Conditional Copper-catalyzed azide alkyne cycloaddition by catalyst encapsulation

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Abstract: Supramolecular encapsulation is known to alter chemical properties of guest molecules. Here we apply this strategy of molecular encapsulation to temporally control the catalytic activity of a stable Cu(I)-carbene catalyst. Encapsulation of the Cu(I)-carbene catalyst by supramolecular host cucurbit[7]uril (CB[7]) resulted in the complete inactivation of a copper catalyzed alkyne-azide cycloaddition (CuAAC) reaction. The addition of a chemical signal achieved the near instantaneous activation of the catalyst, by releasing the catalyst from the inhibited CB[7] catalyst complex. To broaden the scope of our on demand CuAAC reaction, we demonstrated the protein labelling of Vinculin using the Cu(I)-carbene catalyst, to inhibit its activity by encapsulation with CB[7], and to initiate labelling at any moment by adding a specific signal molecule. Ultimately, this strategy allows for temporal control over copper-catalyzed click chemistry, on small molecules as well as protein targets.

In this paper we use an external chemical signal to control the rate of copper catalyzed alkyne-azide cycloaddition (CuAAC) reactions. CuAAC, commonly viewed as one of the primary click reactions[1], is a robust way of 'clicking'[2] a large range of azide and terminal alkyne functionalized molecules together in biological and material-based environments and has been used in many different settings.[3] There is, however, also an increased need for the spatiotemporal control of these click reactions,[4] usually instilled by light activated click chemistry, with potential phototoxicity and side-reactions offering problems in this approach. In expanding the CuAAC toolbox there is therefore a desire to also have a general method to spatiotemporally control the catalytic activity of the CuAAC. Using this tool would allow spatiotemporal control over gel formation[5], polymer conjugation, material properties, fluorescent properties and biomolecule labelling.
Host-guest chemistry is an approach that could serve to control the chemical properties of encapsulated guests.[6] Here, we use

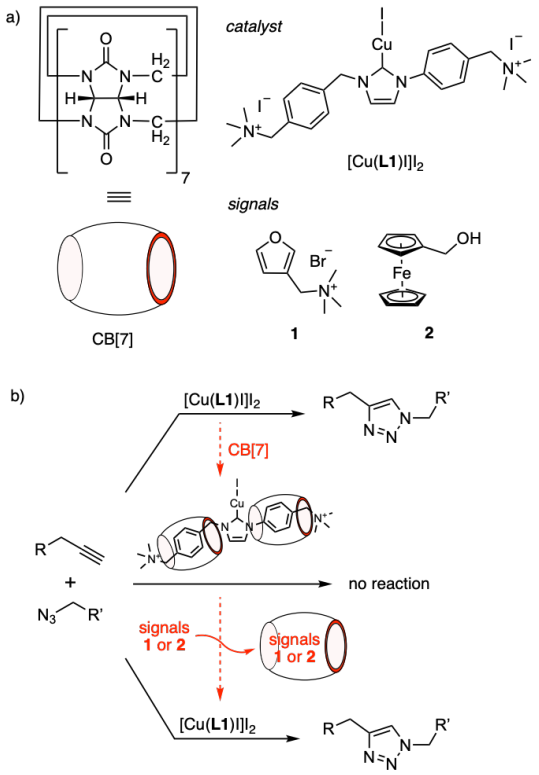

Figure 1. a) Schematic representation of cucurbit[7]uril (CB[7]), molecular structure of Cu(I)-NHC [Cu(**L1**)I]I$_2$, signal molecule **1** (3-((furylmethyl)trimethyl ammonium) bromide) and signal molecule **2** (hydroxymethyl ferrocene). **b**) when [Cu(**L1**)I]I$_2$ is encapsulated by CB[7] the catalytic activity in the CuAAC is 'switched off'. After the addition of the signal molecule **1** or **2**, [Cu(**L1**)I]I$_2$ is released which 'switches on' the catalytic activity.

host-guest chemistry to switch from an inactive catalytic state of the Cu-catalyst to an active one. A promising class of hosts for encapsulating small molecule guests in aqueous environments is

the cucurbituril family. Cucurbituril is a versatile molecular container (Figure **1a**) that is biocompatible, has a relatively low toxicity and has been used in many different systems to encapsulate drugs[7], fluorescent dyes[8] and biologically active molecules[9]. In some specific cases, cucurbiturils can also act as catalysts themselves, for example in the cycloaddition[10] of alkynes and alkyl azides or in promoting acid hydrolysis.[11] Furthermore, compartmentalized structures with a cucurbituril barrier can be used to shield substrate from catalyst, leading to reduced turnover. There, addition of a competitive guest removes the cucurbiturils and restores catalytic activity.[12] In that respect, Leigh and co-workers showed using rotaxane based switchable organocatalysts, that shielding the catalytic center with a macrocycle is an effective approach to regulate catalytic activity.[13] In our work we want to use cucurbiturils to encapsulate a copper catalyst to directly modulate its catalytic activity in the CuAAC.

There are reports of triggered CuAAC, which rely on mechanochemical processes converting an inactive copper(I) biscarbene catalyst to an active copper(I) monocarbene catalyst.[14] Besides mechano-based triggers, on demand CuAAC can also be achieved by electro-[15] and light-based[16] triggers. Another interesting strategy for control over catalytic activity in the CuAAC is reported by Schmittel and co-workers, where they prepared a molecular switch that can release a Cu(I) catalyst.[17] In this paper, the basic switching from an 'off' state to an 'on' state relies on the host guest chemistry between the catalyst and cucurbit[7]uril (CB[7]). The catalyst is designed in such a way that CB[7] binds with high affinity to the N-heterocyclic carbene (NHC) ligand coordinating to the Cu(I) center. When CB[7] is bound to the Cu(I)-NHC, the Cu(I) center is not catalytically active, most likely because it is not accessible for substrates or unable to form a catalytically active species. However, when a stronger binding guest (a chemical signal) is added to the system, the catalyst will be released from CB[7], after which the liberated catalyst can catalyze the click reaction (Figure **1b**). We selected copper carbene catalysts because of their high stability in aqueous environments, high activity in bioconjugation settings[18] and the possibility to modify the NHC ligand in such a way that it binds to CB[7]. The ligand can bind to CB[7] through favorable interactions between its positively charged ammonium groups and the polar portal area of CB[7], as well as interactions between the apolar benzene rings and the apolar cavity of CB[7]. Using this catalyst, we demonstrate temporal control over catalytic activity in copper catalyzed azide alkyne cycloaddition in a controlled model reaction and on a biomacromolecule, where protein labelling is initiated on demand. The catalyst was synthesized in five steps to yield stable Cu(I)-NHC [Cu(**L1**)I]I_2 (elaborate synthesis details in SI). The complex is soluble in a DMSO/MES buffer (100 mM, pH 6.4, 25% v/v DMSO) solution. We used the model reaction shown in Figure **2a** to explore the activity of [Cu(**L1**)I]I_2. Azide **3** and propargyl alcohol (**4**) were selected based on their water solubility and low binding affinity to CB[7] (Figure **SI7**). In a typical reaction, azide **3** and propargyl alcohol (**4**) were dissolved in MES buffer after which the catalyst (2 mol% relative to **3**) dissolved in DMSO was added. Under these conditions at 25 °C, full conversion to triazole **5** was reached after approximately 120 min (Figure **2b**, magenta line). An estimate of the reaction rate constant gave the same order of magnitude value ($(6 \pm 2)*10^4$ M^{-1} s^{-1} (per M Cu), n = 3) as with reported systems using typical Cu(I) with activating triazole ligands in similar reaction conditions (see SI for detailed description).[19]

The binding between CB[7] and [Cu(**L1**)I]I_2 was examined using ^{1}H-NMR and isothermal titration calorimetry (ITC) (Figure **SI4-6**). Using the method of continuous variation (Figure **SI4** and **SI5**) we determined that the binding stoichiometry between CB[7] and [Cu(**L1**)I]I_2 is 2:1, and binding constants K_{a1} and K_{a2} are $(1.21 \pm 0.08)*10^9$ M^{-1} and $(3.5 \pm 0.3)*10^6$ M^{-1}, respectively (Figure **SI6**). When using catalyst [Cu(**L1**)I]I_2 that was pre-mixed with 4.6 equivalents of CB[7] (CB[7]⊂[Cu(**L1**)I]I_2 complex formation is ≥99.99% in these conditions), no formation of triazole **5** was detected over the course of 7.5 h (Figure **2b**, blue, data shown up to 180 min). This result demonstrates that the binding to CB[7] effectively switches off the catalytic activity of [Cu(**L1**)I]I_2. In order to demonstrate the temporal control in CuAAC, an experiment was conducted in which signal molecule **1** 3-(furylmethyl)trimethyl ammonium bromide (Figure **1a**, compound **1**) was added (8.8 equivalents relative to CB[7], compound **1**⊂CB[7] complex formation is ≥99.99% in these conditions) to the CB[7] inhibited catalyst CB[7] complex.

Positively charged signal molecule **1** has a strong interaction (K_a = (1.8 ± 0.2) $*10^7$ M^{-1}) to CB[7] in an aqueous environment. We therefore we expect that the CB[7] bound catalyst (inactive) can be displaced from the CB[7] cavity by adding **1**, activating the catalyst. We added the CB[7]⊂[Cu(**L1**)I]I_2 complex to a mixture of **3** and **4** in MES/DMSO, to confirm that no reaction took place over the course of 60 min. At t = 60 min we added signal molecule **1**, at which point the click reaction yielding triazole **5** immediately started (Figure **2b**, dashed line).

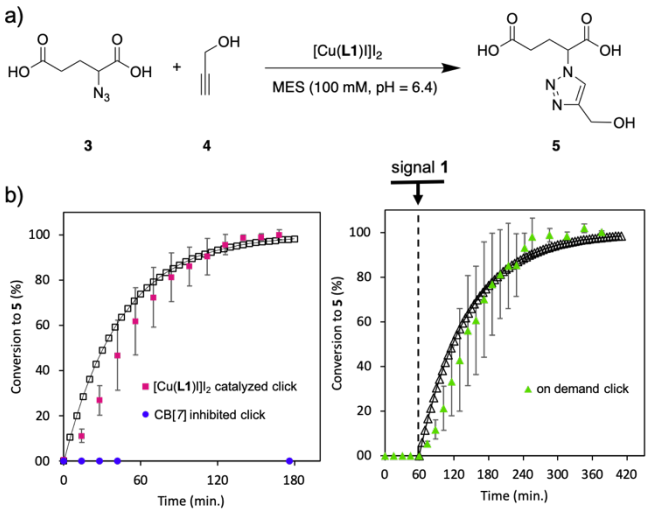

Figure 2. **a**) Model click reaction used to investigate the catalytic activity of [Cu(**L1**)I]I_2. **b left**) formation of triazole **5** in MES buffer (100 mM, pH = 6.4, 25% (v/v) DMSO) catalysed by [Cu(**L1**)I]I_2 (0.4 μM) ([**3**] = 15 μM, [**4**] = 57 μM). Full conversion is reached after 120 min (magenta). Error bars are standard deviations after n = 3 experiments. Open squares represent a pseudo-first order model fit to experimental data. Encapsulating [Cu(**L1**)I]I_2 with CB[7] results in a catalyst CB[7] complex that does not show any catalytic activity (blue). **b right**) In order to restore the catalytic activity, signal molecule **1** is added at t = 60 min. (dashed line) to the inhibited catalyst CB[7] complex. This results in the immediate activation of Cu(I) catalysed click reaction (green). Error bars are standard deviations after n = 2 experiments. Open triangles represent a pseudo-first order model fit to experimental data.

The reaction reached complete conversion after approximately 180 min, showing a reaction rate after activation that is in the

same order of magnitude as the free catalyst rate (Figure **2b**, green line). Combined, these results show that it is possible to deactivate a click catalyst by supramolecular encapsulation, and that it can be reactivated using a chemical signal. With this in hand, we were interested to find out if our method would allow temporal control over protein labelling using a chemical trigger. To test this, we designed an assay of clicking fluorescent molecules to a protein. We obtained recombinant Vinculin[20] equipped with multiple alkyne click handles. Vinculin is a cytoskeletal protein with a molecular weight of 116 kDa and it has been shown to play a role in cell-matrix and cell-cell adhesions.[21] Moreover, it has been shown to be associated with anti-citrullinated protein antibody (ACPA) positive rheumatoid arthritis as an antigen.[22] Using alkyne-modified recombinant Vinculin (35.6 kDa), we sought to attach the azide version of the Alexa 647 fluorescent probe (Figure **3a**). We mixed Vinculin with Alexa 647 in MES buffer (100 mM, pH 6.4, 25% v/v DMSO) and observed that the reaction took place after addition of the catalyst (Figure **3b**, magenta line & **3c** magenta square).

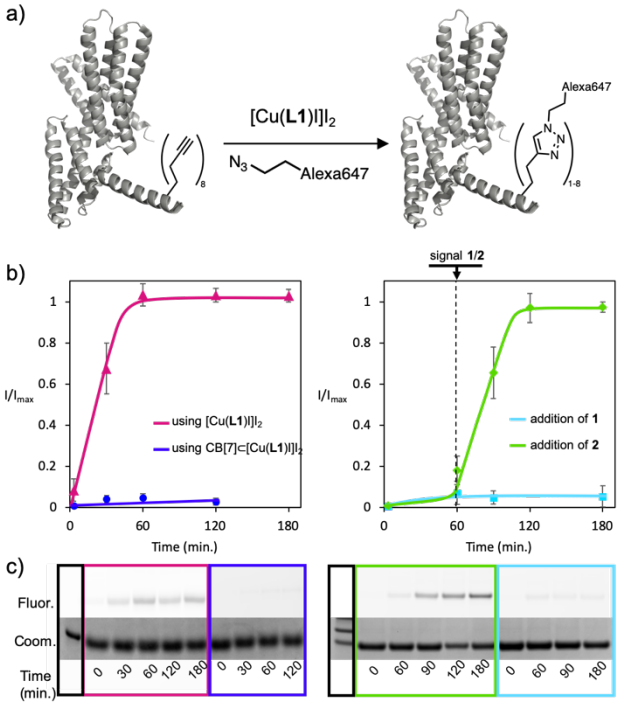

Figure 3. **a**) schematic illustration of alkyne handle modified Vinculin protein, which can be fluorescently labelled with azide-Alexa 647, catalyzed by [Cu(**L1**)I]I_2. The recombinant Vinculin protein has 8 alkyne groups at various positions in its structure. **b**) left panel: relative fluorescence labelling conversion over time, showing uninhibited fluorescence labelling reaching its maximum value after approximately 60 min (magenta); CB[7] inhibited fluorescence labelling, over the course of 120 min no significant labelling is observed (blue). Right panel: activation of fluorescence labelling using signal molecules. After 60 min (dashed line) of reaction using CB[7]-inhibited catalyst, signal molecule **1** was added, showing no catalyst activation (cyan). In a similarly inhibited sample, signal molecule **2** was added after 60 min (dashed line), leading to immediate fluorescent labelling (green). Lines are drawn to guide the eye. **c**) Scans of stained gels with Coomassie (Coom.), and analyzed for fluorescent intensity (Fluor.) over time (min.). Coomassie bands shown in the black frames indicate the 40 kDa protein marker (recombinant Vinculin MW (453-724 amino acid sequence of wild type Vinculin) is 35.6 kDa).

Furthermore, we observed that the fluorescent labelling of Vinculin reaches its maximum relative value after 60 min, suggesting that the solvent available alkyne moieties have been labelled. Next we evaluated if we can inhibit the catalyst with CB[7]. Performing the labelling reaction with a mixture of CB[7] and [Cu(**L1**)I]I_2 (7.4:1 ratio) showed no conversion to the fluorescently labelled protein (Figure **3b** blue line & **3c**, blue square). This result agrees with our previous findings in the small molecule reaction forming triazole **5**. To switch on the catalytic activity and allow for a click reaction to occur, a stronger binding guest (signal molecule) for CB[7] was added as a signal molecule. In the first instance we used signal molecule **1** (Figure **1a**), as this triggered the model click reaction immediately after the addition (Figure **2b**). However, we found that signal molecule **1** was not able to trigger the protein labelling (Figure **3 b**, **c**, cyan data). We tried various high affinity guests for CB[7], such as amantadine (Ka = 4.23 *10^{12} M^{-1})[23], phenylalanine (Ka = 1.8*10^{6} M^{-1})[9c] and dimethylaminomethyl-ferrocene (Ka = 10^{12})[24], but none of these guests triggered labelling of the protein. We hypothesized that these positively charged guests might have a strong non-specific interaction with the protein, due to a large negatively charged patch on the outside of the protein (Figure **SI3**). This patch may bind the guests, thereby preventing the guests from interacting with the inactive CB[7] catalyst complex. In order to test this hypothesis, we used non-charged hydroxymethyl ferrocene **2** (Ka = 3.0*10^{9} M^{-1})[25] (Figure **1a**). The green line in figure **3b** shows that, directly after the addition of signal molecule **2** the protein labelling started. Absolute fluorescence reached its maximum value 60 min after the addition of the signal molecule, again showing a kinetic profile similar to the uninhibited catalyst. This result demonstrates that a competitive guest can act as a signal molecule to activate the Cu(I) catalyst for protein labelling using click chemistry.

To conclude, we synthesized the [Cu(**L1**)I]I_2 catalyst and demonstrated that it effectively catalyzes the azide-alkyne click reaction. The catalyst binds to CB[7] in aqueous environments, leading to a complete loss in catalytic activity. A competitive guest for CB[7] can act as a chemical signal, leading to release and activation of the catalyst, as we have demonstrated in both a small molecule model reaction and in a protein labelling experiment. These results show that host guest chemistry is a powerful tool to exert temporal control over catalytic activity. For future applications it would be interesting to implement this chemically triggered CuAAC in biological processes that are regulated by alkaloids or other small organic cations such as choline, as these are potential signal molecules to activate the CB[7] inhibited catalyst.[26] On that note, cucurbituril complexes are known to facilitate delivery of a broad variety of cargos across the cell membrane.[27] We envision that the here presented chemistry could be used for 'on demand' labelling of biomolecules in the cell, which could have great implications for studying a variety of dynamic biological processes. We are currently looking into enhancing solvent and buffer tolerance to enable these applications in living systems. Lastly, the here presented work can be adopted to different biocompatible metal carbene catalysts such as NHC-Pd[28] and NHC-Ru[29] in order to regulate their catalytic activity.[30]

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Keywords: Cucurbit[*n*]uril • protein labelling • click chemistry • host-guest chemistry • catalysis

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