μ-Acetylide and μ-alkenylidene ligands in "click" triazole syntheses†

Bernd F. Straub*

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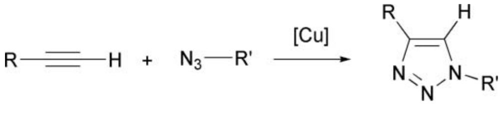
In a computational investigation, dinuclear and tetranuclear copper acetylide complexes display both superior stability and higher reactivity in the CuAAC reaction than do mononuclear complexes due to favored dicopper(I,III) μ-alkenylidene fragments, instead of ring strain in a Cu=C=C intermediate.

Huisgen's cycloaddition of organoazides with alkynes to triazoles has seen a remarkable renaissance in recent years.[1] The discovery of the extreme rate enhancement and 1,4-regioselectivity in the presence of copper(I) catalysts has broadened its field of application.[2] Bioorganic chemistry, material science and polymer synthesis benefit from an orthogonal chemoselectivity of the copper-catalyzed azide alkyne cycloaddition (CuAAC, Scheme 1).[3]



Scheme 1 Copper-catalyzed azide alkyne cycloaddition reaction.

At low copper concentrations and in the presence of *e.g.* a phenanthroline additive, the rate law of the click reaction is second order with respect to the copper concentration.[4,5] Thus, the rate-limiting step comprises double the number of copper atoms than are present in the catalyst resting state. However, the structure of this transition state has remained unclear, as has been the reason for its entropically-disfavored need for at least two copper atoms. So far, only model calculations for mononuclear mechanistic pathways have been reported.[5] Catalytically-active mononuclear copper(I) complexes with an *N*-heterocyclic carbene (NHC) spectator ligand have been investigated,[6] and mononuclear NHC copper(I) acetylide complexes[7,8] and a triazolide complex have been characterized.[8]

Interestingly, copper(I) acetylides without NHC spectator ligands are well known to prefer at least dinuclear structures with bridging μ-acetylide ligands (Fig. 1).[9] The formation of copper acetylide aggregates from rather unreactive copper(I) oxide and non-activated terminal alkynes proceeds rapidly, even at room temperature (Scheme 2).[10] Again, tetranuclear Cu_4C_8 core fragments are observed. Thus, the intermediate formation of tetranuclear, or at least dinuclear, copper acetylide complexes under "click" conditions appears inevitable.

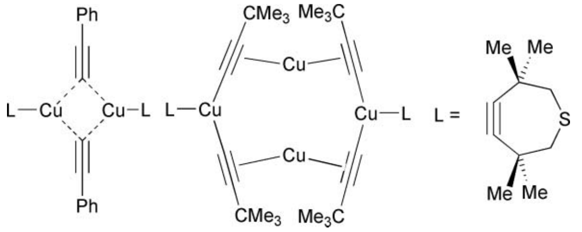
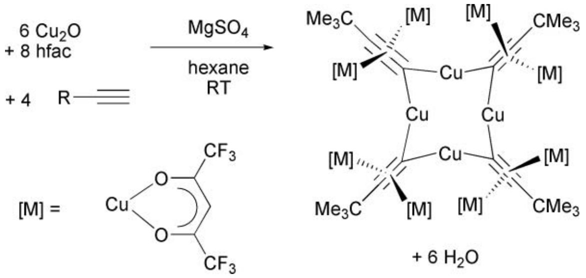


Fig. 1 Dinuclear and tetranuclear copper(I) acetylide complexes.[9]



Scheme 2 Rapid formation of polynuclear copper acetylide complexes investigated by Tasker *et al.*[10]

In our first attempts to obtain a mononuclear copper acetylide complex as a precursor for the stoichiometric reaction with an organoazide to a triazolide complex, we have also observed a tendency towards aggregate formation by spectator ligand dissociation.[8] We thus computed the relative stabilities of uncharged mononuclear, dinuclear and tetranuclear copper(I) complexes with hydroxide, acetylide, organoazide, acetylene, phenanthroline and water ligands. Our first goal was to determine the relative stabilities of these structures. Thermodynamically stable complexes might well be either the catalyst resting state, or at least be a potential intermediate. The ease of formation and stability of dinuclear and tetranuclear copper complexes with bridging acetylide ligands is in accordance with quantum chemical gas phase model calculations at the B3LYP/LACV3P++**//B3LYP/LACVP** level of theory.[11] We are aware that this method does not reproduce cuprophilic interactions.[12] The prediction of a high thermodynamic preference for structures such as **1** must thus be considered as an approximation, and as the best energetic standard for comparison available so far (Fig. 2, top diagram). Nevertheless, the relative stability of the polynuclear species is both observed experimentally as well as predicted quantum-chemically (Fig. 1 and Fig. 2, Scheme 2).[9,10] In contrast, mononuclear complexes such as **2** possess much higher predicted relative energies (Scheme 2, top). The computed Gibbs free energy (173.1 kJ mol^{-1}) of the mononuclear transition state **3**

Freie Universität Berlin, Fabeckstraße 34-36, 14195 Berlin-Dahlem, Germany. E-mail: straub@chemie.fu-berlin.de; Tel: +49 30 838 53291

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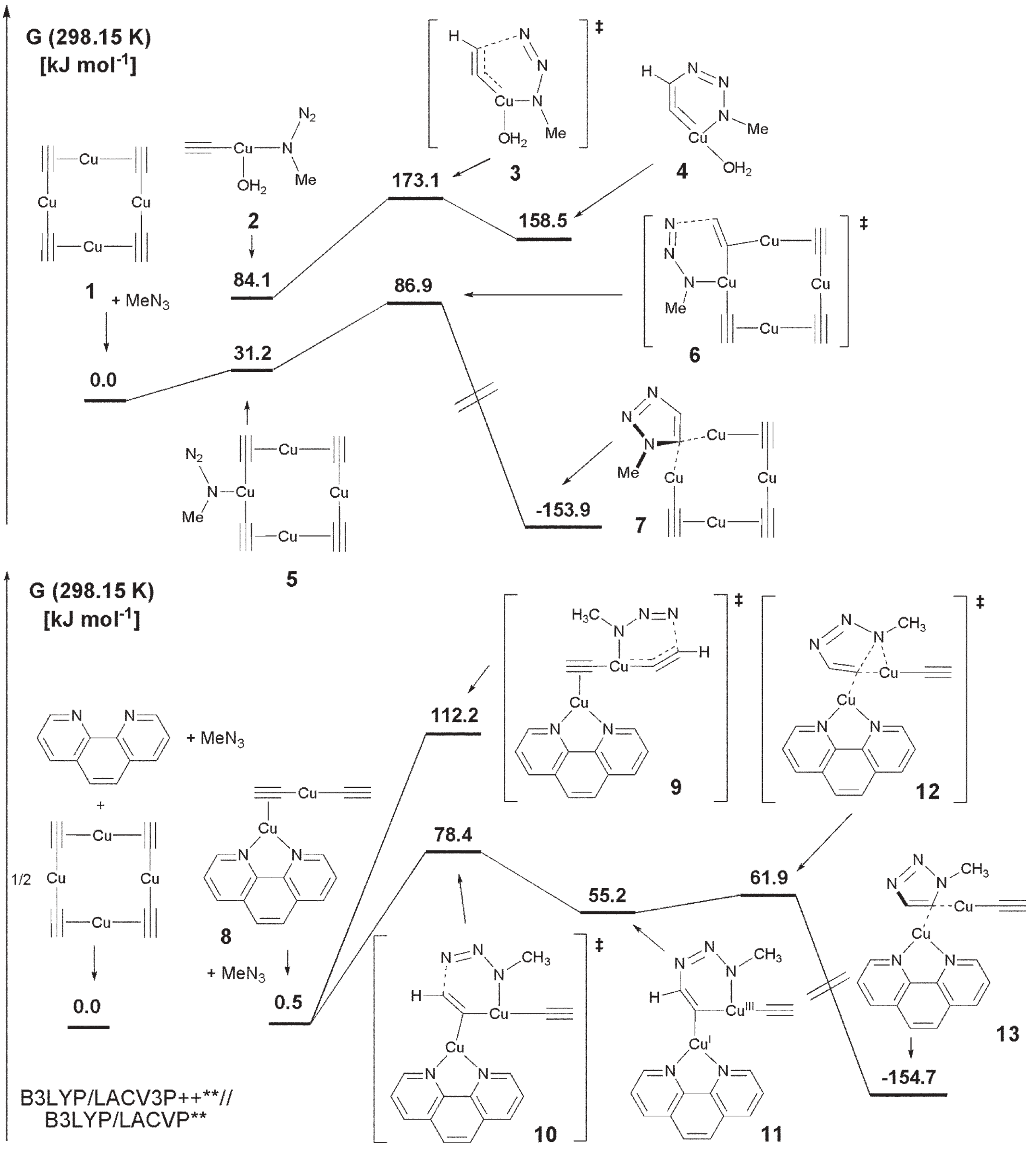

Fig. 2 Computed mechanistic pathways for triazolide formation in tetranuclear copper(I) μ-acetylide aggregates and dinuclear copper(I) phenanthroline complexes.

is equivalent to an overall Gibbs free barrier that is significantly higher than that of the uncatalyzed [3 + 2] cycloaddition (125.1 kJ mol^{-1}), rendering monocopper click pathways questionable.

Computed barriers of 60 to 80 kJ mol^{-1} for the elementary step of C–N bond formation in mononuclear copper organoazide acetylide complexes have already been reported and discussed in detail.[5] However, mononuclear copper(I) acetylides apparently do not represent the catalyst resting state, but high-energy species. The high barrier in the C–N bond formation step of mononuclear complexes originates from the ring strain in the copper(I) alkenylidene intermediate **4**.[13] A carbon atom of an alkenylidene ligand would ideally attempt to obtain an sp hybridization within a linear Cu=C=C fragment. However, a 180° angle is rendered impossible in a six-membered ring, and the computed 131.4° angle disfavors structure **4**. In other words, the bending of the copper alkenylidene fragment opens up a valence for a second copper. After the tetranuclear copper acetylide **1** has coordinated organoazide model substrate, the interaction between the alkenylidene carbon and a second copper is indeed realized. The resulting complex **5** features a high reactivity (*i.e.* a low barrier) for C–N bond formation through transition state **6**, comprising immediate reductive elimination, thereby yielding μ-triazolide complex **7**.

The overall barrier of the C–N bond formation step is apparently lower for μ-acetylide complexes (of course, only as long as a free copper coordination site for the organoazide substrate remains available). The stability of the μ-alkenylidene fragment compared to bent terminal alkenylidene ligands translates into lower barriers,[14] in addition to the significantly higher thermodynamic stability of copper μ-acetylide aggregates as starting materials.

Presumably, the observed rate enhancing effect of chelating nitrogen additives such as phenanthroline has several reasons. Stabilization of copper(I) against disproportionation to copper metal and copper(II) salts has already been proposed.[4] Furthermore, the competitive stability of dinuclear cuprate-type species such as **8** should help to prevent excessive aggregation (Fig. 2, bottom diagram). The organoazide does not voluntarily coordinate to μ-acetylide complex **8**. Transition state **9**, which leads to activation of the terminal acetylide, is too disfavored to account for the experimentally observed rate acceleration.[4,5] In contrast, the computed C–N bond formation barrier, *via* the isomeric transition state **10** to the copper(III) intermediate **11**, is facile. The bridging μ-alkenylidene carbon is not strained, and no electronic price has to be paid for unnatural bond angles. The predicted overall free activation energy of 77.9 kJ mol^{-1} is even smaller than the computed free activation energy for the analogous reaction in the tetranuclear copper acetylide model **1**. The kinetic advantage of C–N bond formation towards a dicopper(I,III) μ-alkenylidene intermediate thus amounts to more than 30 J mol^{-1} compared to the reaction of terminal acetylides to copper(I) alkenylidene intermediates.‡ After reductive elimination through transition state **12**, a μ-triazolide complex, **13**, is formed, awaiting eventual protonation.

Generally, the nature of the catalyst resting state will depend on the presence of halide counterions and nitrogen ligand additives, the copper concentration and the pH value. For high copper concentrations and high pH values, the protonation of the copper triazolide intermediate may well become rate-limiting instead of the alkyne deprotonation–cycloaddition sequence. Nevertheless, the results of this quantum chemical model study clearly demonstrate the importance of copper aggregates in acetylide complexes and the origin of the rate enhancing effect by the second copper atom. However, the presence of a dinuclear pathway for sterically demanding NHC copper catalysts remains unclear.[8]

In summary, copper(I) μ-acetylide complexes have been identified computationally as central intermediates in click triazole syntheses due to their high thermodynamic stability and superior reactivity towards organoazides. Their existence rationalizes the observed second order rate laws with respect to copper concentration in CuAAC reactions,[4,5] since copper(I) alkenylidene complexes can be avoided as highly strained six-membered cyclic intermediates. Considering the high overall barriers of hypothetical mononuclear pathways, the more stable alternatives, strain-free dicopper(I,III) μ-alkenylidene intermediates, are predicted to be formed more rapidly by several orders of magnitude.

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Notes and references

‡ The third isomeric alternative to transition state **10**, starting from organoazide coordination to the phenanthroline copper towards a μ-alkenylidene complex, possesses a relative free energy of 105.3 kJ mol^{-1}.

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