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Au-iClick mirrors the mechanism of copper catalyzed azide-alkyne cycloaddition (CuAAC).

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This report outlines the investigation of the iClick mechanism between gold(I)-azides and gold(I)-acetylides to yield digold triazolates. Isolation of digold triazolates complexes offers compelling support for the role of two copper(I) ions in CuAAC. In addition, a kinetic investigation reveals the reaction is first order in both Au(I)-N and Au(I)-C≡C-R, thus second order overall. A Hammett plot with a r = 1.02(5) signifies electron-withdrawing groups accelerate the cycloaddition by facilitating the coordination of the second gold ion in a π-complex. Rate inhibition by the addition of free triphenylphosphine to the reaction indicates that ligand dissociation is a prerequisite for the reaction. The mechanistic conclusions mirror those proposed for the CuAAC reaction.

Introduction

The cycloaddition of a metal-azide with a metal-acetylide to form bimetallic triazolates was introduced in 2011 and termed inorganic click (iClick) to acknowledge the participation of the metal ions in the reaction (Figure 1: A). Essentially, iClick replaces the R-group on the azide and the proton of a terminal alkyne with a metal ion in well-established copper catalyzed azide-alkyne cycloadditions (CuAAC; Figure 1: B). Others extended iClick to include the already prevalent cycloaddition of an organic substrate to either a metal-azide or metal-acetylide. Important to this work, Gray et al. demonstrated that gold-acetylides and gold-azides will undergo cycloaddition to their organic counterparts.

![Figure 1. Generic iClick (A) and copper-catalyzed azide-alkyne cycloaddition (CuAAC; B).](image)

Despite the fact that several transition metals other than Cu(I) catalyze the azide-alkyne cycloaddition, including ruthenium, silver, and iridium, it became apparent that not all metal-acetylide/azide species will participate in the iClick cycloaddition. In fact, we found that a gold-acetylide is a prerequisite partner for a successful cycloaddition with metal-azides. For example, PPh₃Au-C≡C-C₆H₃p-NO₂ will undergo cycloaddition with (PPh₃)₂Pt(C≡C-Ph); however, (PPh₃)₂Pt(C≡C-PhNO₂) will not add PPh₃AuN₃.

In an effort to expand iClick beyond gold and across the transition metals it was imperative to first, understand why the gold-acetylide was a critical ingredient, and second, to elucidate the mechanism. Scheme 1 summarizes the currently accepted mechanism for CuAAC. We offer, in a somewhat unusual format, essentially the conclusions of this paper in Scheme 1. That is, the data to follow offers compelling support for the proposed mechanism that mirrors CuAAC.

![Scheme 1. CuAAC mechanism overlaid with the proposed iClick mechanism.](image)

In step one of CuAAC a copper ion forms a π-complex with the alkyne that serves to reduce the pKₐ of the proton; a second copper ion then replaces the proton to generate a copper acetylide. Mirroring this step, our kinetic studies indicate loss of PR₃ precedes Au-azide π-complexation with the acetylide. Fokin et al. firmly establish, using isotopically enriched Cu sources, the need for exogenous copper to...
catalyze the cycloaddition, i.e. two Cu\(^{1}\) ions are prerequisite. Also, De Angelis et al. recently detected a dicopper intermediate via electrospray ionization mass spectrometry.\(^{29}\) However, the isolation of a dicopper intermediate still remains elusive.\(^{30}\) Not only do our kinetic results agree, as both the Au-azide and Au-acetylide are first-order participants in the cycloaddition, but also the product of the reactions, by default, are digold triazolates. In addition, we present a Hammett-plot study that clearly indicates the rate of reaction accelerates with electron-withdrawing groups (EWG) in the para-position of the acetylide. The EWG serves to lower the CC π* orbital thus facilitating the recruitment of the second gold ion. Finally, in the Au/Au cycloaddition, the triazolate produced matches the exclusive 1,4 selectivity in the copper-catalyzed reaction (with Au-PR\(_3\) retained in the C5 position; Scheme 1).

The following text communicates the results and data that support the Au/Au cycloaddition mechanistic claims presented in Scheme 1.

**Results and Discussion**

![Scheme 2](image)

Scheme 2. iClick reaction between Au(I)-azide (1) and Au(I)-acetylides (2-R).

The following mechanistic studies center on the general reaction depicted in Scheme 2. Treating PPh\(_3\)-Au-N\(_3\) (1) with PPh\(_3\)-Au-C≡C-Ph-R (2-R) provides the digold triazolates 3-R (where, R = H, NO\(_2\), F, and OMe). The electronic supporting information contains multinuclear NMR data, 2D-NMR spectra, and combustion analysis for all new bimetallic complexes. An X-ray diffraction experiment, performed on a single crystal grown via pentane diffusion into a chloroform solution of 3-NO\(_2\), provides unambiguous solid-state characterization for the bimetallic triazolate. Figure 2 depicts the solid-state structure of 3-NO\(_2\).\(^{31}\) Complex 3-NO\(_2\) is C\(_2\)-symmetric and crystallizes in the P\(_\text{I}\) space group with two lattice molecules of chloroform. The geometry of each Au(I) ion is nearly linear (P1-Au1-C1 = 174.44(8)° and P2-Au2-N1 = 172.64(7)°). The nitro-phenyl ring is nearly coplanar (“12.5°”) with the triazolate, perhaps providing stabilization through electron delocalization across the two aromatic systems.

![Figure 2](image)

Figure 2. Molecular structure of 3-NO\(_2\) with ellipsoids drawn at the 50% probability level. Two lattice molecules of chloroform, disordered atoms, and hydrogen atoms are removed for clarity.

In the CuAAC mechanism the second Cu(I), of unknown coordination number and geometry, binds to the acetylide. Presumably, the Cu(I) ion is a low-coordinate species. In support of this contention, and according to Scheme 1, loss of PR\(_3\) is a requirement in the reaction between 1 and 2-R. Adding free PPh\(_3\) to the reaction between 1 with 2-R depresses the rate. Figure 3 depicts \(k_{\text{obs}}\) as a function of [PPh\(_3\)] and the data indicate the inhibition is first-order.

![Figure 3](image)

Figure 3. Rate inhibition by addition of free PPh\(_3\) to the reaction between 1 and 2-NO\(_2\).

Further confirming the need for a \(k\) low coordinate intermediate, NHC ligands shut-down the cycloaddition. 1,3-Diisopropylbenzimidazolin-2-ylidene (Bimz),\(^{32}\) an NHC ligand of intermediate basicity, and comparable size\(^{33-34}\) to PPh\(_3\) was chosen. No cycloaddition products form upon treating (Bimz)AuN\(_3\) (4)\(^{35}\) with (Bimz)Au-C≡C-Ph (5)\(^{36}\) at ambient temperature or 65 °C (Scheme 3). Unable to dissociate,\(^{37}\) the gold ion cannot access a lower coordination state, thus no cycloaddition occurs. NHC-supported gold(I)-acetylides and azides are competent in cycloadditions,\(^{38-39}\) but the reactions always include one organic counterpart (either the azide or alkyne) or are facilitated with a copper(I) catalyst.
Fokin et al. convincingly demonstrate that exogenous Cu(I) participates in CuAAC. Mirroring this requirement, the iClick reaction exhibits first-order dependence in both the gold-azide (1) and gold-acetylide (2-NO₂). Integration of a downfield doublet ($^1H$ NMR) at 8.59 ppm in the $^1H$ NMR spectrum of the product 3-NO₂ relative to hexamethyldisiloxane as an internal standard, provides quantitative concentration versus time data for the progression of the reaction between 1 and 2-R. Figure 4 depicts a ln$[1]$ versus time plot under pseudo-first-order conditions in 2-H. The linear plot signifies first-order dependence in 1. Confirming a first order dependence in gold-acetylide, Figure 5 depicts linear plots of ln$[2\text{-H}]$ versus time under five different pseudo-first-order concentrations of 1. Again, the linear plots for each concentration signifies the reaction is first-order in 2-H. These results are significant because we are able to control both the concentration of the Au-azide and Au-acetylide independently. Exploiting this even further, plotting $k_{\text{obs}}$ as a function of $[1]$ in Figure 6 provides the rate constant $k = 7.6(5) \times 10^{-3}$ M$^{-1}$s$^{-1}$ for the cycloaddition from the slope.

The kinetic data clearly point to a digold intermediate, but not the identity of the transition state. However, there is precedence for σ- and π-interactions between Au(I) ions and alkynes that look conspicuously similar to the dicopper intermediate proposed in Scheme 1. Depicted in Figure 7 are σ–π-digold acetylide complexes isolated by Himmelspach et al. Aiding the formation of the complexes is an aurophilic interaction between the Au(I) centers. It is reasonable to expect that similar interactions occur during the reaction between 1 and 2-R, and in CuAAC.

In addition to the σ– and π-interactions, precedence exists for an azido-bridged digold complex. Figure 8 depicts the isolable azide bridging digold complex [PPh₃][μ-N₃].

Scheme 3. No reaction is observed when NHC ligands replace PR₃ in Au(I)-acetylide/azide cycloadditions.
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Fokin et al. propose a nucleophilic attack of acetylide on azide in CuAAC. \(^{28}\) iclick offers an opportunity to probe this proposal. Figure 9 depicts a Hammett plot for the reaction of 1 with 2-R. The reactions all proceed with quantitative conversion (NMR) to their respective dinuclear triazolate products (3-R). Electron withdrawing groups significantly accelerate the reaction. Plotting the log(kp/kh) versus published substituent constants (\(\rho\))\(^{43}\) for the different functional groups, provides \(\rho = 1.02(5)\). The positive value for \(\rho\) indicates that a negative charge develops on 2-R in the rate determining step. Stabilization of the negative charge build-up with an EWG is consistent with the recruitment of the electron-rich gold ion as a \(\pi\)-complex, according to Scheme 1. Also, Fokin proposes an oxidation state change from Cu(I)\(\rightarrow\)Cu(II) as the first C-N bond forms. For Au(I) on oxidation state change is unlikely, but also unnecessary, since Au(I) already has the Au(I)-N bond preformed as the “R-group” substituent on the azide.

\[
\begin{align*}
\text{Figure 9. Hammett plot depicting substituent effects for the reaction between 1 and 2-R (R = OMe, H, F, NO}_2\text{).}
\end{align*}
\]

Finally, measuring the rate constant for the cycloaddition between 1 and 2-NO\(_2\) within the temperature range of 20 °C - 60 °C enables the construction of an Eyring\(^{44}\) plot (Figure 10). From the plot in Figure 10, the activation parameters \(\Delta H^\ddagger = 15.5(5) \text{ kcal/mol and } \Delta S^\ddagger = -12(2) \text{ cal/molK, are determined. The large and negative entropy of activation is significant. Mirroring the proposed multinuclear transition state in CuAAC, the cycloaddition between 1 and 2-NO}_2\) must also proceed through a highly ordered transition state.

\[
\begin{align*}
\text{Figure 10. Eyring plot for the reaction between 1 and 2-NO}_2\text{ (20 – 60 °C).}
\end{align*}
\]

Conclusions

The goal of this work was to understand the mechanism of gold iClick reactions and why Au-acetylenes are prerequisites. It is clear now that the Au(I)-acetylide plays the same role as the Cu(I)acetylide in CuAAC. In addition, our kinetic studies complement the CuAAC mechanism and offer additional support for the presence of exogenous Cu(I). By employing Au(I)-acetylenes and -azides we are able to exert exquisite control over the reaction conditions enabling conclusive evidence for the participation of two gold ions in the mechanism. Loss of PPh\(_3\) is a prerequisite for the reaction suggesting the second gold ion is low-coordinate and likely to bind to the alkyne triple bond. Hammett plot data point to a stabilization of electron density as the second gold ion binds to the acetylide \(\pi\)-bond. Taken together these conclusions reflect the proposed mechanism for CuAAC.\(^{28}\)

EXPERIMENTAL

Glassware was oven dried before use. Pentane, toluene, and methylene chloride were sparged with ultra-high purity argon, and dried using a GlassContours drying column. Methanol was degassed, dried over copper sulfate and distilled prior to use. Chloroform-\(d\) (Cambridge Isotopes) was dried over sodium hydride, distilled, and stored over 4 Å molecular sieves. Me\(_2\)S-Au-Cl, TMS-N\(_3\), 1-ethynyl-4-fluorobenzene, 1-ethynyl-4-nitrobenzene, 1-ethynyl-4-methoxybenzene, triphenylphosphine, were purchased from commercial sources, and used without further purification. Commercially available phenylacetylene was distilled from calcium hydride before use.

Ph\(_3\)PAuN\(_3\)\(^{22}\) was prepared according to literature procedures using freshly synthesized Ph\(_3\)PAuCl.\(^{45}\) PPh\(_3\)Au–C\(_3\)CPh, and PPh\(_3\)Au–C\(_3\)CPh-R (R = OMe, F, NO\(_2\))\(^{46}\) were synthesized according to the literature with a slight modification; a fresh batch of NaOMe in MeOH was made by dissolving sodium metal in dry methanol directly before each synthesis. (Bimz),\(^{32}\) (Bimz)AuN\(_3\)\(^{35}\), and (Bimz)Au-C\(_3\)C-Ph\(^{36}\) were synthesized according to literature procedures.

NMR spectra were obtained with either Varian Mercury or Varian Inova instruments, operating at 300 MHz or 500 MHz for proton, respectively. Chemical shifts are in ppm on the TMS scale and were referenced to the residual signal of the chloroform solvent (7.26 ppm for proton and 77.4 ppm for carbon), and \(^{31}\)P\(_{\text{H}}\) NMR chemical shifts were referenced to an external standard of 85% H\(_3\)PO\(_4\) in D\(_2\)O. Elemental analyses were performed at Complete Analysis Laboratory Inc., Parsippany, New Jersey. Kinetic experiments were performed on a Varian Inova 500 MHz spectrometer.

The general procedure followed for the iClick reaction between PPh\(_3\)Au-N\(_3\) (1) and PPh\(_3\)Au-C\(_3\)C-Ph-R (2-R, R = H, NO\(_2\), F, OMe) to yield 3-R is as follows. Complex 1 was taken up in CDCl\(_3\) (0.3 mL) and added to a solution of 2-R also in CDCl\(_3\) (0.3 mL). The reaction mixture was transferred to a sealable NMR tube and the reaction progress was monitored via \(^{31}\)P and \(^1\)H NMR. The reactions all proceed quantitatively by NMR and the products can be isolated by removing all the volatiles in vacuo and then triturating with pentane.

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Synthesis of 3-NO₂

General synthetic scheme followed. 94% Yield (41 mg, 0.037 mmol). 1H NMR (300 MHz, CDCl₃): δ 8.59 (s, 3H, J₉₈ = 8.5 Hz, 2H, C₄-H), 8.11 (d, J₂₃ = 8.5 Hz, 2H, C₅-H), 7.47 (m, 18H, aromatic), 7.30 (m, 12H, aromatic). 13C NMR Shifts (indirect detection through J₁ₙˌ₄₃°C gHMBC and J₁ₙˌ₄₃°C gHSQC (500 MHz, CDCl₃)): δ 149.7 (C2), 145.3 (C6), 143.5 (C3), 134.2 (C7, C8, C11, C12), 131.7 (C10, 131.6 (C14), 129.1 (C9, C13), 125.9 (C4), 123.7 (C5) (Note: C1 is not observed). 31P¹H NMR (121.4 MHz, CDCl₃): δ 44.39 (s, P1), 31.77 (s, P2). Anal. Calcd for C₃₁H₆₄Au₂P₃N₂O₂: C, 47.95; H, 3.25; N, 3.65. Found: C, 47.95; H, 3.25; N, 3.65.

Synthesis of 3-F

General synthetic scheme followed. 90% Yield (38 mg, 0.035 mmol). 1H NMR (300 MHz, CDCl₃): δ 8.32 (d, J₉₈ = 8.2 Hz, 2H, C₄-H), 7.46 (m, 18H, aromatic), 7.30 (m, 12H, aromatic), 6.84 (d, J₉₈ = 8.2 Hz, 2H, C₅-H), 3.81 (s, 3H, OCH₃). 13C NMR Shifts (indirect detection through J₁ₙˌ₄₃°C gHMBC and J₁ₙˌ₄₃°C gHSQC (500 MHz, CDCl₃)): δ 157.8 (C6), 151.2 (C2), 134.2 (C7, C8, C11, C12), 131.6 (C10, C14), 129.6 (C3), 129.1 (C9, C13), 127.6 (C4), 113.4 (C5), (Note: C1 is not observed). 31P¹H NMR (121.4 MHz, CDCl₃): δ 44.50 (s, P1), 31.77 (s, P2). Anal. Calcd for C₃₁H₆₄Au₂P₃N₂F: C, 49.79; H, 2.97; N, 3.80. Found: C, 49.79; H, 3.25; N, 3.65. General Guidelines for Kinetic Experiments

All kinetic experiments were run using CDCl₃ stock solutions spiked with hexamethyldisiloxane (HMDSO) as an internal standard (0.005 M) against which the product integrations could be referenced. For each set of experiments, a fresh stock solution of azide and acetylide was created. In order to minimize the time a sample was mixed before spectra began to be collected, a NMR tube charged with a premeasured volume of Au(İ)-acetylide solution was brought to the NMR instrument, and the azide stock solution added to the tube directly prior to loading the sample into the magnet. A lock was already established on the NMR instrument with a similar sample, but to ensure accurate integrations, a new lock and shims were established for each sample. Two steady state scans were executed in order to stabilize the magnetization prior to collection of each spectrum. If a third stock solution needed to be added to the tube (triphenylphosphine), it was mixed with the azide solution directly prior to mixing the azide with the acetylide.

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References

Isolated digold-triazolate products and first-order kinetic profiles for Au-acetylide/azide reactants in iClick provide compelling support for two copper ions in CuAAC.