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Copper(I)-Chelated Cross-Linked Cyclen Micelles as a Nanocatalyst for Azide-Alkyne Cycloaddition in Both Water and Cells

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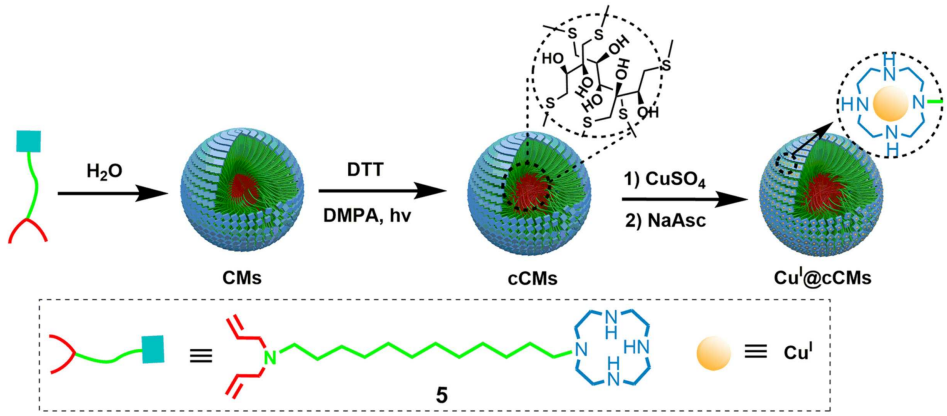
Abstract: Featuring the dendrimer-like properties, the cross-linked small-molecule micelles (cSMs) have been shown to be a good alternative to dendrimers in many applications. Following this trend, herein the copper(I)-chelated cross-linked cyclen micelles (Cu^{I}@cCMs) were created as a nanocatalyst for azide-alkyne cycloaddition. Both alkynes and azides with diverse structures performed with excellent reactivity in water at the parts-per-million (ppm) catalyst usage. Recycle experiments disclosed that the nanocatalyst had only slight decrease of catalytic efficiency after reusing many times. Importantly, the Cu^{I}@cCMs could easily enter cells and carry out the intracellular catalysis for lighting up and/or killing cancer cells.

Keywords: Cross-linked small-molecule micelles; Cyclen; Azide-alkyne cycloaddition; Cu^{I}; Intracellular catalysis

Introduction

The copper catalyzed azide-alkyne cycloaddition (CuAAC) has proven to be a pivotal advance in chemical ligation strategies, with applications ranging from synthetic organic chemistry to material chemistry, and to biomedicinal chemistry.[1] However, the classical CuAAC reactions suffer from problems of high catalyst dosage and absent recyclability.[2] In this case, copper catalysts supported in organic nanomaterials have recently attracted attention due to their superiority in overcoming these problems.[2b,3] Among them, polymer nanoparticles and dendrimers are currently two main supports for the loading of coppers. However, most of the polymer nanoparticle supported copper catalysts are heterogeneous and face the shortcoming of low activity due to the diffusion limitations;[4] besides, polymer nanoparticles suffer also the stability issue due to their non-covalent bond synthesis. The dendrimers, benefited from their precise molecular weight, spherical nanostructure, functionalized exterior, and superstability, can take the advantages of both heterogeneous and homogenous catalysts,[2b,5] and seem to be a more superior catalyst carrier. In this regard, Astruc and coworkers did seminal studies,[5b] and in some of them the copper dosage was even reduced to parts-per-million (ppm) level and could be recycled many times.[3b,c] However, although these dendrimer supported metal catalysts are promising, the dendrimer carriers themselves require complex chemical synthesis. Moreover, the copper ions were always protected in the dendrimer's cavity which was unfavorable to the contact between copper ions and substrates, thus resulting in the reaction kinetic drop.[6]

The cross-linked small-molecule micelles (cSMs) are covalently surface- or core-captured spherical micelles assembled by the amphiphiles with typically molecular weight below 1000.0 Da.[7] Featuring the dendrimer-like properties (e.g., spherical shape, controllable size, functionalized exterior, and good stabil-



Scheme 1. Schematic illustration of the preparation of Cu^{I}@cCMs

ity), the cSMs have been shown to be a good alternative to dendrimers in many applications.[7,8] In organic synthesis, the cSMs supported rhodium catalyst,[9] zinc complex,[10] gold(0) nanoclusters,[11] and copper(0) nanoparticles[12] have successfully been developed to catalyze various organic reactions in aqueous phase with excellent catalytic efficiency, selectivity, and recyclability.

In this study, we reported the copper(I)-chelated cross-linked 1,4,7,10-tetraazacyclododecane (cyclen) micelles (Cu^{I}@cCMs) as a nanocatalyst for azide-alkyne cycloaddition in both water and cells. As shown in Scheme 1, the cyclen group can not only provide the hydrophilic part of the micelles, but also locate the copper ions on the surface of micelles through coordination so as to facilitate the contact between substrates and catalytic centers. Under the optimized reaction condition of 20 ppm Cu^{I}@cCMs and 35 °C for 24 h, the click reaction reached 82–99% isolated yields for twenty substrates. The Cu^{I}@cCMs maintained a high catalytic efficiency (>90%) even after five-time recycles. Importantly, the Cu^{I}@cCMs could easily enter cells and carry out the intracellular catalysis for lighting up and/or killing cancer cells. The killing efficiency was even twice higher than that of the directly use original drug. With the help of cyclen on the particle surface, the cCMs can also coordinate other transition metal ions easily and therefore hold great potential as a general platform for the synthesis of various nano-catalysts according to need.

Results and Discussion

Compound **5** was prepared in two steps by the alkylation of di-allylamine with readily available 1,12-dibromododecane, followed by the alkylation of compound **4** with 1,4,7,10-tetraazacyclododecane (Scheme 1). The amphiphile **5** was spontaneously assembled into cyclen micelles (CMs) above its critical micelle concentration (CMC, ~65.8 μM, Figure S1) with a hydrodynamic diameter of ~36.0 nm (Figure 1a). The cross-linked cyclen micelles (cCMs) were prepared by adding dithiothreitol (DTT) and 2,2-dimethoxy-2-phenylacetophenone (DMPA, a photo-initiator) to CMs solution under UV (254 nm) irradiation. The disappearance of alkenyl protons in ^{1}H NMR spectra demonstrated the successful cross-linking of the micelles (Figure S2). Notably, the average diameter of cCMs was around 45.0 nm (Figure 1a), a little bit larger than that of CMs. This is reasonable considering that the cross-linking agents were introduced into the micelle core after cross-linking.[7,8b]

The preparation of the nanocatalyst Cu^{I}@cCMs involved addition of anhydrous $CuSO_4$ to cCMs

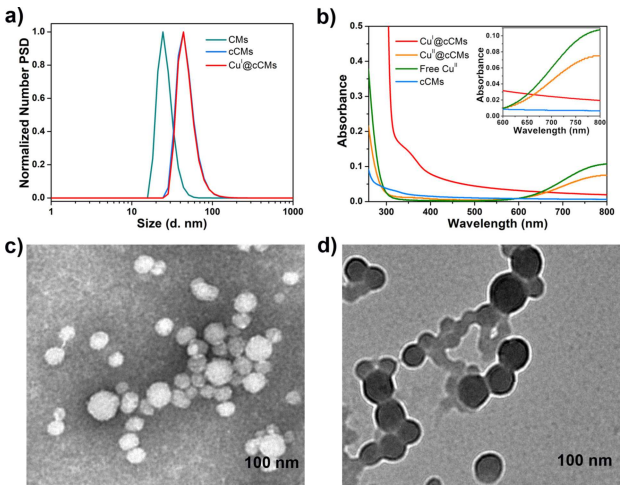


Figure 1. Characterization of the cCMs and Cu^{I}@cCMs. a) Distribution of the hydrodynamic diameters of CMs, cCMs and Cu^{I}@cCMs. b) UV-vis spectroscopy of cCMs, free Cu^{II}, Cu^{II}@cCMs and Cu^{I}@cCMs. c) TEM micrograph of cCMs. d) TEM micrograph of Cu^{I}@cCMs. All samples were stained with an aqueous solution of 2% phosphotungstic acid.

solution and then *in situ* reduction of the precatalyst Cu^{II}@cCMs by dropwise addition of sodium *L*(+)-ascorbate (NaAsc) under nitrogen atmosphere (Scheme 1 and see the Supplementary Information for details). The preparation process of Cu^{I}@cCMs was monitored by UV-vis spectroscopy, dynamic light scattering (DLS), and transmission electron microscopy (TEM). As shown in Figure 1b, in UV-vis spectroscopy, an aqueous solution of $CuSO_4$ had an absorption in the range of 650–800 nm, which is attributed to the Cu^{II} d-d transition.[13] The Cu^{II}@cCMs showed also an absorption peak at 650–800 nm while the intensity weakened, which indicated that the Cu^{II} was located on cyclen successfully (Figure 1b).[13–14] The Cu^{I}@cCMs demonstrated no absorption at 650–800 nm, while a new peak appeared between 300 and 400 nm (main absorption at 370 nm, Figure 1b) which was attributed as a metal to ligand charge transfer (MLCT) transition.[14] The DLS measurement revealed that the average diameter of Cu^{I}@cCMs was around 45.0 nm, consistent with the size of cCMs. The TEM characterization showed the Cu^{I}@cCMs have similar morphology and size with the cCMs (Figure 1c, d). Interestingly, by dyeing with phosphotungstic acid, the Cu^{I}@cCMs was positively stained while the cCMs was negatively stained.[15] This phenomenon happened possibly because the coordination of Cu^{I} changed the combination way between phosphotungstic acid and cCMs, consequently leading to the change of staining mode (Figure 1c, d). Since the cyclen has a strong coordination ability toward a variety of cations, we used Ti^{III}, Pd^{II}, Fe^{III} to chelate with cCMs in aqueous phase, respectively. It was found that they were all successfully coordinated with cCMs according to the characterization of UV-vis, Zeta potential and inductively coupled plasma-atomic emission spectroscopy (ICP-AES) (Figure S3–S6, see Supplementary Information for details). This result suggests that the cCMs are a general platform to form various metal nanocatalysts.

The reaction between benzyl-azide and phenylacetylene was set as the standard model to test the catalytic efficiency of Cu^{I}@cCMs with various amounts of Cu^{I} under nitrogen atmosphere at 35 °C in aqueous solution (Table S1). The studies showed that the best condition was 20 ppm Cu^{I}@cCMs under nitrogen atmosphere and 35 °C for 24 h, which led to a full conversion of starting substrates and 90% isolated yield. It should be noted that the addition of 20 mol% triethylamine did not improve the catalytic efficiency (Table S1, entries 2 and 4), suggesting that the cyclen served a dual role in this regard. At the end of the reaction, the copper content of Cu^{I}@cCMs was determined via ICP-AES, which showed that the residual Cu was 19.3 ppm, very close to the copper content of Cu^{I}@cCMs without catalysis (20.0 ppm) (see the Supplementary Information for details), suggesting the stability of the Cu^{I}@cCMs. Then, to verify the generality of Cu^{I}@cCMs, a series of cycloaddition reactions between azides and alkynes under the optimal reaction condition were conducted (Table 1). To our delight, the click reactions between the azides with either donating or withdrawing substituting groups and terminal alkyne with different substituents both obtained good yields (entries 1–18). The functional biomolecules with fluorogenic and medicinal interests were synthesized by the click reaction in aqueous media, and the separation yields of both were above 90% (entries 19 and 20). In general, twelve different azides and five different terminal alkynes underwent Cu^{I}@cCMs catalyzed click reaction, with isolated yields ranging from 82% to 99% under the optimal reaction condition, validating the quite substrate adaptability of Cu^{I}@cCMs.

To test the recyclability of the Cu^{I}@cCMs, phenylacetylene and benzyl-azide were employed as the model substrates. At the end of each cycle, the catalyst was recovered by extraction-filtration process, and the organic layer containing the click products was concentrated and analyzed by ^{1}H NMR spectroscopy. In this way, the catalyst still maintained its catalytic efficiency above 90% after the fifth cycle (Figure 2, see the Supplementary Information for details). These results suggested that the Cu^{I}@cCMs would be served as an economical nanocatalyst for organic synthesis.

After confirming the excellent reaction efficiency of Cu^{I}@cCMs in aqueous phase, their potential to act as an intracellular catalyst was tested in living cells. As

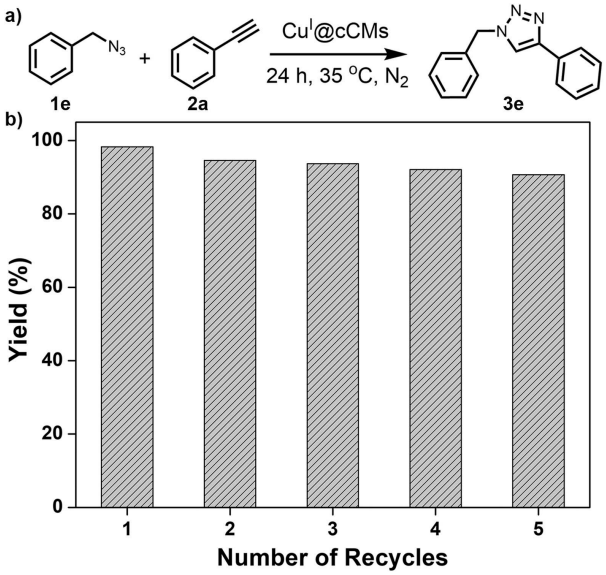
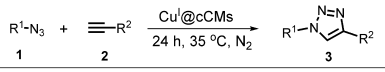


Figure 2. Recyclability of the Cu^{I}@cCMs ([Cu] = 100 ppm) in click reaction in water. a) The click reaction between benzyl azide (0.2 mmol) and phenylacetylene (0.201 mmol) under nitrogen at 35 °C. b) The relationship between the number of cycles of Cu^{I}@cCMs and the catalytic efficiency.

Table 1. Click" reactions between various terminal alkynes and azides using Cu^{I}@cCMs in water[a]



Entry	Azide	Alkyne	Product	Yield[b] (%)
1	1a	2a	3a	91
2	1b	2a	3b	92
3	1c	2a	3c	91
4	1d	2a	3d	89
5	1e	2a	3e	90
6	1f	2a	3f	90
7	1g	2a	3g	94
8	1h	2a	3h	89
9	1i	2a	3i	99
10	1j	2a	3j	96
11	1a	2b	3k	93
12	1e	2b	3l	90
13	1b	2b	3m	93
14	1f	2b	3n	89
15	1g	2b	3o	86
16	1h	2b	3p	87
17	1e	2c	3q	86
18	1e	2d	3r	82
19	1k	2a	3s	94
20	1l	2e	3t	93

a well-known coumarin derivative, 3-azido-7-coumarin is often used in the alkyne-azide cycloaddition reaction to determine whether the reaction takes place by generating new "light up" coumarin derivatives.[12,16] Thus, the potential for intracellular Cu^{I}@cCMs catalysis of the click reaction between 3-azido-7-coumarin (**1k**) and phenyl-acetylene (**2a**) were tested in living cells using confocal microscopy (Figure 3a). Briefly,

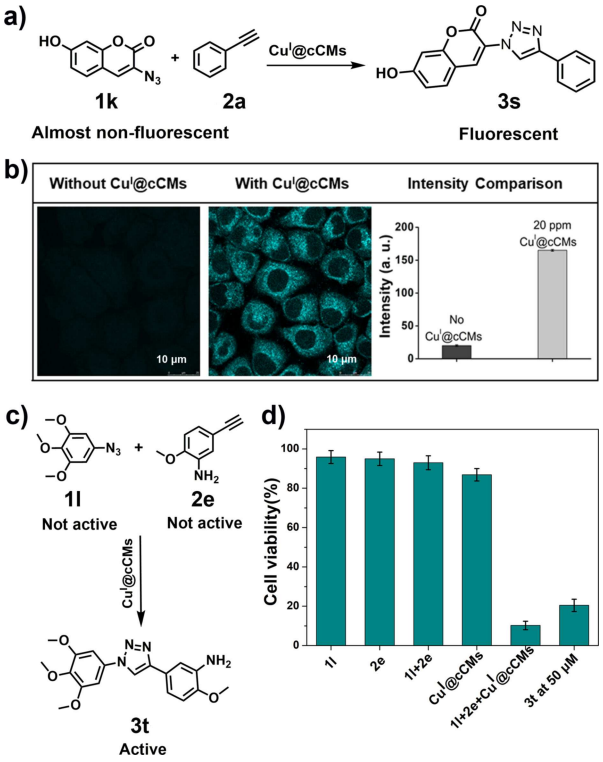


Figure 3. Investigation of the catalytic activity of Cu^{I}@cCMs in living cells. a) The Cu^{I}@cCMs mediated cycloaddition of 3-azido-7-coumarin (**1k**) and phenyl acetylene (**2a**). b) Confocal laser-scanning microscopy (CLSM) and intensity comparison of the intracellular catalysis of Cu^{I}@cCMs on the "click" reaction between precursors **1k** (50 μM) and **2a** (50 μM). c) Model study of the intracellular synthesis of anticancer agent **3t** from precursors **1l** and **2e** in HeLa cells, catalyzed by Cu^{I}@cCMs. d) Viability of HeLa cells in precursors **1l**, **2e** and **3t**.

human cervical cancer (HeLa) cells were preincubated with Cu^{I}@cCMs ([Cu] = 20 ppm in Dulbecco's modified

Eagle medium, DMEM) for 1 h; the DMEM was removed and the cells were washed three times by phosphate buffered saline (PBS) to eliminate extracellular Cu^{I}@cCMs, and subsequently incubated with **1k** (50 μM) and **2a** (50 μM) substrates at 37 °C for 1 h. As seen in Figure 3b, only weak fluorescence could be observed in the absence of Cu^{I}@cCMs, whereas cells were intensely fluorescent in the presence of the catalyst, suggesting the generation of

fluorescent molecule 1a. High resolution mass spectrometry (HR-MS) confirmed that compound **3s** with a molecular weight of 306.0874 was synthesized in cells ($[M+H]^+$, Figure S9). The experimental results showed that the Cu^I@cCMs is not only an excellent solution catalyst, but also an ideal catalyst for intracellular click reaction.

To further investigate the application scope of Cu^I@cCMs, intracellular generation of active drugs for cancer therapy was conducted in HeLa cells. Typically, the triazole-containing anticancer agent **3t**, which is known to inhibit tubulin polymerization to interfere with the mitotic spindle assembly during cell division, was synthesized from two benign precursors **1l** and **2e** (Figure 3c).[12,16] As shown in Figure 3d, when HeLa cells were incubated with different combinations of precursor **1l**, **2e**, [**1l**+**2e**], and Cu^I@cCMs for 24 h, there showed negligible cytotoxicity. By contrast, the combination of [**1l**+**2e**+Cu^I@cCMs] showed remarkable cytotoxicity to HeLa cells. The HR-MS confirmed the formation of compound **3t** in the cells with the molecular weight of 357.1563 ($[M+H]^+$, Figure S10). Interestingly, the cytotoxicity of [**1l**+**2e**+Cu^I@cCMs] was even twice than that of anticancer agent 1b (10.2% vs 20.5%), possibly owing to the high uptake rate of precursors and subsequently *in situ* generation of high local concentration of active drugs realized by the Cu^I@cCMs near the nucleus.[17] Thus, the Cu^I@cCMs catalyzed *in situ* generation of active drugs seems to be an effective strategy to improve the utilization rate of drugs.

The biocompatibility of Cu^I@cCMs was finally evaluated (see the Supplementary Information for details). As shown in Figure S7, the cCMs demonstrated no cytotoxicity even at a concentration of 150 μg/mL. Due to the protection of cyclen of cCMs, the Cu^I@cCMs showed little cytotoxicity as well, with full cell viability at concentrations up to 100 ppm. However, the conventional catalyst CuBr exhibited significant concentration-dependent cytotoxicity with the survival rate of treated cells less than 80% at a concentration of 2.5 ppm Cu^I and less than 50% at 50 ppm Cu^I (Figure S8).

Conclusions

In summary, we developed cross-linked cyclen micelles for copper(I)-chelation (Cu^I@cCMs) to catalyze the azide-alkyne cycloaddition. Featuring the robust stability, water solubility, easy contact with substrates, and biocompatibility, the Cu^I@cCMs exhibited remarkable catalytic activity both in water and cells at the parts-per-million (ppm) level. The nano-catalyst could be recovered easily and had only slight decrease of catalytic efficiency after reusing five times. Besides copper, the cross-linked cyclen micelles could coordinate other transition metals as to form various nano-catalysts, which would play a role in wide organic synthesis.

Experimental Section

General Procedure for the Cu^I@cCMs Catalyzed Azide-Alkyne Cycloaddition in Water

A 20 ppm of catalyst Cu^I@cCMs, alkyne (0.105 mmol), organic azide (0.1 mmol), and 1.0 mL water were added to a Schlenk flask. The reaction mixture was then stirred at 35 °C under nitrogen atmosphere for 24 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with EtOAc (3×5 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum/ EtOAc) to afford the acquire product.

Catalytic Activity Study of Cu^I@cCMs in Living Cells

HeLa cells were plated in DMEM in a 96-well plate grown for 24 h at 37 °C with 5% CO_2. The medium was removed and a solution of Cu^I@cCMs ([Cu] = 20 ppm) in DMEM was added and incubated for 1 h at 37 °C. Then the medium was removed, and 3-azido-7-coumarin (**1k**, 50 μM) and phenylacetylene (**2a**, 50 μM) were added. The solution was incubated for 1 h at 37 °C. As a control, the samples without any catalyst were incubated for the same time at 37 °C. After incubation, cells were washed twice with PBS, and the fluorescence of compound **3s** was detected by confocal laser-scanning microscopy. The catalytic activity of the nanocatalyst in living cells was determined by the quantitative fluorescence signals as a function of time.

Cu^I@cCMs Catalyzed Intracellular Azide-Alkyne Cycloaddition for *in situ* Generation of the Anticancer Agent 3t

HeLa cells were plated in DMEM in a 96-well plate and grown for 24 h at 37 °C with 5% CO_2. Then the medium was removed and a solution of Cu^I@cCMs ([Cu] = 20 ppm) in DMEM was added and incubated for 1 h. Then the medium was removed, and different combinations of precursor **1l** (50 μM), **2e** (50 μM), [**1l** (50 μM) + **2e** (50 μM)] and **3t** (50 μM) were added and incubated for 24 h. After the incubation, the culture media was removed and fresh media (100 μL) containing CCK-8 (10 μL) was added to each well. The plates were incubated at 37 °C for another 2 h. The absorbances of each sample at 450 nm were measured using a varioscan flash microplate reader. The generation of anticancer agent **3t** was determined by a cell viability assay (vide infra).

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UPDATES

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