Click Mechanism

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A Fluxional Copper Acetylide Cluster in CuAAC Catalysis**

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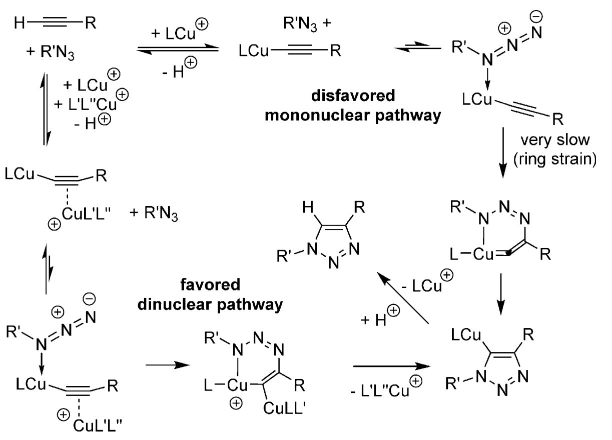
Abstract: *A molecularly defined copper acetylide cluster with ancillary N-heterocyclic carbene (NHC) ligands was prepared under acidic reaction conditions. This cluster is the first molecular copper acetylide complex that features high activity in copper-catalyzed azide–alkyne cycloadditions (CuAAC) with added acetic acid even at −5°C. Ethyl propiolate protonates the acetate ligands of the dinuclear precursor complex to release acetic acid and replaces one out of four ancillary ligands. Two copper(I) ions are thereby liberated to form the core of a yellow dicationic C_2-symmetric hexa-NHC octacopper hexaacetylide cluster. Coalescence phenomena in low-temperature NMR experiments reveal fluxionality that leads to the facile interconversion of all of the NHC and acetylide positions. Kinetic investigations provide insight into the influence of copper acetylide coordination modes and the acetic acid on catalytic activity. The interdependence of "click" activity and copper acetylide aggregation beyond dinuclear intermediates adds a new dimension of complexity to our mechanistic understanding of the CuAAC reaction.*

A range of organic transformations with alkyne substrates are mediated by copper compounds. Reactions featuring terminal alkynes and copper include Reppe's ethynylation of carbonyl compounds,[1] A^3 coupling reactions for alkyne aminoalkylation,[2] the standard Sonogashira cross-coupling of terminal alkynes with aryl halides,[3] and oxidative coupling reactions as developed by Glaser,[4] Hay,[5] Eglinton,[6] and Cadiot and Chodkiewicz.[7] The research groups of Meldal and Sharpless discovered the copper-catalyzed azide–alkyne cycloaddition (CuAAC),[8,9] which has emerged as one of the most important examples of click reactions and has found broad application in preparative organic chemistry, polymer science, materials chemistry, and especially in bioconjugation reactions.[10] Copper acetylides are intermediates for both copper-mediated and copper-catalyzed transformations of terminal alkynes. The coordination of more than one copper(I) ion at the acetylide anion drastically increases the acidity of terminal alkyne substrates by about ten orders of magnitude.[11,12] Copper(I) complexes with N-heterocyclic carbene ancillary ligands or carboxylate ligands are the most active CuAAC catalysts known to date.[13–15] The isolation of molecularly defined and catalytically active NHC copper acetylide complexes and clusters from a copper carboxylate precursor is thus an important goal. As for the mechanism of the CuAAC reaction, many experimental results point to the participation of two copper(I) ions in the rate-determining step (Scheme 1).



Scheme 1. The disfavored mononuclear pathway and favored dinuclear pathway in the CuAAC click reaction. R, R′ = alkyl, aryl, silyl, carbonyl groups; L = NHC; L′ = NHC or solvent; L″ = solvent, acetylide, carboxylate, halide.

The postulation of a mononuclear pathway is incompatible with the following experimental results 1) a rate law with a second-order dependence on the copper(I) concentration,[16] 2) only slow stoichiometric reaction of a mononuclear NHC copper acetylide complex with an organoazide to form an eventually isolated triazolide complex,[17] 3) the superior catalytic activity of dicopper complexes,[13] 4) the decisive catalytic role of copper salts added to a mononuclear copper acetylide,[18] 5) the results of copper isotope studies,[18] and 6) intercepted crucial dicopper intermediates detected by mass spectrometry.[19] Despite these experimental data and theoretical rationalizations[20,21] in favor of a dinuclear CuAAC mechanism, pathways with mononuclear copper acetylide intermediates were still put forward in a recent theoretical study.[22]

A stoichiometric CuAAC reaction of benzyl azide with a tricopper diacetylide complex has been reported, but this reaction did not proceed catalytically.[16] It is thus of central importance for the understanding of the CuAAC mechanism as well as for the further development of better-performing CuAAC catalysts to provide direct experimental data on the influence of bridging acetylide ligands on the stability and activity of molecularly defined copper catalysts.

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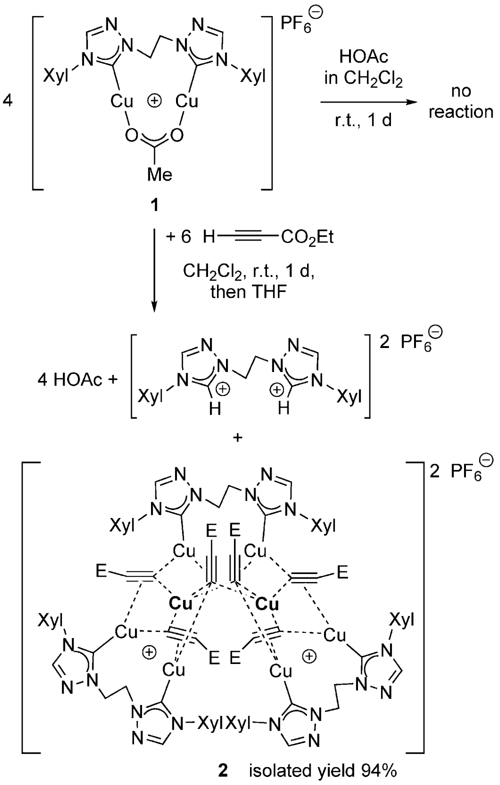
Our research group has developed and prepared dinuclear copper complex **1**, which features a bidentate ethylenebis-1,2,4-triazol-5-ylidene ancillary ligand. It shows outstanding catalytic activity in CuAAC reactions in organic solvents such as dichloromethane.[13] We herein report the stoichiometric reaction of this dicopper complex with an excess of the terminal alkyne ethyl propiolate to yield a yellow solution of the new octacopper(I) hexaacetylide cluster **2** and a bistriazolium salt as precipitate (Scheme 2).



Scheme 2. Protonation of the dinuclear CuAAC catalyst complex **1** with ethyl propiolate to give cluster **2**. E = CO_2Et, Xyl = 3,5-dimethylphenyl.

Addition of a large excess of acetic acid to a dichloromethane solution of cluster salt **2** leads to reappearance of the dicopper complex **1**, which is stable in this acidic solution for at least one day.

Apparently, heterolysis of the NHC–copper bond is readily accomplished via copper acetylide intermediates, but it cannot be achieved by direct protonation of the NHC–copper moiety when acetic acid is added to complex **1**. Protonation of an even more basic imidazol-2-ylidene ancillary ligand of a mononuclear copper(I) complex by phenylacetylene has already been described by Díez-González and Nolan.[14] To the best of our knowledge, however, protonation of a copper(I) carboxylate complex by an alkyne to yield free carboxylic acid and a molecularly defined copper acetylide has not been reported to date.

Acetylide complex **2** is air-stable in the solid state and air-stable for at least three days in dichloromethane solution. Single crystals suitable for X-ray diffraction analysis were grown from CH_2Cl_2/Et_2O (Figure 1). The C_2-symmetric dication comprises three bis-NHC ligands, eight copper(I) ions, and six acetylide ligands. Nine cuprophilic interactions with copper–copper distances of 243.7 pm, 245.9 pm, 261.5 pm, 268.3 pm (each twice), and 264.3 pm thermodynamically stabilize the cluster.[23]

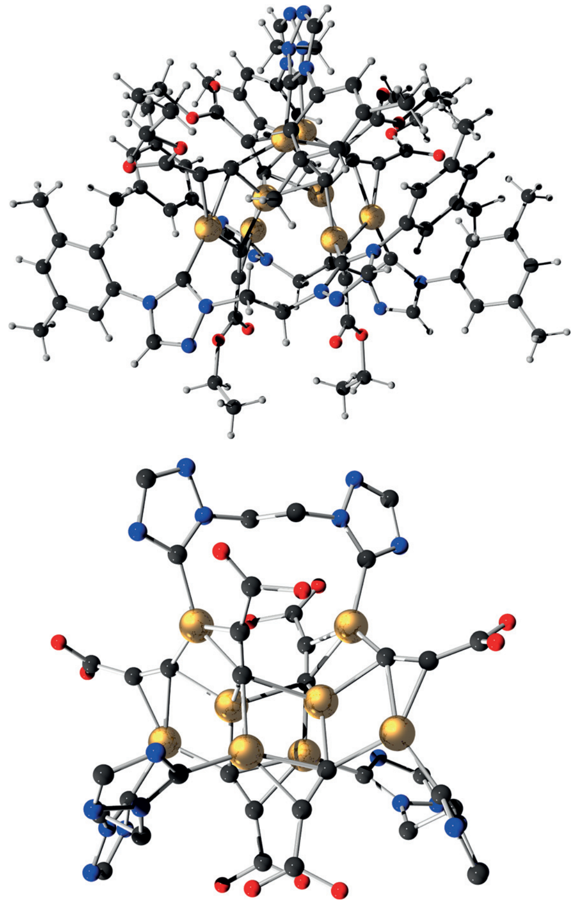


Figure 1. Ball-and-stick models of the dicationic copper(I) acetylide cluster **2** in the solid state (CCDC 1042359).[24] Hexafluorophosphate counterions were omitted for clarity. All hydrogen atoms, six 3,5-xylyl, and six ethyl groups were removed in the bottom structure fragment. Colors: C dark gray, H light gray, O red, N blue, Cu orange.

The two central copper(I) ions are σ-coordinated by four acetylide ligands and each copper center features 18 valence electrons. The six 16-valence-electron copper–NHC fragments are each coordinated by an acetylide ligand in σ-mode and an acetylide ligand in π-mode (Figure 2, middle structure). All acetylide ligands coordinate to one copper ion in π-

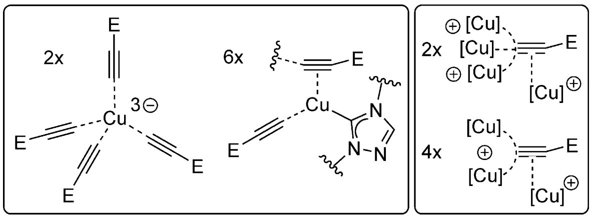


Figure 2. Coordination environments of the eight copper atoms (left side) and the six acetylide ligands (right side) in cluster **2**.

mode and to two or three copper ions in σ-mode. The proposed key intermediate in the currently accepted mechanistic picture of CuAAC, however, is a dicopper monoacetylide that features one σ-coordinated and one π-coordinated copper ion at the acetylide. In this proposed intermediate, the 14-valence-electron copper ion binds the organoazide so that the first C–N bond can be formed (Scheme 1).[11]

A recurring issue for quantum-chemical calculations in this field is the presumed binding of aquo ligands at copper ions with low coordination number in CuAAC model intermediates, and the proposal of these copper aquo complexes as catalyst resting states.[21,22,25] Such an approach neglects pre-equilibria of presumably unstable copper(I) aquo acetylide complexes with the actual catalyst resting state. According to the Cambridge Structural Database, only one copper(I) acetylide complex with aquo ligands has been characterized crystallographically in the solid state. Its copper ions are coordinatively saturated by bridging chloride ligands, and the aquo ligand is stabilized by the hydroxymethyl substituent of the acetylide.[26] Future theoretical studies can rely on coordination modes as found in cluster **2** to search for catalyst model structures with lower energy.

At room temperature, the ^{1}H and ^{13}C{^{1}H} NMR spectra of cluster **2** only show one set of signals. This provides evidence for a rapid degenerate rearrangement. The signal of the anionic terminal carbon of the acetylide at approximately 104 ppm coalesces near room temperature, and the internal acetylide carbon signal at 123 ppm is also broadened (Figure 3).

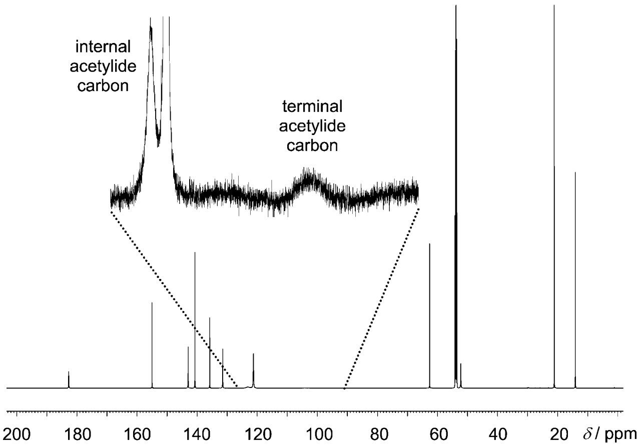


Figure 3. ^{13}C{^{1}H} NMR spectrum of cluster **2** (150.93 MHz, 295 K, CD_2Cl_2, 40960 scans).

A Gibbs free energy of activation of $\Delta G_C^{\neq} = (50 \pm 3)\,\mathrm{kJ\,mol^{-1}}$ for the interconversion of the three pairs of homotopic xylyl triazolylidene fragments and of the three pairs of homotopic acetylide ligands can be derived from the coalescences of six signal groups observed in variable-temperature ^{1}H NMR spectroscopy (Figure 4). The fluxionality of cluster **2** is in good agreement with the structural diversity of copper acetylide aggregates in the solid state observed by Tasker and co-workers, who have found a variety of cluster structures depending on subtle changes in the substituents or solvent environment.[27]

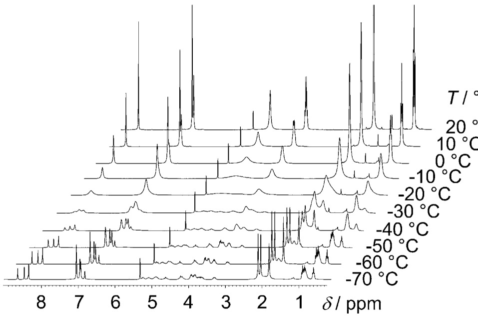


Figure 4. Temperature-dependent ^{1}H NMR signal coalescence for cluster **2** (300.13 MHz, CD_2Cl_2).

We used ethyl propiolate and benzyl azide in CD_2Cl_2 at room temperature for a kinetic comparison. Owing to the highly exothermic nature of the triazole formation, high dilution of the reaction mixtures is imperative to ensure an isothermal reaction and to prevent thermal runaway within minutes. Exclusion of air is mandatory for meaningful kinetic measurements because of the dioxygen-sensitivity of complex **1** in solution. The concentration of cluster **2** was adjusted to one third of the concentration of dinuclear complex **1** to account for the three ancillary ligands in cluster **2**. The catalytic activity of the dicopper complex **1** is significantly higher than that of cluster **2** (Figure 5).

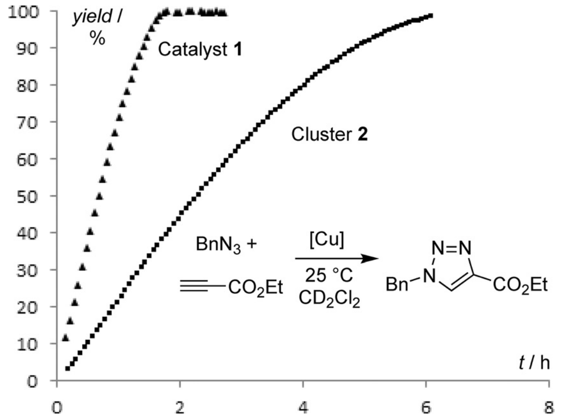
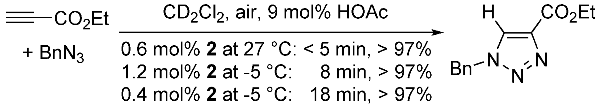


Figure 5. Conversion versus time diagram for the CuAAC reaction of ethyl propiolate (0.11 M) with benzyl azide (0.1 M) in CD_2Cl_2 at 25 °C, catalyzed by 0.9 mol% complex **1** (1.8 mol% Cu) or 0.3 mol% cluster **2** (2.4 mol% Cu).

Nonetheless, cluster **2** is the first molecularly defined copper acetylide complex that shows catalytic click activity.[16,28] We observed that heterogeneous catalysis with 17 mol% copper(I) acetate proceeds only slightly faster than homogeneous catalysis with only one seventh of the copper amount in the form of cluster **2** (see the Supporting Information). Cluster **2** is thus significantly more catalytically active than "free" copper(I). This excludes the possibility that the catalytic activity of the cluster relies solely or mainly on the release of free copper(I).

Addition of acetic acid greatly increases the rate of the CuAAC reaction of ethyl propiolate and benzyl azide catalyzed by cluster **2**. Under aerobic conditions and in non-purified solvent at 27°C, the yield of triazole product is essentially quantitative after the few minutes necessary for the NMR shimming procedure (Scheme 3).



Scheme 3. Very rapid CuAAC reactions of ethyl propiolate (0.36 M) and benzyl azide (0.36 M) with catalyst **2** under aerobic conditions at 27°C and −5°C.

The rate-accelerating effect of NHC ligands and of acetic acid leads to outstanding catalytic activity, which is demonstrated by the high CuAAC rate at an unparalleled reaction temperature of −5°C, with half-conversion times of less than two minutes with 1.2 mol% **2** and less than five minutes with 0.4 mol% **2**.

Upon addition of acid, cluster **2** serves as a precatalyst by releasing active dinuclear species such as complex **1**. According to its thermodynamic stability, cluster **2** is the catalyst resting state in CuAAC reactions without added acid. By NMR spectroscopy, we observed the disappearance of cluster **2** upon addition of a slight excess of benzyl azide under aprotic conditions, but we have not yet been able to isolate the products and determine their structures. The liberation of acetic acid from dinuclear complex **1** might account for its higher catalytic activity compared to the carboxylate-free cluster **2**. The rational design of more efficient CuAAC catalysts relies on an understanding of copper acetylide stability and reactivity. For exceptional catalytic activity, linked bis-N-heterocyclic carbenes have already been put forward as ideally suited ancillary ligands to ensure the beneficial presence of two copper atoms in a catalyst complex.[13] Another desired feature is irreversibility of the coordination of the ancillary ligand at copper(I), since this leads to a lower rate of catalyst decomposition. Furthermore, the electronic and steric stabilization of reactive dinuclear acetylide intermediates by coordinatively unsaturated copper(I) is paramount. Hindering the thermodynamically favored aggregation promotes the coordination and transformation of the organoazide substrate.

In summary, we present a missing link between the well-established copper(I) acetylide chemistry focusing on structural and spectral properties, and research on CuAAC reactions that aims at improved catalytic activity and mechanistic insight. Beyond the controversy of monocopper versus dicopper pathways, copper acetylide aggregation leads to thermodynamically more stable species in non-acidic media. The high catalytic activity of the investigated air-sensitive dicopper complex and of the air-stable acetylide cluster even at −5°C imparts a unique significance to their properties, since previous mechanistic reports were based on indirect studies, stoichiometric reactions, or structurally ill-defined active species. Complexes with acetylide ligands that coordinate to three copper ions are candidates for catalyst resting states in non-acidic CuAAC reaction mixtures. A better understanding of copper acetylide chemistry will provide a foundation for the development of even more efficient CuAAC catalysts and presumably also for the advancement of copper-mediated transformations of terminal alkynes in general.

Keywords: catalysis · click chemistry · copper · CuAAC · terminal alkynes

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