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Click Catalysis and DNA Conjugation using a Nanoscale DNA/Silver Cluster Pair

Caleb J. Setzler[a] and Jeffrey T. Petty[a,*]

DNA-bound silver clusters are most readily recognized by their strong fluorescence that spans the visible and near-infrared regions. From this suite of chromophores, we chose a green-emitting Ag_{10}^{6+} bound with $C_4AC_4TC_3GT_4$ and describe how this DNA/cluster pair is also a catalyst. A DNA-tethered alkyne conjugates with an azide via cycloaddition, an inherently slow reaction that is facilitated through the joint efforts of the cluster and DNA. The Ag_{10}^{6+} is the catalytic core in this complex, and it has three distinguishing characteristics. It facilitates cycloaddition while preserving its stoichiometry, charge, and spectra. It also acidifies its nearby alkyne to promote H/D exchange, suggesting a silver-alkyne complex. Finally, it is markedly more efficient when compared with related multinuclear DNA-silver complexes. The Ag_{10}^{6+} is trapped within its $C_4AC_4TC_3GT_4$ host, which governs catalytic activity in two ways. The DNA has orthogonal functional groups for both the alkyne and cluster, and these can be systematically separated to quench the click reaction. It is also a polydentate ligand that imprints an elongated shape on its cluster adduct. This extended structure suggests that DNA may pry apart the cluster to open coordination sites for the alkyne and azide reactants. These studies indicate that this DNA/silver cluster pair work together with catalysis directly driven by the silver cluster and indirectly guided by the DNA host.

Introduction

Size dictates the chemical and optical properties of noble metal nanomaterials, with distinctive behaviors emerging at nanometer scales.[1] For example, while gold in its bulk form is inert, its nanoparticles catalyze CO oxidation with a sharp 100-fold jump in efficiency for sizes $\lesssim$6 nm.[2, 3] This pronounced activity develops because high surface areas expose coordination sites for exogenous reagents.[4] This surface chemistry and catalysis is now more precisely controlled using noble metal nanoclusters.[5, 6] These are more precisely described as nanoscale molecules because they have a well-defined number of metals and ligands, organized as a metal core in a ligand shell.[7] Now, size becomes a less relevant metric, and stoichiometry, structure, charge, and coordination environment dictate catalytic efficiency.[8] Their catalysis is being studied and optimized through a fruitful collaboration of experimental and theoretical studies. A suite of synthetic methods can manipulate both the metal core and ligand shell at the atomic level.[9] X-ray diffraction along with a diverse set of analytical tools atomically map these complexes.[10] High-level theoretical calculations develop models to understand and optimize catalysis.[11] Here, we describe a nanoscale molecule comprised of a silver cluster within a DNA, and this complex collectively catalyzes a cycloaddition reaction.

Transition metal cations are the linchpin of alkyne-azide cycloadditions because they catalyze these click reactions with rates that are 10^7-10^8 faster rates faster than the original Huisgen reaction.[12-15] These catalyzed reactions are efficient at room temperature and in dilute solutions and are consequently used to link modular units and synthesize novel nanomaterials.[16-19] A metal center facilitates stepwise annulation by coordinating with an alkyne and azide in its open sites.[20] This metal also activates these pendant ligands because it is an electrophile. For example, Cu^+ coordinates across alkyne p-bonds to withdraw electron density and acidify the terminal proton.[15] A nucleophilic acetylide then attacks its neighboring azide, and the resulting C-N bond sets the foundation for an eventual triazole ring closure.[13] While a single Cu^+ facilitates alkyne-azide cycloadditions, multinuclear complexes are more efficient. Two copper coordination sites are supported by kinetic studies that establish a second-order rate law with respect to copper.[21] A dimeric Cu(I) catalyst is supported because a copper acetylide assembles with a Cu(I) complex and exchanges ^{63}Cu and ^{65}Cu isotopes.[22] The pendant ligands freely migrate between the two coordination centers. Cu^+ can also be assembled by polydentate amine-based ligands that are included in the reaction mixture.[23-25] The diverse end-on and side-on coordination modes of copper acetylides may underlie this enhanced activity because these interlinked complexes readily evolve to copper-triazole intermediates.[26-28] To precisely control metal stoichiometry, molecular and nanoscale complexes have been synthesized.

Click reactions are widely used because they can be adapted and optimized for diverse reaction conditions, so these 'black box' approaches have motivated the search for more precisely defined catalysts.[19, 23, 29, 30] For example, di-nuclear Cu^+ complexes are bridged by a bidentate carbene and labile acetate, and these complexes are effective homogeneous catalysts in a range of solvents.[31] Larger nanoscale molecules offer new opportunities to explore metal stoichiometry, structure, and coordination environment. One such nanocluster complex incorporates eight Cu^+ that are internally linked by acetylides and peripherally capped by carbenes.[32] The acetylides link coppers via both s and p bonds, and the complex fluctuates with rapidly exchanging ligands. A Cu_{20} complex is concentrically organized around a partially reduced Cu_4^{2+} core with an outer shell having 12 acetylide ligands bridging 16 Cu^+.[33] The acetylides chemically exchange with exogenous alkynes to yield a mixture of triazole products. A Cu_{58} cluster is a click catalyst whose activity is enhanced by excising a single copper atom.[34] This Cu_{57} may be more active because the coppers and ligands around the vacated site reorganize. Mixed Au/Cu and Ag/Cu clusters highlight and electronic synergism that can facilitate alkyne/azide annulations.[35, 36]

[a] *Department of Chemistry, Furman University, Greenville, SC, USA 29613*

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Besides Cu(I), other transition metals catalyze click reactions, and we consider a silver molecule.[13, 37, 38] Again highlighting size dependent properties, these molecular forms of silver are fluorophores that are ~10^{10} and ~10^{2} brighter than bulk and nanoparticle forms of silver, respectively.[39, 40] The diverse spectra of these fluorophores are revealed using DNA.[41] Single-stranded oligonucleotides coordinate silvers via their electron-rich, heterocyclic nucleobases, and multiple nucleobases frame binding pockets for a specific multinuclear cluster. Besides protecting it's adducts, DNA is programmable because its sequence and structure encode specific chromophores with spectra that span the visible and near-infrared and brightnesses that vary by ~10^{3}.[42, 43] Here, we consider this spectroscopic DNA code from a chemical perspective. Silver clusters are protected within their DNA shell, but this matrix is permeable. To illustrate, embedded clusters can be selectively etched and regrown using oxidizing and reducing agents, and electronically excited, metastable clusters react with O_2 to yield smaller clusters, still trapped in the DNA host.[44-47] Here, we study a DNA/silver cluster pair that catalyzes alkyne-azide cycloadditions, a favored and selective reaction that is not perturbed by the diverse functional groups in DNA.[48] We first describe the DNA scaffold that shares both a silver cluster and an alkyne. This DNA-tethered alkyne reacts with azides with no associated changes in the cluster, and a covalent triazole linkage was confirmed by etching the cluster from its DNA matrix. The cluster/DNA complex in D_2O reveals that the cluster acidifies its neighboring alkyne, possibly via a silver-alkyne complex. The click reaction efficiency depends on the cluster-alkyne proximity, which was controlled by inserting thymine spacers in the DNA strand. The solution pH also impacts the reaction efficiency. Our overall goal was to understand and develop this DNA/silver cluster pair as a catalyst for alkyne-azide cycloadditions.

thus prescribes the coordination environment. We hope to modify the DNA polymer to fine-tune how click reagents access open coordination sites and bind with exposed silvers. Our overall conclusion is that silver molecules are effective click catalysts, and their activity can be directed by a DNA scaffold.

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Author contributions

C. Setzler and J. Petty conducted the experiments, analyzed the data, and wrote the manuscript. We strongly encourage authors to include author contributions and recommend using CRediT for standardised contribution descriptions. Please refer to our general author guidelines for more information about authorship.

Conflicts of interest

There are no conflicts to declare.

Data availability

Data for this article, including supplemental figures and tables are available at [name of repository] at [URL – format https://doi.org/DOI].

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The acknowledgements come at the end of an article after the conclusions and before the notes and references.

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‡ Footnotes relating to the main text should appear here. These might include comments relevant not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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