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Abstract

Creation of synthetic catalysts with enzyme-like behavior is challenging despite strong interest in such systems. Extraction of tetrachloroaurate into the hydrophilic core of an interfacially cross-linked reverse micelle (ICRM) produced an artificial "metalloenzyme" with highly unusual catalytic properties. The ICRM pulled the substrate toward the catalytic metal, which converted it efficiently to the product that was rapidly ejected. These features enabled greatly reduced catalyst loading (30–100 times lower than typical levels used in literature examples), constant high reaction rate throughout the course of the reaction, lack of the hydrolyzed side product, and substrate selectivity unobserved in conventional gold catalysts.

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Metalloenzyme-Mimicking Supramolecular Catalyst for Highly Active and Selective Intramolecular Alkyne Carboxylation

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Supporting Information

ABSTRACT: Creation of synthetic catalysts with enzyme-like behavior is challenging despite strong interest in such systems. Extraction of tetrachloroaurate into the hydrophilic core of an interfacially cross-linked reverse micelle (ICRM) produced an artificial "metalloenzyme" with highly unusual catalytic properties. The ICRM pulled the substrate toward the catalytic metal, which converted it efficiently to the product that was rapidly ejected. These features enabled greatly reduced catalyst loading (30−100 times lower than typical levels used in literature examples), constant high reaction rate throughout the course of the reaction, lack of the hydrolyzed side product, and substrate selectivity unobserved in conventional gold catalysts.

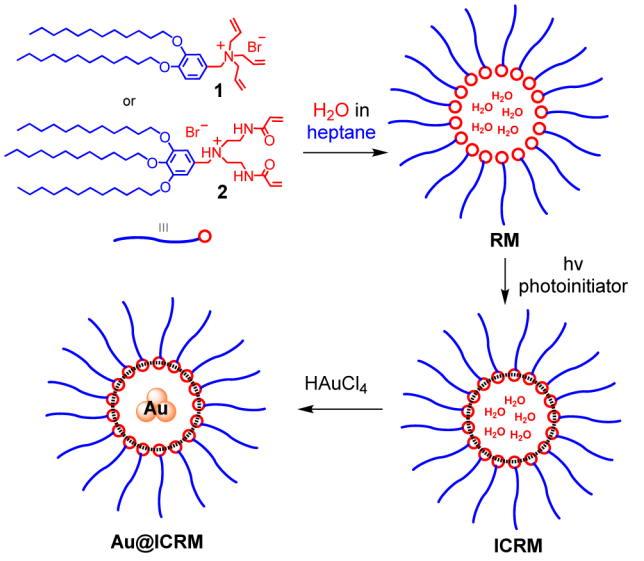
Enzymes frequently perform chemical reactions with efficiency and selectivity that are difficult from a pure synthetic perspective. Different from most synthetic catalysts that primarily accomplish their catalytic tasks by lowering the activation energy of a reaction, enzymes often are characterized by additional features, including selective binding of the substrate via noncovalent forces, correct positioning of appropriate functional groups on the substrate and within the enzyme active site for optimal reactivity, and preferential binding of the substrate over the product.[1] Moreover, selectivity in enzymatic reactions is often accomplished through second-sphere or even more distal control instead of first-sphere interactions as in typical organic, metallic, and organometallic catalysts.[2]

In the past decades, supramolecular chemists have made tremendous progress in making receptors for small molecules.[3] Binding affinities approaching those in biological complexation (e.g., biotin−streptavidin) have been obtained in some cases.[4] Nonetheless, bottom-up construction of enzyme-like supramolecular catalysts remains challenging, especially those with the above-mentioned biocatalytic features.[5] The challenge is understandable. If preparation of a catalytic center (organic, metallic, or organometallic) itself can require significant synthetic effort, building additional binding and regulating features around the catalytic center would certainly demand more sophisticated design and synthesis.[2,5]

Herein, we report a facile bottom-up assembly of an artificial "metalloenzyme" for efficient intramolecular alkyne carboxylation. The supramolecular organization turns a mundane aurate salt into a highly active and selective catalyst with unusual features such as zero-order dependence of the reaction rate on the substrate and selectivity unobserved in conventional gold catalysts.

The design of the artificial "metalloenzyme" is based on our recently synthesized interfacially cross-linked reverse micelles (ICRMs).[6] As shown in Scheme 1, ICRM is prepared by polymerization of cross-linkable surfactants such as **1** or **2** in the reverse micelle (RM) configuration. Our previous work utilized the thiol−ene addition reaction between **1** and dithiothreitol (DTT) to cross-link the RM. Surfactant **2** was cross-linked directly by free radical polymerization of the acrylamide. Because the ICRM core is lined with a layer of quaternary ammonium groups, the cross-linked micelle could easily extract tetrachloroaurate from aqueous solution into its hydrophilic core. The bromide counteranions within the ICRM(**1**) (i.e., ICRM prepared from **1**) in a prior work were shown to reduce aurate spontaneously to form luminescent gold clusters (Au_4 to Au_{23}).[6,7] Complexed with the bromide ions, the overall negatively charged cluster prefers to stay within the positively charged ICRM core. Since gold nanoparticles can catalyze a variety of reactions[8] and gold clusters often have even higher activity due to their higher surface-to-volume ratio,[8,9] we

Scheme 1. Synthesis of ICRM from Cross-Linkable Surfactant and Incorporation of Aurate



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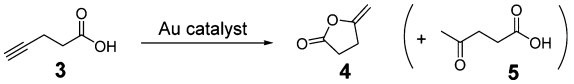
reasoned that the gold clusters within ICRMs might be particularly active catalysts and ICRM could be used to facilitate the substrate binding. Essentially, in this metalloenzyme-mimicking supramolecular catalyst (Au@ICRM), the metal cluster serves as the catalytic center[10] and the ICRM as a biomimetic scaffold to modulate the catalysis.[11]

One reaction catalyzed by gold is the cyclization of ω-alkynoic acid (Scheme 2). AuCl, $AuCl_3$, Au_2O_3, and other gold

Scheme 2. Gold-Catalyzed Cyclization of 4-Pentynoic Acid



compounds have been reported to catalyze the reaction, typically at a 3−10 mol% level.[12] We envisioned that Au@ICRM was ideally suited for this reaction for two primary reasons. First, the carboxylic acid group should be attracted to the ICRM core by the ammonium headgroups of the cross-linked surfactant in a nonpolar solvent. Even if a complete ion exchange (to form R'_4N^+ ^-OOCR and HBr) might not be favorable, to the extent this exchange could occur during the reaction, the substrate would be concentrated around the ICRM core. Not only would the effective concentration of the substrate near the catalytic center be enhanced, but the nanometer-sized ICRM core suggests that the substrate and the catalyst would be in close proximity. Second, once cyclized, the substrate **3** loses the binding functionality COOH, and the relatively nonpolar product **4** should prefer the nonpolar solvent instead of the hydrophilic ICRM core, vacating the binding site(s) for new substrates to come in. Thus, even with a simple structure, Au@ICRM should mimic key catalytic features of enzymes in substrate binding and product turnover.

The initial experiments showed some promise. As shown in Table 1 (entries 1 and 2), 1 mol% Au@ICRM(**1**) was indeed able to catalyze the cyclization, albeit in fairly low yields (17−23%). An encouraging observation was the lack of hydrolysis of **4**, as the hydrolyzed product **5** was not observed at all. Apparently, even though the ICRM had a hydrophilic core and mostly likely some water in the core,[13] **4** must have been released sufficiently fast to avoid hydrolysis.

To our delight, Au@ICRM(**2**) under the same conditions gave dramatically better results: even at 1 mol% catalyst loading (vs 3−10 mol% used in the literature[12]), the reaction went to completion within 3 h at room temperature, also without any hydrolytic side reaction (Table 1, entries 3 and 4). Three hours of reaction time turned out unnecessary, as the reaction was complete in 1 h as well (entry 5). Notably, although Au@ICRM(**2**) was formed from $HAuCl_4$ under spontaneous reduction, $HAuCl_4$ itself was not a good catalyst and afforded only 24% yield, with nearly half of the enol lactone hydrolyzed (entry 11). When un-cross-linked **2** was used instead of the ICRM, no product was observed at all under identical conditions, confirming the importance of the cross-linking (entry 12). Our previous work indicated that, without cross-linking, $AuCl_4^-$ simply was extracted into the organic phase by these surfactants and turned into $AuBr_4^-$ via ligand exchange with the bromide counterions.[7]

To understand the oxidation state of the active Au catalyst involved, we performed the cyclization under different atmosphere, with reduced amount of catalyst (0.1−0.2 mol%) and shorter reaction time (1 h). As shown by Figure S1

Table 1. Intramolecular Cyclization of 4-Pentynoic Acid Catalyzed by 1 mol% Au@ICRMs[a]

entry	ICRM[b]	Au loading[c] (%)	time (h)	yield (%) **4** + **5**	selectivity **4**:**5**
1	ICRM(**1**), W_0 = 5	10	3	17	–[d]
2	ICRM(**1**), W_0 = 5	20	3	23	–[d]
3	ICRM(**2**), W_0 = 5	10	3	>95	–[d]
4	ICRM(**2**), W_0 = 5	20	3	>95	–[d]
5	ICRM(**2**), W_0 = 5	10	1	>95	–[d]
6	ICRM(**2**), W_0 = 5	10	1	75[e]	–[d]
7	ICRM(**2**), W_0 = 5	10	1	22[f]	–[d]
8	ICRM(**2**), W_0 = 5	10	1	6[g]	–[d]
9	ICRM(**2**), W_0 = 2	10	1	>95	–[d]
10	ICRM(**2**), W_0 = 10	10	1	>95	–[d]
11	–[h]	$HAuCl_4$	3	24	53:47
12	–[i]	$HAuCl_4$	3	0	–

[a]All reactions were performed with 0.25 mmol of 4-pentynoic acid with 1 mol% gold catalyst in 0.2 mL of benzene-d_6 at room temperature. The yield was determined by ^{1}H NMR spectroscopy. [b]ICRM(**1**) and ICRM(**2**) were prepared by polymerization of cross-linkable surfactant **1** and **2**, respectively. [c]Aurate loading was the aurate/surfactant ratio in the template synthesis of the gold clusters. [d]Hydrolyzed product **5** was not observed. [e]Solvent for reaction = 0.1 mL benzene-d_6 + 0.1 mL $CDCl_3$. [f]Solvent for reaction = 0.1 mL benzene-d_6 + 0.1 mL MeOH-d_4. [g]Solvent for reaction = 0.1 mL benzene-d_6 + 0.1 mL DMSO-d_6. [h]No ICRM was used, and $HAuCl_4$ was used directly as the catalyst. [i]Un-cross-linked surfactant **2** was used instead of the ICRM, with the ratio of [$HAuCl_4$]/[**2**] = 1:10.

(Supporting Information), oxidative conditions (under air or O_2) were clearly better than inert or reducing conditions (under N_2 or H_2). Thus, the most likely catalytic species was oxidized gold(I or III) on the gold cluster, consistent with other literature reports.[12]

Our hypothesized attraction of the substrate by the ICRM core was supported by solvent effects. Although the reaction proceeded smoothly in benzene (a nonpolar solvent), adding an equal volume of $CHCl_3$, MeOH, or DMSO to benzene lowered the reaction yield progressively, from quantitative all the way to 6% (Table 1, entries 5−8).

The importance of substrate binding to the catalysis was verified additionally by a competitive study. As shown by Figure 1, small-molecule carboxylic acids exhibited powerful inhibition of the cyclization, with even 1 mol% of the acid lowering the yield from quantitative to 40−80%. The inhibition followed a clear trend of acid size: acetic acid > dodecanoic acid >1-adamantanecarboxylic acid. The strong inhibition suggests that a small number of highly active catalytic sites were responsible for the activity (considering that carboxylic acid was abundant in the reaction mixture from the starting material itself). It also appears that metal−ligand complexation between gold and alkyne was *not* the main driving force for the substrate binding. Otherwise, the carboxylic acid inhibitors, lacking the alkyne group, would not have been so effective at such low levels (1 mol%).

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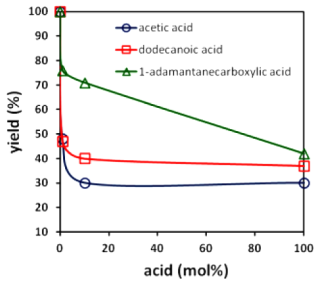


Figure 1. Reaction yield of cyclization of 4-pentynoic acid catalyzed by 1 mol% Au@ICRM(**2**) in the presence of carboxylic acid competitors.

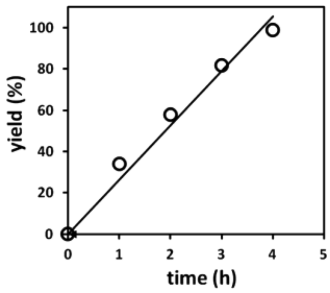


Figure 2. Reaction yield of cyclization of 4-pentynoic acid catalyzed by 0.1 mol% Au@ICRM(**2**) over time.

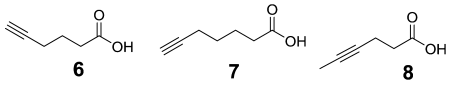
We initially suspected the much higher activity of Au@ICRM(**2**) over Au@ICRM(**1**) was caused by different-sized gold clusters formed in the ICRM core. The size of the gold clusters formed in the ICRM-templated synthesis depends on the amount of aurate loading (the aurate/surfactant ratio) and W_0 (water/surfactant ratio),[6,7,14] and typically could be determined by the emission wavelength of the gold clusters.[6,15] Au@ICRM(**1**) at W_0 = 5 and 10−20% aurate loading emitted at 476 nm, corresponding to Au_{9-10} clusters[6] (Figures S2). (As a reference, Au_8 clusters emit at ∼450 nm.)[16] Au@ICRM(**2**), on the other hand, emitted at 440 nm (Figures S3) or blue-shifted by 36 nm from the emission of Au@ICRM(**1**). However, when we examined the effect of W_0 on the catalysis of Au@ICRM(**2**), the different particle size did not seem to be important. For example, Au@ICRM(**2**) at W_0 = 2 and 10 gave quantitative yield in both cases in the intramolecular alkyne carboxylation (Table 1, entries 9 and 10), even though Au@ICRM(**2**) with W_0 = 10 clearly contained larger clusters than Au@ICRM(**1**).[17] Hence, the ICRM framework instead of the gold clusters most likely was controlling the catalytic activity.[18] In the literature, gold nanoparticles supported on various metal oxides either were completely inactive or gave very low yields at much higher catalyst loading.[12d]

The results so far suggest that Au@ICRM(**2**) indeed appeared to function as a metalloenzyme-mimicking supramolecular catalyst in cyclizing **3**. Noncovalent binding between the substrate and the ICRM was critical to the catalysis, as any disruption of this binding (by solvents or competitive carboxylic acids) dramatically hindered the conversion. The supramolecular organization of the catalyst already made it far more active than conventional gold salts with or without special ligands.[12] Since the reaction went to completion in 1 h with 1 mol% catalyst, we decided to reduce the level of catalyst further.

The results were illuminating. At 0.1 mol% catalyst loading (30−100 times lower than what was used in the literature), the reaction still proceeded to completion within 4 h at room temperature. Most amazingly, unlike typical reactions that slow down as the starting material is consumed, cyclization of **3** catalyzed by Au@ICRM(**2**) showed practically no sign of slowing down all the way to the completion of the reaction (Figure 2).

The above results together point to a mechanism in which the carboxylic acid of **3** enabled its binding to Au@ICRM(**2**). The binding and product release must have been faster than the cyclization. In this way, the local concentration of the substrate near the catalyst was essentially constant throughout the reaction, as supported by the zero-order dependence of reaction rate on the substrate (Figure 2).

The importance of ICRM to the catalysis was already shown by the enormously different activity of Au@ICRM(**1**) and Au@ICRM(**2**). We then studied cyclization of different substrates (**6**−**8**), curious whether the ICRM would impart any special substrate selectivity to the catalysis. Typical gold catalysts such



6 **7** **8**

as AuCl showed no distinction in cyclizing 4-pentynoic acid (**3**) or 5-hexynoic acid (**6**), although 6-heptynoic acid (**7**) showed lower reactivity.[12b,e] In our hands, only 7−18% cyclization occurred with **6** (Table 2, entries 1−3), in contrast to the quantitative conversion of 4-pentynoic acid **3** (Table 1, entries 5, 9, and 10). Even when the reaction time was prolonged to 8 h, the reaction did not go to completion, giving 40−60% yield depending on the W_0 of the ICRM (Table 2, entries 4−6). Furthermore, hydrolysis (10−15%) of the lactone product was observed for this compound. Not surprisingly, 6-heptynoic acid (**7**) was completely inactive, even after 24 h (entry 7).

Table 2. Intramolecular Cyclization of Alkynoic Acids Catalyzed by 1 mol% Au@ICRM(2)

entry	W_0	substrate	time (h)	yield (%)
1	2	**6**	1	14
2	5	**6**	1	18
3	10	**6**	1	7
4	2	**6**	8	60[a]
5	5	**6**	8	54[a]
6	10	**6**	8	40[a]
7	2, 5, 10	**7**	8−24	0
8	5	**8**	1	19
9	5	**8**	8	90[b]
10	5	**8**	24	>95[b]

[a]Hydrolysis (10−15%) of the enol lactone was observed. [b]*Z*:*E* = 78/22.

To understand the reason for the substrate selectivity, we studied another substrate, 4-hexynoic acid (**8**). It contains the same number of carbons as the much less reactive **6** but forms the same five-membered ring enol lactone as the most reactive **3**. The reaction of **8** was clearly slower than that of **3** but faster than that of **6**: 19% at 1 h, 90% at 8 h, and quantitative at 24 h (Table 2, entries 8−10). Importantly, although both *Z* and *E* isomers formed for this product (as expected), no hydrolysis of the lactone occurred under the same reaction conditions.

Supramolecular engineering can be a powerful tool to modulate catalysis.[19] As demonstrated by this work, the high activity and selectivity for 4-pentynoic acid by Au@ICRM(**2**) did not originate from the catalytically active gold center but from the organic ICRM framework that pulled the substrate

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from the environment to the catalyst. It is not clear why Au@ICRM(**2**) had substrate reactivity unobserved in conventional gold catalysts. The catalyst, nonetheless, did appear to be "optimized" for the five-membered-ring enol lactone: not only was **3** (and **8**) much more reactive than **6** and **7**, but also the five-membered-ring lactone was the only one showing no hydrolysis under identical reaction conditions. The most interesting finding was the role of carboxylic acid of **3** in the catalytic reaction. When it was responsible for the (fast) binding of the substrate and meantime was the exact group to be converted in the catalysis, the entire system behaved like a catalytic nanomachine: the ICRM pulled the substrate to the catalytic center and the appropriately positioned gold cluster turned it into the product, which preferred the nonpolar environment instead of the ICRM core and was thus rapidly released. The result was extremely high activity compared to conventional gold catalysts (for similar reactions) and highly unusual zero-order kinetics. We believe these features are not unique with the Au@ICRMs. Similar designs potentially can turn other conventional catalysts into artificial "enzymes" having novel, useful, biomimetic functions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details for the syntheses and additional figures. 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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(13) We did not attempt to exclude moisture in the reaction because the strongly hydrophilic ICRM core was likely to retain water molecules. The residual moisture present in the solvent and the starting material could also be responsible for the hydrolysis of the product, as suggested by entry 11, Table 1.

(14) Because the reduction of the aurate was induced by the bromide counteranion in the ICRM core, an increase of W_0 increased the amount of surfactant and thus the bromide counterion available for the reduction.

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(17) The larger cluster size of Au@ICRM(**2**) at W_0 = 10 was evident from its longer emission wavelength (496 nm) (Figure S4).

(18) It is not entirely clear to us why ICRM(**2**) gave so much better results than ICRM(**1**). We suspect that the different functional groups in the headgroup of the cross-linkable surfactant might be responsible. ICRM(**1**), for example, utilized thiol in the cross-linking. If any residual thiol (e.g., from singly reacted DTT) was left in the core, it might greatly suppress the most active catalytic site. In our hands, 1 mol% externally added DTT completely shut down the catalysis.

(19) For some examples of related encapsulated catalysts, see: (a) Vriezema, D. M.; Aragones, M. C.; Elemans, J.; Cornelissen, J.; Rowan, A. E.; Nolte, R. J. M. *Chem. Rev.* **2005**, *105*, 1445−1489. (b) Akiyama, R.; Kobayashi, S. *Chem. Rev.* **2009**, *109*, 594−642. (c) Price, K. E.; McQuade, D. T. *Chem. Commun.* **2005**, 1714−1716. (d) Helms, B.; Guillaudeu, S. J.; Xie, Y.; McMurdo, M.; Hawker, C. J.; Frechet, J. M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6384−6387. (e) Chi, Y. G.; Scroggins, S. T.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6322−6323.