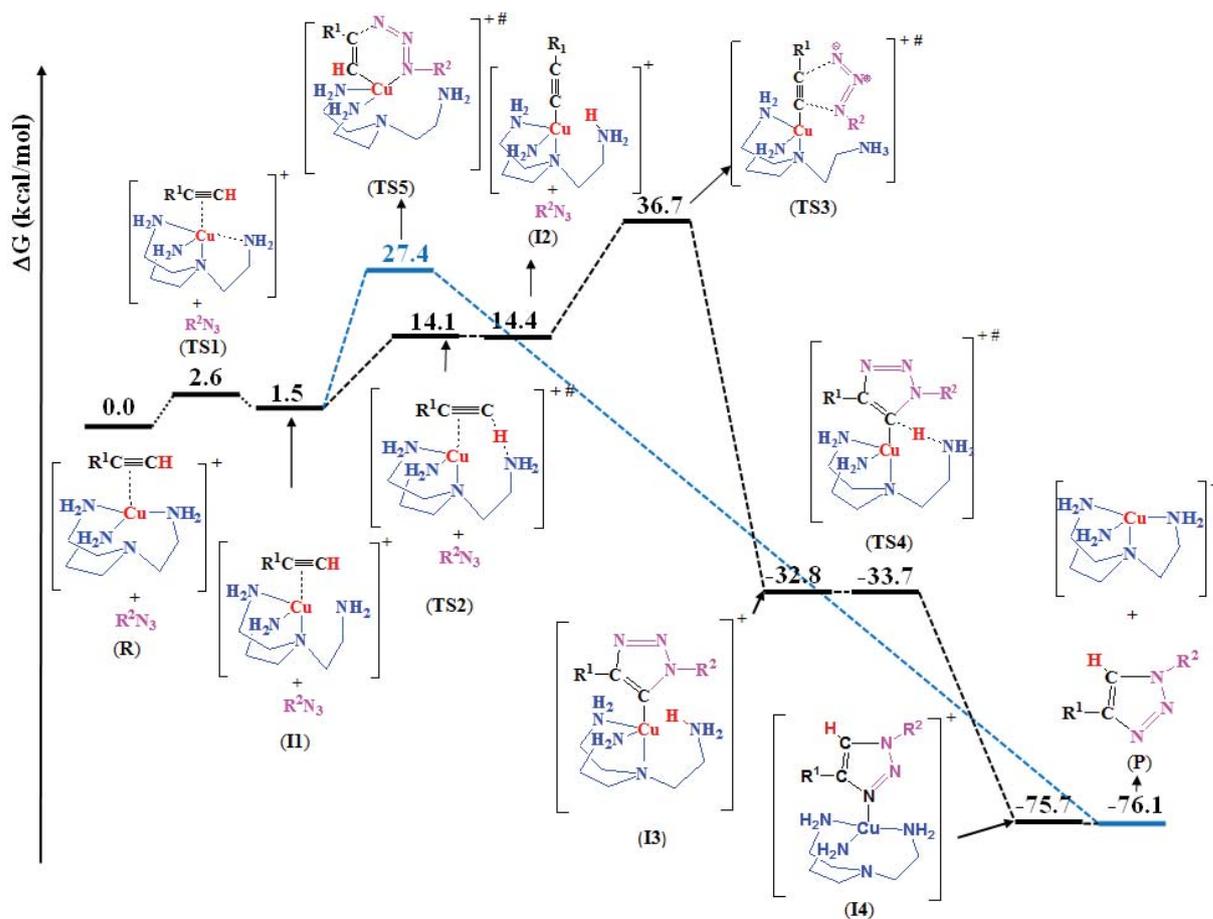


Figure 2. Computed free energy profiles for the two investigated mechanisms of the CuAAC reaction catalyzed by $[\text{Cu}(\text{tren})]^+$ ($\text{R}^1 = \text{R}^2 = \text{H}$). In black: direct attack of the azide on the α -alkynyl carbon. In blue: attack of the azide on the metal.

When looking for a pathway related to mechanism B in Figure 1, *i.e.*, a direct attack of the azide on the copper center of the alkyne intermediate **I2**, only the attack on the α -alkynyl carbon was found to occur. In fact, the metal attack of the azide was found to take place on the η^2 -alkyne intermediate **I1**. The corresponding mechanism is sketched in blue in Figure 2. The azide attack directly leads to the final products of the reaction through a metallacyclic transition state (**TS5**, see Figure 3). The global free energy barrier (27.4 kcal/mol) is 9.3 kcal/mol lower than that of mechanism A, indicating that the privileged pathway involves the attack of the azide directly on the metal center. Thus the possibility for a mechanism of type A (Figure 1) is unlikely, at least within regular experimental conditions.

An NBO analysis [41] indicates important ionic character of the copper-ligand bonds in the stationary points of Figure 2 which are all consistent with one major Lewis structure exhibiting an isolated Cu^+ ion. In **I1** for example, the Cu-N and Cu-C average natural bond orders computed within the Natural Resonance Theory (NRT) framework are found to be 97% and 95% ionic for rather low total values of 0.024 and 0.058, respectively. Despite of the weak covalent character of Cu(I), it is worth noting that the metal maintains its 18-electron configuration all along along the

low-energy pathway. This is consistent with significant second-order interaction energies between ligand lone pairs and accepting localized copper orbitals. For example in **II**, the interaction energies involving the nitrogen lone pairs and the C-C σ -bonding pair are 21 kcal/mol and 16 kcal/mol, respectively. From NRT analysis, the low-energy transition state **TS5** is found best described by a single Lewis structure as drawn in Figure 2, but neglecting the dotted lines and Cu-ligand bonds.

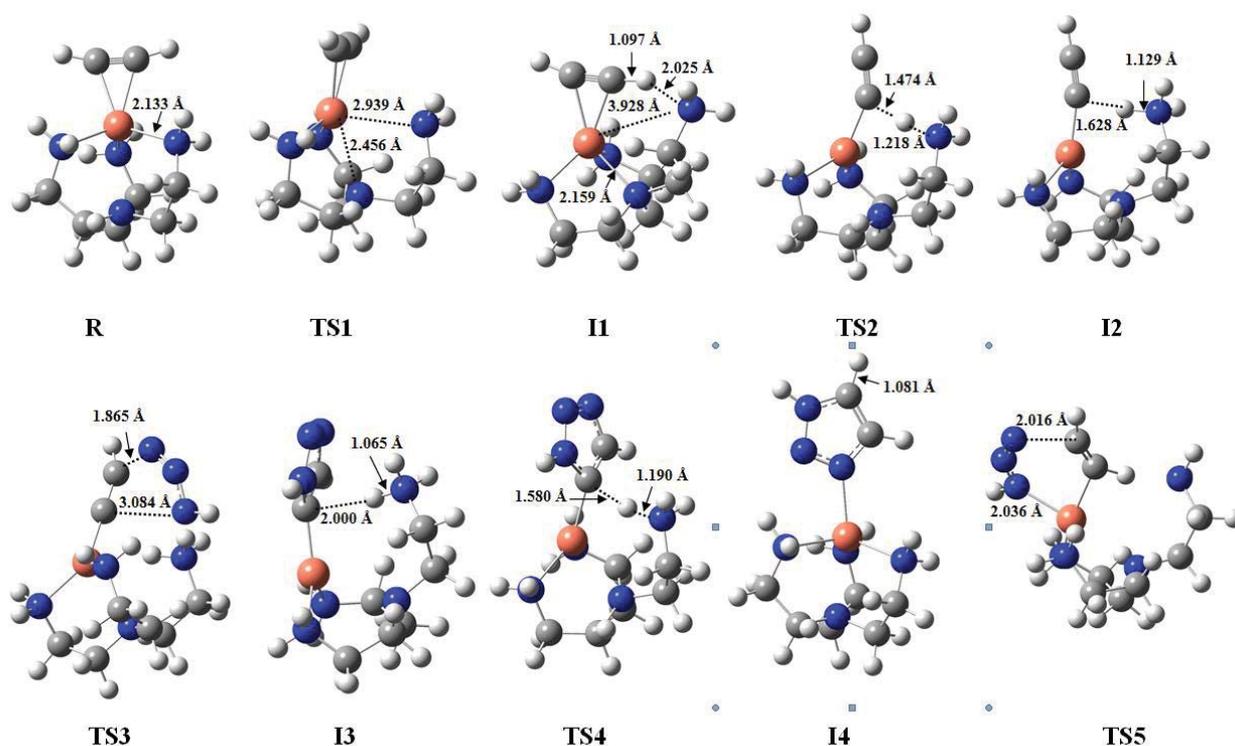


Figure 3. Structures of the stationary points involved in the two mechanisms of Figure 2.

Recently, Zhou and coworkers published the first example of rare-earth catalyzed cycloadditions between terminal alkynes and terminal azides, resulting in the formation of 1,5-disubstituted 1,2,3-triazoles. [15] The catalytic systems that they used consist in a complex of the type $\text{Ln}[\text{N}(\text{SiMe}_3)_2]$ (Ln, Y, Nd, Sm, Gd) in the presence of $n\text{-BuNH}_2$. This report incited us to computationally explore their proposed mechanism of Figure 4, using the same modelization approach as used above and considering the $\text{Y}[\text{N}(\text{SiH}_3)_2]_3$ (YL_3) simplified precatalyst. The induction part of the mechanism (path **a** in the left side of Figure 4b), which corresponds to the formation of an alkynyl intermediate and a protonated ligand, is computed to proceed through the formation of a weakly bonded (η^2 -alkyne) complex of $\text{Y}[\text{N}(\text{SiH}_3)_2]_3$ intermediate (Figure 5). In the reaction product, the protonated ligand (LH) is still somewhat bonded to the alkynyl complex. Its full decoordination brings the total free energy of the system 2.7 kcal/mol above the starting reactants. The overall free energy barrier, that is associated to the transfer of the alkyne proton on the ligand, is rather low (11.1 kcal/mol). Assuming that the protonated ligand is easily displaced by the

incoming azide, we have investigated the **B** to **E** transit as proposed by Zhou and coworkers [15] (see Figure 4b). No low-energy pathway connecting **B** to **D** was found. On the other side, the optimization of **C** led to a somewhat different structure in which the metal is bonded only to the nitrogen atom. Nevertheless, no low-energy pathway could be found connecting **B** to this species. Rather, a single step was found connecting **B** to **E** (Figure 6). In a last step (path a in Figure 4b), the **E** intermediate adds an entering alkyne molecule giving rise to the acetylide-indazole complex that can release 1, 5-indazole and the reacting species to **A**, thus closing the catalytic cycle. The rate-determining step is the one connecting **B** to **E**, with a transition state that is situated 10.1 kcal/mol above **B**. These results confirm the proposed mechanism of Zhou and coworkers (path a in Figure 4b), apart from the **B** to **E** pathway that is computed to be a single step process.

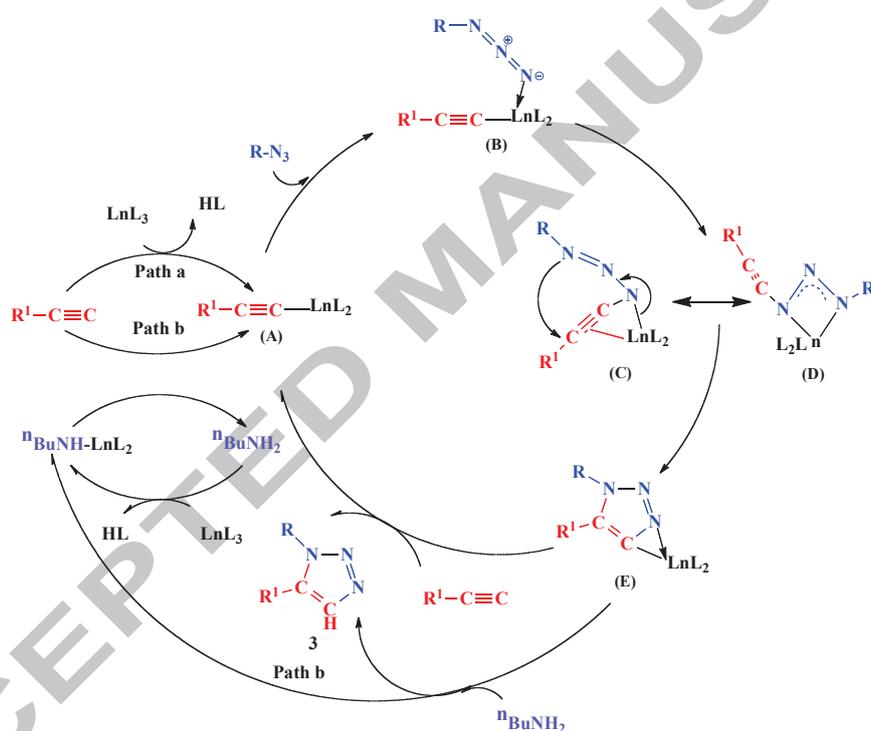


Figure 4. Reaction pathway for the $\text{Ln}[\text{N}(\text{SiMe}_3)_2]_3$ -catalyzed cycloaddition between terminal alkynes and azides ($\text{L} = \text{N}(\text{SiMe}_3)_2$; adapted from ref. 15).

As we were writing this manuscript, a computational investigation by Li and coworkers of the same catalytic process was published [49]. Their DFT calculations were performed considering the $\text{L}_2\text{Sm}(\text{CCPh})$ pre-catalyst model ($\text{L} = \text{acetylide}$) and benzyl azide. The results are at variance from ours since their **B** intermediate was found to lead directly to the formation of an η^1 complex of the (not observed) 1,4-trz isomer. Rather, they found that the observed 1,5 isomer was produced from the formation of a **B'** intermediate resulting from the azide coordination on $\text{L}_2\text{Sm}(\text{CCPh})$ through its substituted nitrogen atom. Our calculation found that this pathway leads only to the formation of the 1,4-trz isomer (Figure 8) through a mechanism that is

similar to that of Figure 6, but with a higher energy barrier. The differences between our results and those of Li and coworkers may originate from the different types of modelizations that are used in both studies. Model systems considering various substituted alkynes and azides, but still with the $\text{Ln}[\text{N}(\text{SiH}_3)_2]_3$ ($\text{Ln} = \text{Y}, \text{Sm}$) precatalyst, will be the object of future investigations in our group.

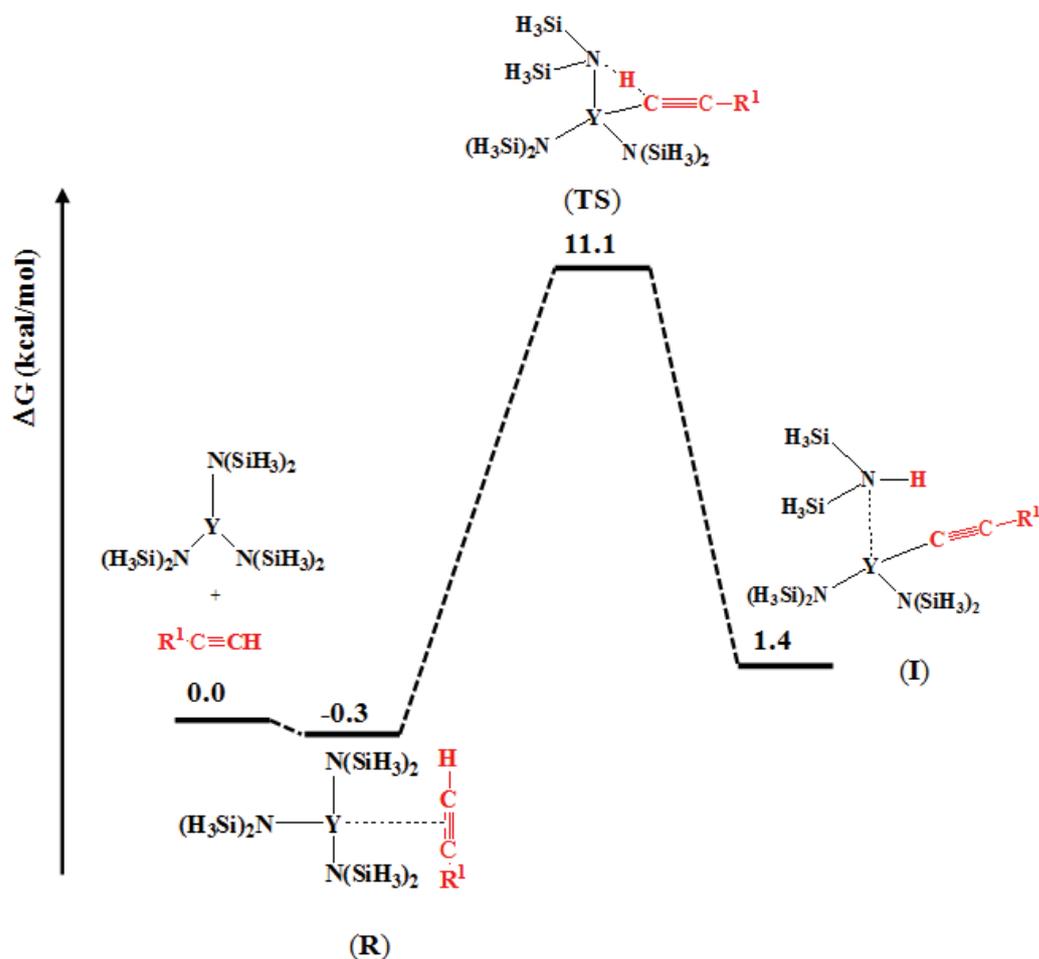


Figure 5. Computed free energy profile for the pathway associated with the formation of the R^1CCYL_2 catalyst from the YL_3 pre-catalyst in the presence of R^1CCH ($\text{R}^1 = \text{H}$) (see ref. 15).

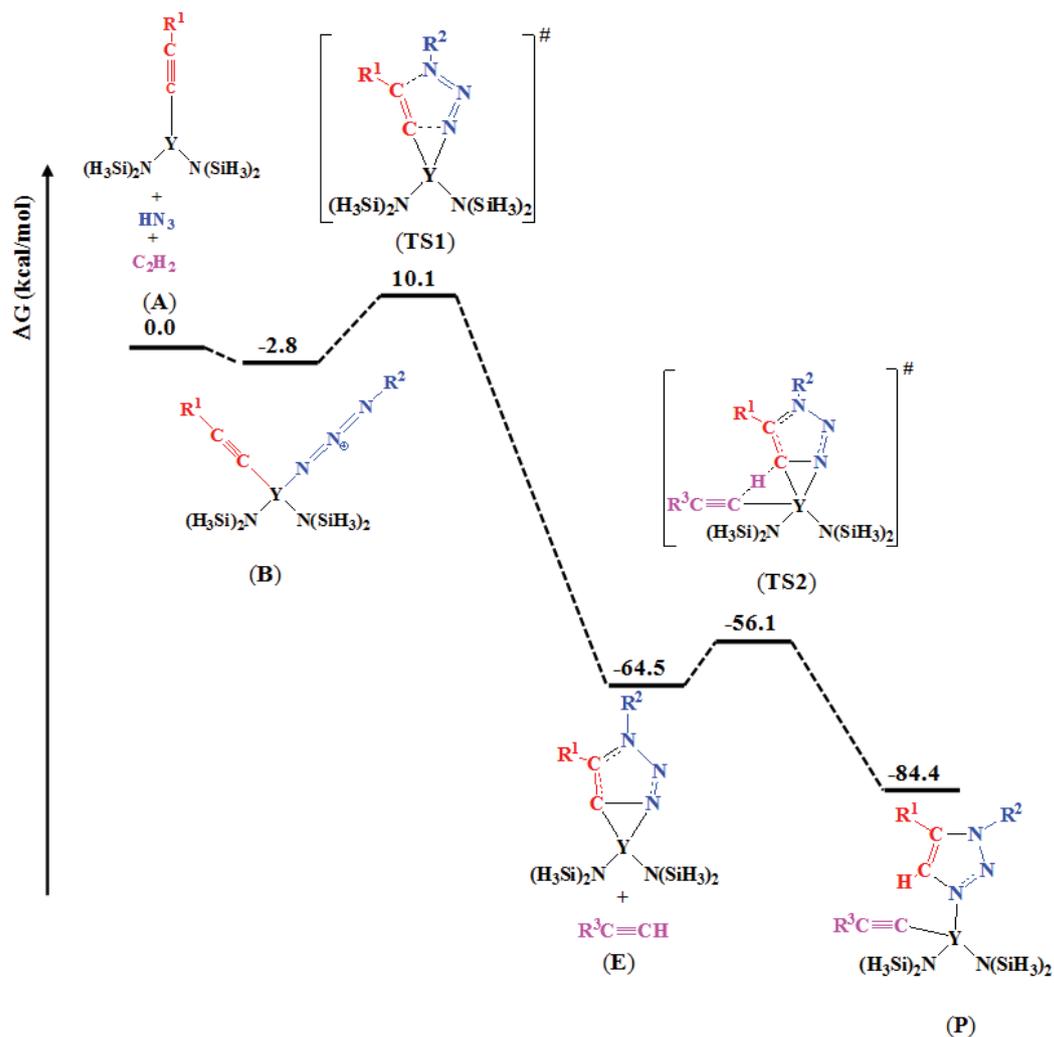


Figure 6. Computed free energy profile for the mechanism of the formation of 1,5-trz catalyzed by a rare-earth complex, as reported in ref. 15 ($R^1 = R^2 = H$). Structures of the corresponding stationary points are shown in Figure 7.

The NBO analysis [41] of the stationary points of Figures 5, 6 and 8 is consistent with a more covalent character of yttrium(III), as compared to Cu(I) (see above). All the computed minima can be described with one major Lewis structure exhibiting Y-N and/or Y-C bonding pairs and consistently with corresponding NRT-computed natural bond orders equal or close to 1, with corresponding yttrium natural atomic valencies equal or close to 3 or 4. Obviously, in these reactions the metal tends to maintain a stable tri- or tetra-coordination mode. Another stabilizing effect which is present in all the computed stationary points is the donation from σ -type bonding pairs of the N(SiH₃)₂ substituents into unoccupied metal π -type orbitals. Corresponding computed second-order interaction energy terms lie in the range 10-20 kcal/mol. Thus the nature of the ligand is also an important factor for providing low-energy reaction pathways.

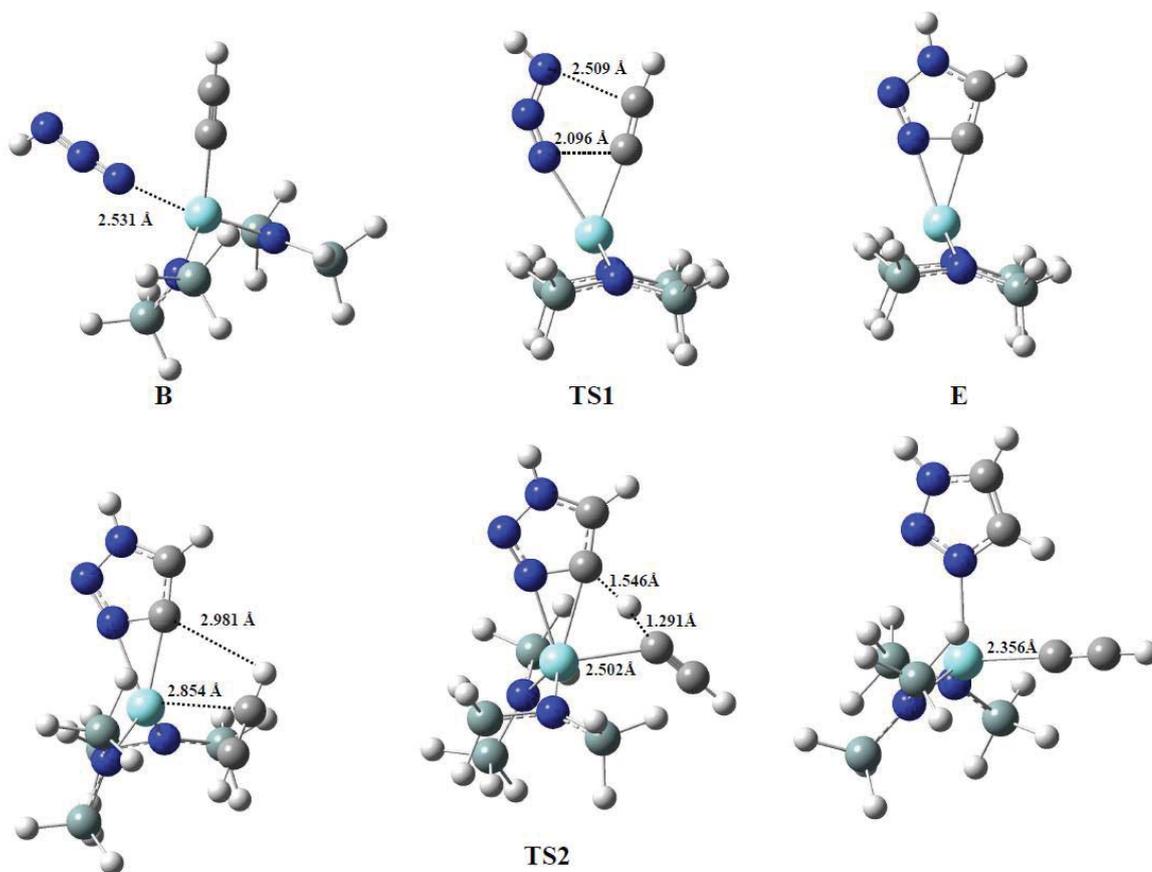


Figure 7. Structures of the stationary points involved in the mechanism of Figure 6.

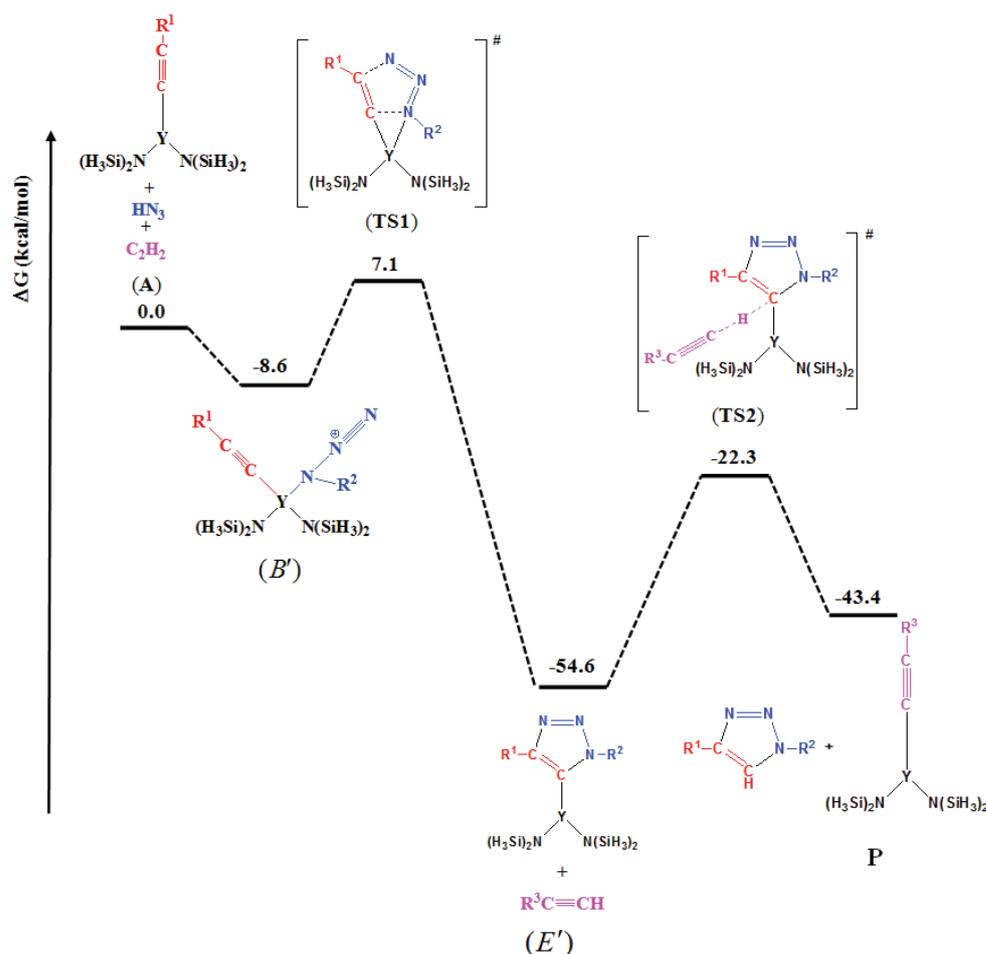


Figure 8. Computed free energy profile for the mechanism of the formation of 1,4-triazole catalyzed by a rare-earth complex, as reported in ref. 15 ($R^1 = R^2 = H$).

4. Conclusion

In summary we have investigated at the PBE0/LANL2DZ level two recently described click MAAC reactions producing 1,2,3-triazoles. The first one is a mononuclear CuAAC reaction catalyzed by a $[\text{Cu}(\text{tren})]^+\text{Br}^-$ complex [43]. Calculations show that none of the two mechanisms that were *a priori* postulated, and that both presuppose a metal alkynyl intermediate, is the lowest energy pathway. The most favorable mechanism involves a direct attack of the azide on a η^2 -alkyne intermediate complex, directly leading to the 1,4-triazole isomer. The other type of investigated system involves the rare earth $\text{Ln}[\text{N}(\text{SiMe}_3)_2]$ (Ln , Y, Nd, Sm, Gd) system that catalyzes the formation of 1,5-disubstituted 1,2,3-triazoles in the presence of a base [15]. Our model calculations that consider the $\text{Y}[\text{N}(\text{SiH}_3)_2]_3$ acetylene and hydrogen azide system involve the formation of a key alkynyl azido intermediate that directly isomerizes in a triazolyl η^2 complex that after protonation liberates the trz.

Our results are somewhat different from those of Li and coworkers [49] who used a different modelization approach. Further investigations on this type of rare-earth catalyzed AAC reaction are underway in our group to understand these differences.

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ACCEPTED MANUSCRIPT

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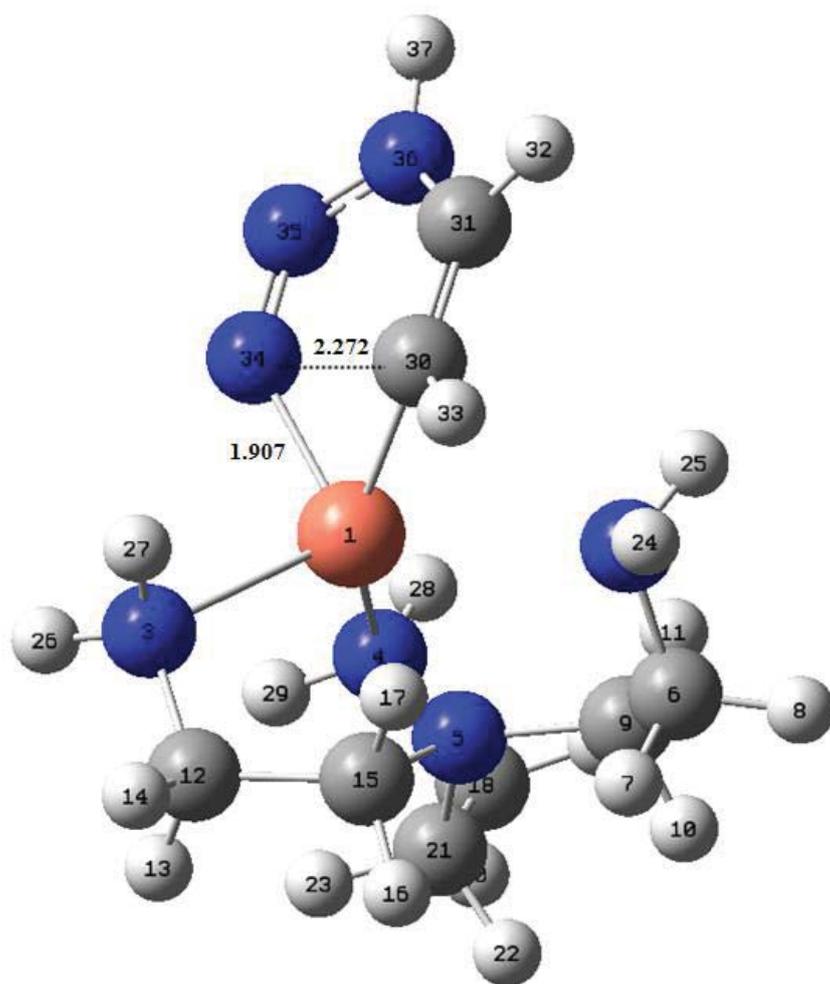
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Graphical abstract



Highlights

Two MAAC reaction mechanisms have been investigated by DFT calculations.

The $[\text{Cu}(\text{tren})]^+$ catalyzed pathway involves a direct azide attack on a copper alkyne intermediate.

The $\text{Y}[\text{N}(\text{SiH}_3)_2]_3$ catalyzed pathway involves the formation of a key alkynyl azido intermediate.

ACCEPTED MANUSCRIPT