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Enhanced Reactivity of Dinuclear Copper(I) Acetylides in Dipolar Cycloadditions

Mårten Ahlquist[†,‡] and Valery V. Fokin*[,†]

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry, Technical University of Denmark, Building 201 Kemitorvet, 2800 Kgs. Lyngby, Denmark

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Summary: Dinuclear alkynyl copper(I) complexes exhibit superior reactivity toward organic azides compared to their monomeric analogues. DFT studies indicate that the second copper center facilitates the formation of the cupracycle in the rate-determining step and stabilizes the metallacycle intermediate itself. These findings support the experimentally determined rate law and shed light on the origin of high reactivity of the in situ generated copper acetylides.

Coordination compounds of copper are ubiquitous in both biological and abiological systems and often contain two or more metal atoms in close association.[1−5] The tendency toward clustering is most apparent among copper(I) species, and the extent of polynucleation has a significant effect on the stability, properties, and catalytic activity of copper(I) complexes. Copper(I) acetylides have a long history, dating back to Glaser's discovery of oxidative dimerization of phenylacetylide of copper in 1869.[6] Transformations involving copper acetylides now extend well beyond the oxidative coupling reactions, yet the precise nature of the reactive alkynyl copper species is not always known, underscoring the facility of the ligand exchange at the copper center and the involvement of multiple equilibria. Nevertheless, that copper(I) complexes with terminal alkynes are usually highly aggregated species, engaging in a range of σ- and π-interactions, has been demonstrated.[7−9]

The copper-catalyzed azide−alkyne cycloaddition (CuAAC)[10,11] reaction is a recent addition to the family of transformations involving alkynyl copper compounds. Therein, copper(I) acetylides are generated *in situ* by the action of a copper(I) complex on a terminal alkyne and are immediately engaged in an efficient sequence leading to the regiospecific formation of a 1,2,3-triazole heterocycle. This catalytic version of the Huisgen's 1,3-dipolar cycloaddition is accelerated by as much as 10^7 compared to the thermal process and exhibits excellent scope and exquisite selectivity. A stepwise mechanism involving copper(I) acetylides was proposed[11] (Figure 1, top) and computationally investigated soon thereafter.[12] Here we present the results of a density functional theory (B3LYP) investigation of the reaction between dinuclear copper(I) acetylide complexes and an organic azide, revealing a substantial further drop in the activation barrier already reported for the monocopper ensemble.

The first DFT treatment of the triazole-forming sequence by Himo et al.,[12] based on a monocopper acetylide model, correlated well with the observed high regioselectivity and the large rate increase. Formation of the copper metallacycle species **2** (Figure 1) was found to be the rate-limiting step (activation energy was calculated to be 18.7 kcal/mol ($L = H_2O$)). Soon afterward, careful kinetic investigation of the reaction of phenylacetylene and benzyl azide by Rodionov et al. revealed a strict second-order dependence on copper under the catalytic conditions.[13] Knowledge of the requirement of two copper atoms in the transition state complex triggered our search for its role. Localization of electron density on C^1 in complex **2**, seen computationally, suggests that the introduction of a second copper atom in proximity to C^1 may offer additional stabilization of this intermediate and of the transition state on the path of **2** to the triazole heterocycle.

Calculations were performed at the B3LYP/LACV3P*+ level of theory as implemented in the Jaguar 6.5 program.[14] All geometries were fully optimized including the PBF-solvation model with the default values of the parameters for simulation of water. Since the treatment of solvation in the PBF model is slightly different from that used in the original calculations, the reaction was remodeled, and the new overall barrier for the union of the azide **3** with the acetylide **4** was calculated at 17 kcal/mol (**TS-mono**). Formation of the resulting metallacycle **2** was found to be endothermic by 11.2 kcal/mol. Both values are in good agreement with those reported previously.

To probe the hypothesis that a second copper center positioned closely to C^1 can have a favorable influence on the transition state leading to the metallacycle **2**, two transition states containing a second copper(I) center were located. The two transition states differed only in the spectator ligand on the second copper atom. In the first, it was an acetylide (**TS-di$^{\mathbf{alkyne}}$**), and in the second the spectator ligand was a chloride

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* Corresponding author. E-mail: fokin@scripps.edu.

[†] The Scripps Research Institute.

[‡] Technical University of Denmark.

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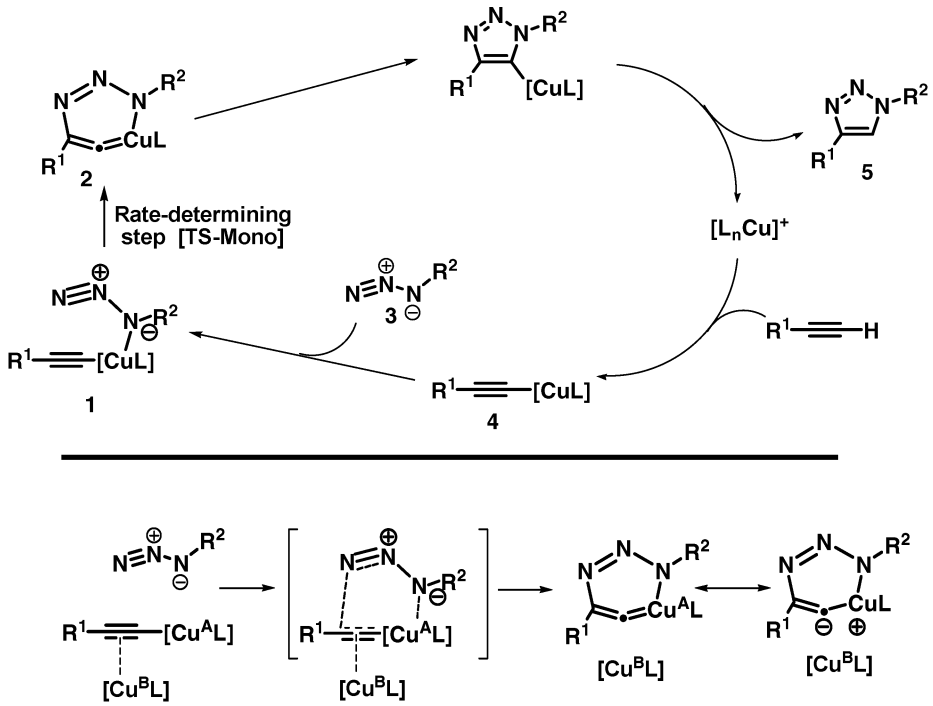

Figure 1. Reported mechanism of the reaction between a mononuclear copper(I) acetylide and an organic azide (top).[12] Introduction of a second copper(I) atom may favorably influence the energetic profile of the reaction (bottom). L = H_2O.

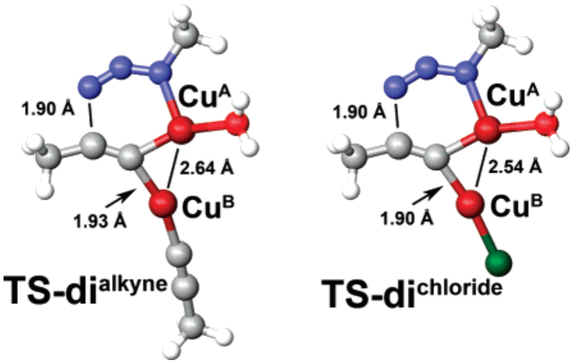

Figure 2. Interaction of the second copper atom with the transition state 1 to 2.

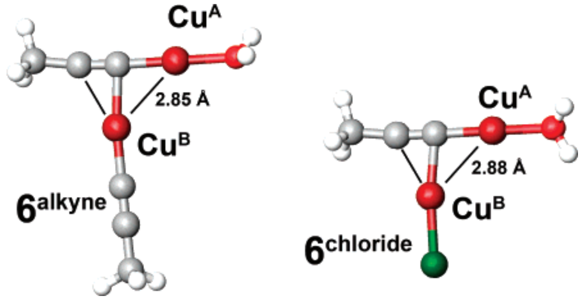

Figure 3. Optimized structures of dinuclear copper acetylides.

(**TS-di**$^{\textbf{chloride}}$), Figure 2. In both **TS-di**$^{\textbf{alkyne}}$ and **TS-di**$^{\textbf{chloride}}$ the second copper atom, Cu^B, forms a bond with C^1. The distances are calculated to be 1.93 and 1.90 Å for **TS-di**$^{\textbf{alkyne}}$ and **TS-di**$^{\textbf{chloride}}$, respectively. This short distance indicates a strong interaction between the second metal atom and the reacting copper acetylide.[15]

The interaction of the Cu^B with the proposed intermediates in the triazole-forming sequence and with the transition state indicates that a second copper atom is involved in the key steps of the CuAAC process. To compare the reactivity of the dinuclear copper complexes to their monocopper analogue, the transition state energy was compared relative to the azide and dicopper species in isolation. The geometries of dinuclear copper acetylide species **6**$^{\textbf{alkyne}}$ and **6**$^{\textbf{chloride}}$ (Figure 3) were found to be quite similar. The reacting acetylide is σ-coordinated to Cu^A, while the second metal center, Cu^{B}X (where X is acetylide or chloride), exhibits a stronger interaction with C^1, with possible interactions between Cu^B and C^2 and Cu^A. Interestingly, the strict μ^2-mode of coordination of the alkyne was not observed unless two identical spectator ligands were present on both copper atoms (e.g., $[MeCC(CuCl)_2]^-$). The barrier for the addition of methyl azide (**3**, R = Me) to the dinuclear copper acetylide complex **6**$^{\textbf{alkyne}}$ was calculated to be 12.9 kcal/mol. The corresponding barrier for the chloride analogue **6**$^{\textbf{chloride}}$ was found to be even lower, 10.5 kcal/mol. Compared to the mononuclear copper acetylides, for which an overall barrier of 17 kcal/mol was calculated (*vide supra*), the reactivity of the dinuclear complexes is expected to be several orders of magnitude higher.

Furthermore, a similar effect of the second copper center was observed in the six-membered intermediates **7**$^{\textbf{alkyne}}$ and **7**$^{\textbf{chloride}}$ (Figure 4). Both transformations of **6** to **7** were found to be endothermic by 6 and 3.6 kcal/mol for **7**$^{\textbf{alkyne}}$ and **7**$^{\textbf{chloride}}$, respectively, substantially lower endothermicity than for the corresponding monocopper transformation (11.2 kcal/mol). When the two dinuclear copper complexes **6**$^{\textbf{alkyne}}$ and **6**$^{\textbf{chloride}}$ were compared, **6**$^{\textbf{chloride}}$ was more reactive. This is likely due to the lower trans influence of the chloride compared to the σ-acetylide ligand and thus a higher stabilizing ability of the Cu^{B}X fragment on ligands trans to X, in this case stabilization of the electron density buildup on C^1.

In addition to providing support for the experimentally observed second-order rate law in [Cu],[13] this DFT study points to the more reactive nature of dinuclear copper complexes, which involve σ-, μ-, and π-modes of coordination, in dipolar cycloadditions compared to their monomeric congeners. The

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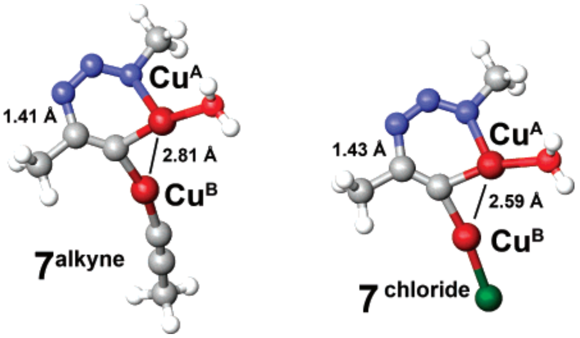

Figure 4. Optimized structures of the dinuclear analogues of the metallacycle **2**.

involvement of a second copper center in the catalysis may also explain the high activity of heterogeneous catalysts, including bulk copper metal[11,12] and nanoclusters.[16,17] Furthermore, similar dinuclear intermediates are likely involved in other transformations involving copper(I) acetylides, and further examination of their properties should help elucidate the origin of the exceptional reactivity of *in situ* generated copper(I) acetylides, in particular in aqueous solutions.

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Supporting Information Available: Cartesian coordinates, absolute energies, and zero-point energy corrections for all calculated geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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