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Metallo-Folded Single-Chain Nanoparticles with Catalytic Selectivity

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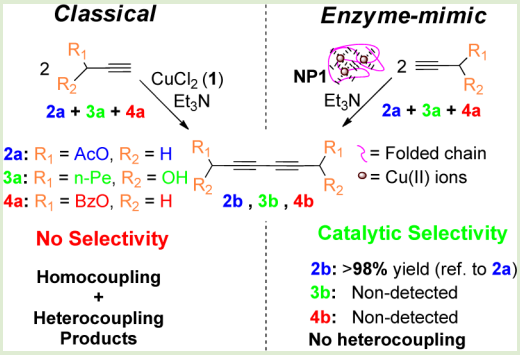
Supporting Information

ABSTRACT: Mimicking the substrate specificity and catalytic activity of enzymes is of great interest for different fields (e.g., chemistry, biology, nanomedicine). Enhanced reaction rates using artificial, enzyme-mimic catalysts based on a variety of molecular structures and nanoentities (e.g., macrocyclic compounds, star and helical polymers, dendrimers) have been previously reported. However, examples of enzyme-sized soft entities displaying substrate specificity are certainly scarce. Herein, we report the synthesis and characterization of single-chain nanoparticles based on metallo-folded polymer chains containing complexed Cu(II) ions showing catalytic specificity during the oxidative coupling of mixtures of chemically related terminal acetylene substrates. This work paves the way for the easy and efficient construction of other Pd-, Ni-, Co-, Fe-, Mn-, or Mo-containing soft nanoentities approaching the substrate specificity of natural enzymes for a variety of organic reactions.



Enzymes showing outstanding catalytic activity and extreme substrate specificity are a continuing source of inspiration for green chemistry practitioners. Concerning catalytic activity, several artificial enzyme-mimic molecular structures and soft nanoentities approaching the size of natural enzymes have been synthesized based on macrocyclic compounds,[1] star,[2] hyperbranched,[3] and helical[4] polymers as well as dendrimers,[5] among other systems.[6] However, examples of soluble nanosized soft catalysts displaying pronounced enzyme-like substrate specificity are relatively scarce. For instance, limited control over substrate specificity was achieved with 4-(dialkylamino) pyridine-functionalized polymers during the solvolysis of *p*-nitrophenyl alkanoates in aqueous methanol solution.[7] Also, efficient hydrolysis of a phenyl ester compound was shown by a molecularly imprinted soluble polymer nanogel having a molecular weight of 40 kDa.[6c] To our best knowledge, no example of extraordinary catalytic specificity (i.e., reaction of only one substrate from a mixture of chemically related substances) has been reported by using synthetic soft nanoentities approaching the size of natural enzymes (5−15 nm).

The synthesis of biomimetic catalysts based on individual self-cross-linked polymer chains (single-chain nanoparticles, SCNPs) is challenging due to the polydisperse nature in size and composition of current synthetic polymers and the lack of efficient folding protocols.[8,9] Consequently, current SCNPs mimic the structure of folded biomacromolecules only in an approximate manner.[10] In spite of these limitations, SCNPs have been revealed as simple model systems to which valuable enzyme-like activity can be endowed by means of imprinted particle,[6c] hydrophobic cavity,[11] or concurrent binding/folding[12] strategies. In particular, the recently reported "concurrent" strategy opens new, promising avenues for endowing SCNPs with enzyme-mimetic properties such as outstanding catalytic activity and extreme substrate specificity.

Herein, we demonstrate how metallo-folded SCNPs containing complexed Cu(II) ions produced by means of such a versatile approach (Scheme 1, **NP1**) display catalytic specificity during the oxidative coupling of mixtures of chemically related terminal acetylene substrates. Such specificity is not affordable by classical catalysts (i.e., $CuCl_2$, $Cu(OAc)_2$, $Cu(acac)_2$) under exactly the same reaction conditions. Moreover, a wide range of other metallo-folded SCNPs can be envisioned by appropriate selection of metal ions (e.g., Pd, Ni, Co, Fe, Mn, Mo), pointing to the potential broad scope of the concurrent binding/folding strategy.

We have prepared metallo-folded SCNPs based upon previously synthesized copolymers[10] containing methyl methacrylate (MMA) and 2-(acetoacetoxy)ethyl methacrylate (AEMA) repeat units (Scheme 1, **P1**, see Supporting Information, SI) that feature *β*-ketoester reactive functions which serve as handles for concurrent binding/folding via

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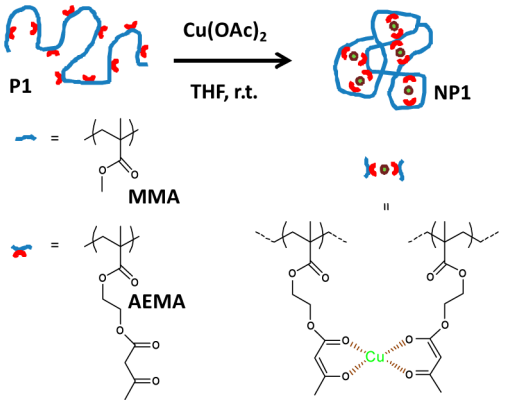
Scheme 1. Idealized Picture of Metallo-Folded Single-Chain Nanoparticle NP1 Synthesized from Precursor P1



intrachain Cu(II) complexation of AEMA units. SCNP formation was carried out under very mild conditions, in THF at room temperature by using $Cu(OAc)_2$ as reagent at high dilution conditions (1 mg/mL) to minimize, as much as possible, unwanted interparticle coupling events. We selected precursor **P1** with a content of reactive AEMA units of 30 mol %, relatively high M_w (weight-average molecular weight, M_w = 375 kDa), and relatively low dispersity ($Đ$ = 1.4) to facilitate accurate detection of size reduction upon SCNP formation by combined size-exclusion chromatography/multiangle laser light scattering (SEC/MALLS) measurements. The collapse of the linear copolymer precursor **P1** to SCNP **NP1** upon progressive addition of $Cu(OAc)_2$ is illustrated in Figure 1A. A significant increase in retention time was observed for **NP1** when compared to **P1** as a consequence of the reduction in hydrodynamic size upon SCNP formation, an observation which is consistent with previous works in this field.[13] The average radius of gyration was found to decrease from 26 nm for **P1** to 15 nm for **NP1**, as determined by the MALLS technique.

Evidence of AEMA complexation by copper ions was obtained by infrared (IR) spectroscopy, in which characteristic vibration bands located at 1600 cm^{-1} (stretching C═O vibration, enol tautomer bonded to Cu) and 1515 cm^{-1} (stretching C═C vibration, enol tautomer bonded to Cu) were observed in the IR spectrum of **NP1** (Figure 1B). In good solvent, **NP1** shows a more compact conformation than that of precursor **P1**, as revealed by small angle neutron scattering (SANS) experiments (see Figure 1C and Figure S1, SI). The spherical shape of **NP1** in the dry state is shown in Figure 1D. The copper incorporated into **NP1** amounted to 26 mol % with respect to AEMA units as deduced from thermal gravimetric analysis (TGA) (see Figure S2, SI). The oxidation state of copper ions in the $Cu(AEMA)_2$ complexes of **NP1** was determined to be +2 by means of X-ray photoelectron spectroscopy (XPS) measurements (see Figure S3, SI). The amount of metal incorporated into **NP1** was similar to that in organometallic nanoparticles synthesized through intramolecular chelation of individual ROMP-derived poly(1,5-cyclooctadiene) chains by Rh(I) ions.[14]

Having shown a mild and efficient synthetic procedure to prepare metallo-folded SCNPs containing complexed Cu(II), we turned our attention toward the potential enzyme-mimic properties of these soft nanoentities when compared to classical catalysts (i.e., $CuCl_2$, $Cu(OAc)_2$, $Cu(acac)_2$). Hence, to

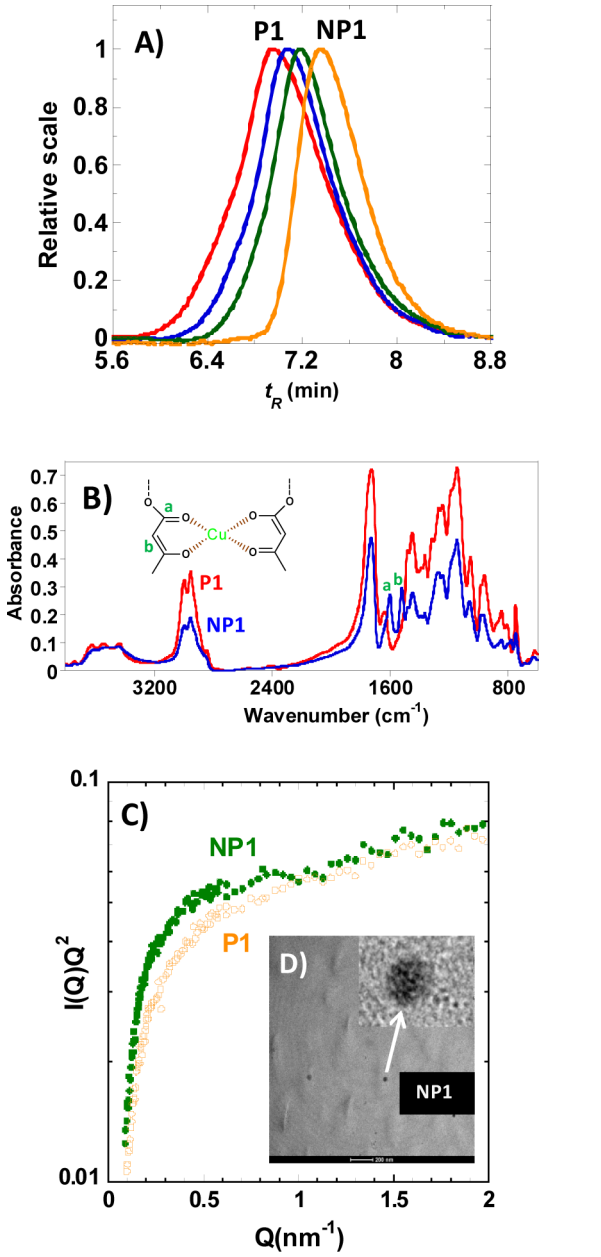


Figure 1. (A) Size-exclusion chromatography traces in THF corresponding to the formation of **NP1** by progressive addition of $Cu(OAc)_2$: 0.17 mM (blue curve), 0.34 mM (green curve), and 0.51 mM (orange curve) to a P1 solution (red curve). (B) IR spectra of precursor **P1** and **NP1** showing specific vibration bands (a, b) arising from $Cu(AEMA)_2$ complexes. (C) SANS Kratky plots of **P1** and **NP1** solutions. A shoulder is observed at low Q values due to a more compact conformation of **NP1** in solution when compared to that of **P1** (see SI). (D) TEM image of **NP1** in the dry state (inset is a magnification; **NP1** size ≈ 20 nm).

evaluate the catalytic activity and substrate specificity of copper-containing SCNPs, we explored their use as soft catalysts in an environmentally friendly, economical, and efficient method[15a] for transforming terminal acetylenes into 1,3-diynes via oxidative coupling. It is worth mentioning that 1,3-diynes have attracted significant interest as building blocks for the construction of supramolecular materials,[16] π-conjugated acetylenic oligomers and polymers,[17] industrial and pharmaceutical intermediates,[18] as well as antitumor agents.[19]

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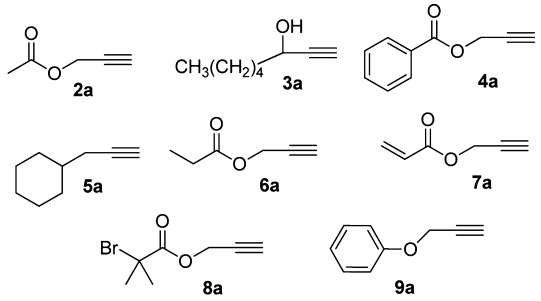
Thus, as a first control experiment we performed the coupling of a series of terminal alkyne compounds to 1,3-diynes under optimized reaction conditions[15b] involving the use of catalytic amounts of $CuCl_2$ (**1**) (3 mol %) and Et_3N (3 mol %). These acetylenic compounds were selected to cover a broad range of chemically related substrates (Scheme 2). The bulk

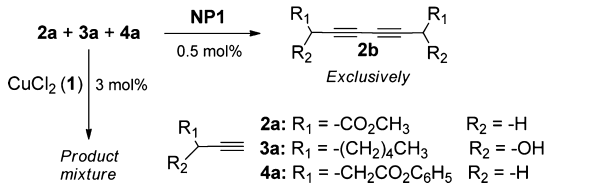
Scheme 2. Chemical Structures of Terminal Alkynes Used in This Work



homocoupling procedure gave the corresponding diynes in good to excellent yields (36−99%, Table 1) with the exception of compound **8a** having a bromo functional group (Table 1, entry 8). As expected, catalyst **1** showed no specificity since binary or ternary mixtures of terminal alkynes, as reagents, lead to complex mixtures of diynes, as products, due to both homo- and cross-coupling reactions (Table 1, entries 19, 21, 23, and 25 and Figure 2). By reducing the amount of catalysts to 0.5 mol % Cu no reaction was observed to take place. The catalyst was found to work also in the presence of aromatic solvents (Table 1, entry 2).

Interestingly, when we replaced the classical catalyst **1** by the metallo-folded SCNP **NP1** at a lower concentration of 0.5 mol % Cu we observed unprecedented catalytic specificity toward the propargylic substrate **2a** (>98% yield, $R_1 = -CO_2CH_3$) and, to a minor extent, also toward the related compound **6a** (27% yield, $R_1 = -CO_2CH_2CH_3$) (see Table 1 and Figure 2). Very good yield was also observed by running the reaction in aromatic solvent (Table 1, entry 11). Moreover, in competitive experiments involving ternary mixtures of **2a**, **3a**, and **4a** (Table 1, entry 26) no sign of cross-coupling products was observed by GC, giving only **2b** as the product in a highly selective manner. **NP1** showed catalytic selectivity toward the propargylic substrates in mixtures of **2a**, **3a**, and **6a** (Table 1, entry 28). Moreover, this selectivity toward **2a**, and to a minor extension **6a**, was maintained in control experiments using compounds with a group more bulky than a proton near the acetate or having an additional methylene group between the acetate group and the alkyne moiety (see SI). It is worth mentioning that neither $Cu(OAc)_2$ nor $Cu(acac)_2$ compounds were found to display significant catalytic activity at a concentration of 0.5 mol % Cu for compounds **2a**−**9a**. Although this behavior could be tentatively attributed to a local environment in **NP1** with a high enough amount of Cu complex concentration since the presence of a competitive solvent such as ethyl acetate slows the reaction, no reaction was observed in control experiments by increasing the $Cu(acac)_2$ concentration even to 3 mol % Cu (see SI). At this stage, one can hypothesize that the pronounced substrate specificity displayed by **NP1** when compared to $Cu(OAc)_2$ and $Cu(acac)_2$ complexes could result from the formation of multiple, compartmentalized local catalytic sites composed of $Cu(AEMA)_2$ complexes surrounded

Table 1. Unprecedented Catalytic Selectivity of NP1 When Compared to $CuCl_2$ (1) during the Coupling of Terminal Alkynes to 1,3-Diynes under Solvent-Free Conditions



entry	catalyst[a]	reagents	products[b]	yield (%)[b]	selectivity
1	**1**	**2a**	**2b**	>98	-
2	**1**	**2a**	**2b**	93[c]	-
3	**1**	**3a**	**3b**	>98	-
4	**1**	**4a**	**4b**	57	-
5	**1**	**5a**	**5b**	>98	-
6	**1**	**6a**	**6b**	>98	-
7	**1**	**7a**	**7b**	36	-
8	**1**	**8a**	**8b**	0	-
9	**1**	**9a**	**9b**	77	-
10	**NP1**	**2a**	**2b**	>98	-
11	**NP1**	**2a**	**2b**	91[c]	-
12	**NP1**	**3a**	**3b**	0	-
13	**NP1**	**4a**	**4b**	0	-
14	**NP1**	**5a**	**5b**	0	-
15	**NP1**	**6a**	**6b**	27	-
16	**NP1**	**7a**	**7b**	0	-
17	**NP1**	**8a**	**8b**	0	-
18	**NP1**	**9a**	**9b**	0	-
19	**1**	**2a+3a**	mixture[d]	97	No
20	**NP1**	**2a+3a**	**2b**[e]	>98[f]	Yes
21	**1**	**2a+4a**	mixture[d]	51	No
22	**NP1**	**2a+4a**	**2b**[e]	>98[f]	Yes
23	**1**	**3a+4a**	mixture[d]	52	No
24	**NP1**	**3a+4a**	mixture[g]	0	Yes
25	**1**	**2a+3a+4a**	mixture[d]	84	No
26	**NP1**	**2a+3a+4a**	**2b**[e]	>98[f]	Yes
27	**NP1**	**2a+3a+4a**	**2b**[e]	>98[c,f]	Yes
28	**NP1**	**2a+3a+6a**	mixture	66[h]	Yes

[a]Reaction conditions: solvent-free, 1 mmol of alkyne, Et_3N (3 mol %), **1**: 3 mol % Cu, or **NP1**: 0.5 mol % Cu, 60 °C, 8 h, air. [b]From GC and ^{1}H NMR data. [c]Diluted with toluene to half of the original alkyne concentration. [d]Mixture of products as a result of combined homo- and cross-coupling reactions. [e]No byproducts from cross-coupling reactions were detected. [f]Referred to **2a**. [g]Reaction time: 24 h. [h]Referred to (**2a+3a+6a**).

by an environment of methyl methacrylate repeat units allowing an optimum transition state stabilization for the propargylic substrate **2a** and, to a minor extent, **6a**.[6d,12]

To further investigate the origin of the catalytic selectivity, the electronic absorption spectra of $Cu(OAc)_2$, $Cu(acac)_2$, and **NP1** in dimethyl sulfoxide (DMSO) were recorded as illustrated in Figure 3. The UV−vis spectrum of the $Cu(OAc)_2$ complex showed one very broad d−d band at 720 nm and a band in the UV region centered at 260 nm due to Cu-to-OAc metal to ligand charge transfer (MLCT) transitions.[20] The $Cu(acac)_2$ complex displayed only a MLCT band at 297 nm, whereas the **NP1** showed a MLCT band centered at 271 nm, a value in between those observed for the $Cu(OAc)_2$ and $Cu(acac)_2$ complexes. Both steric and electronic complementarities of the catalytic sites for **2a** and to minor extent **6a** in the rate-determining transition step could be responsible for the

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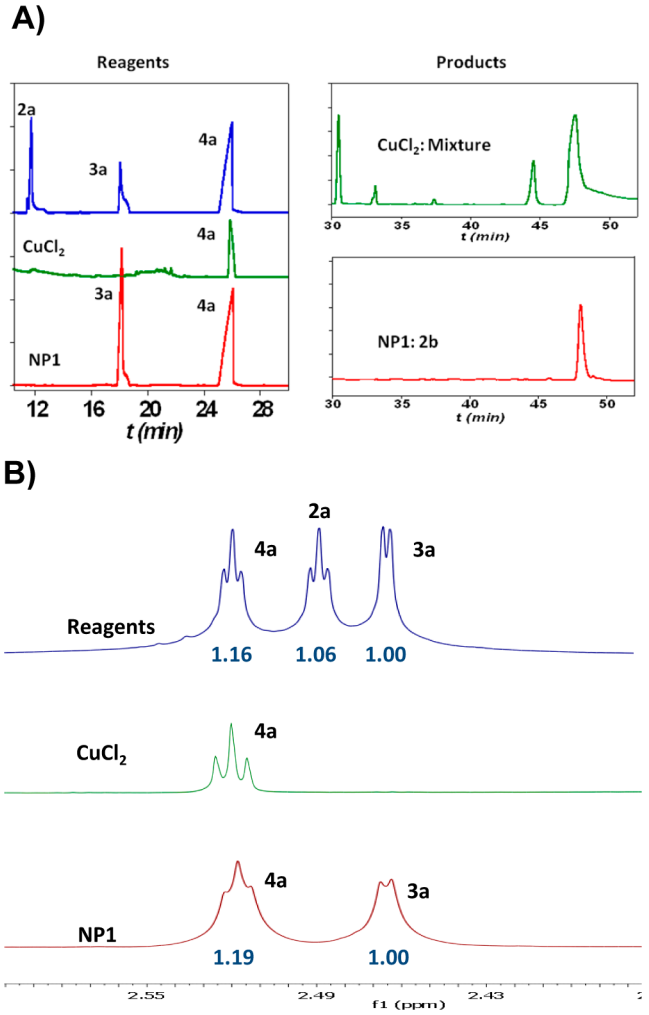

Figure 2. (A) Gas chromatography (GC) traces of the **2a** + **3a** + **4a** reagent mixture (blue trace) and products obtained by using $CuCl_2$ (**1**) (green curve) or metallo-folded SCNPs **NP1** (red curve) as catalysts during oxidative coupling. (B) ^{1}H NMR spectra showing signals from acetylenic protons of the **2a** + **3a** + **4a** reagent mixture (blue trace) and the same spectral zone after reaction using $CuCl_2$ (**1**) (green trace) or metallo-folded SCNPs **NP1** (red trace) as catalysts during oxidative coupling. The peak area relative to that of peak **3a** is indicated for the blue and red traces.

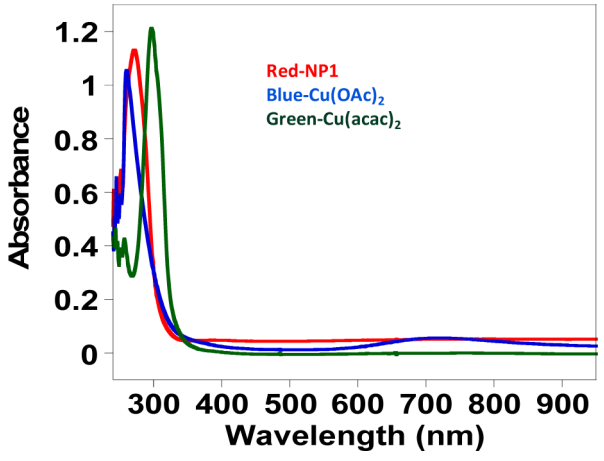

Figure 3. UV–vis spectra of $Cu(OAc)_2$, $Cu(acac)_2$, and **NP1** in DMSO.

catalytic selectivity displayed by **NP1**. Analysis of kinetics data using **2a** as a reagent (see SI) provided a value of the apparent catalytic constant of k_{cat}(app) = 8.8 × 10^{-3} s^{-1}, which is higher than that determined for molecularly imprinted soluble polymer nanogels (k_{cat} = 1.2 × 10^{-6} s^{-1})[6c] and similar to that reported very recently for hydrophobic cavity-based catalytic SCNPs (k_{cat} = 5.3 × 10^{-2} s^{-1}).[11a]

In summary, we have synthesized catalytically active single-chain nanoparticles based on metallo-folded polymer chains containing complexed Cu(II) ions by means of a mild and versatile concurrent binding/folding strategy. These synthetic soft nanoentities approaching the size of natural enzymes display catalytic specificity at low concentration of Cu(II) ions during the oxidative coupling of mixtures of chemically related terminal acetylene substrates, which cannot be attained with classical catalysts such as $CuCl_2$, $Cu(OAc)_2$, or $Cu(acac)_2$. Such substrate specificity has been tentatively attributed to the presence in the metallo-folded nanoparticles of multiple, compartmentalized local catalytic sites composed of Cu-$(AEMA)_2$ complexes surrounded by an environment of methyl methacrylate repeat units allowing an optimum transition state stabilization for the preferred substrates. The specificity displayed by the metallo-folded SCNPs is very promising, and the preparation of other metallo-folded soft nano-objects (based on Pd, Ni, Co, Fe, Mn, and Mo instead of Cu) as well as the study of their enzyme-mimic characteristics is anticipated.

■ ASSOCIATED CONTENT

Supporting Information

Materials and methods, characterization techniques, supporting data, and references. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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