# **Amphiphilic Block Polypeptide-Type Ligands for Micellar Catalysis in Water**

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**Abstract:** Novel amphiphilic block polypeptide ligands were synthesized and showed excellent behavior in the metal-catalyzed organic transformations in pure water. The catalytic activity and/or recycling properties of the catalysts are the result of the micellar structure of the polymeric system in water.

**Keywords:** alkene metathesis; block copolymers; catalysis in water; ketone hydrogenation; micellar catalysis

Although water is the most abundant and ecologically benign solvent in Nature, it is still relatively unexplored as a solvent for organic transformations.<sup>[1]</sup> With regard to catalysis, the incompatibility of some catalytic systems with water and the low solubility of most organic compounds are the major limitations for performing organic reactions in aqueous media. Nevertheless, there are a growing number of catalytic processes that use water as a reaction medium.<sup>[2]</sup> It has been shown that surfactants can greatly increase both the activity and selectivity of the metal-based catalytic transformations in water due to the formation of micelles.<sup>[3]</sup> It was recently demonstrated that an amphiphilic block copolymer containing a ligand at the repeating unit of the hydrophobic block can be used in place of small organic surfactants in micellar catalysis.<sup>[4]</sup> The polymers were obtained via a statistical living cationic ring-opening polymerization reaction. The reported system has shown catalytic activity in the palladium-catalyzed coupling of carbon-phosphorus bonds in pure water. Further modifications of the original poly(oxazoline)-based system resulted in highly reactive recyclable micellar catalysts for crosscoupling reactions, alkene hydrogenation, alkene metathesis reactions, ATRP and hydroformylation.<sup>[5]</sup> In this work, we present a new approach toward highly reactive amphiphilic block copolymer catalysts that utilizes modified polypeptides as the hydrophobic block with the catalyst attached to each of the amino acid residues.

Micellar amphiphilic block copolymers containing a hydrophobic polypeptide block have received much attention, mainly due to the possible applications in drug delivery.<sup>[6]</sup> The side chain carboxy groups in these polymers provide a convenient anchoring point for drug attachment. A recent example involves the successful incorporation of the transition metal-based drug, cisplatin, into the poly(ethylene glycol)-blockpoly( $\alpha$ , $\beta$ -asparate) micelle, which remained strongly attached to the micelle inner core under physiological conditions.<sup>[7]</sup> We were interested in using a similar design for the preparation of a block polypeptide ligand for micellar catalysis in water. The synthetic strategy toward such a ligand is shown in Scheme 1. Poly(ethylene glycol) (PEG) was chosed as the hydrophilic block for our system. PEG-NH<sub>2</sub> ( $M_w =$ 5,000 Da) was used as the initiator of the ring-opening polymerization of the  $\alpha$ -N-carboxyanhydride of a  $\omega$ protected L-lysine to give the block copolymer 1 containing eight repeating units of L-lysine.<sup>[8]</sup> The removal of the protection group in 1 gave the block copolymer 2, which was reacted with HPPh<sub>2</sub>/CH<sub>2</sub>O to furnish the desired ligand 3. The  ${}^{31}P{}^{1}H$  NMR of 3 in DMSO- $d_6$  at room temperature showed a singlet at -28.8 ppm, as expected for this type of ligand.<sup>[9]</sup> Interestingly, the <sup>1</sup>H NMR spectrum of **3** in the same solvent showed a significantly lower polypeptide to PEG ratio than expected for a polymer containing eight Llysine units due to the lower mobility of the former at ambient temperature. However, measuring the NMR spectrum at high temperature (100°C) restored the correct integration ratio between the two blocks.<sup>[10]</sup> Ligand 3 showed moderate solubility in water. When





Scheme 1. Synthesis of catalyst 4.

dissolved in  $D_2O$ , 3 gave no signals due to the hydrophobic block in either <sup>31</sup>P or <sup>1</sup>H NMR spectra, likely as a result of the micelle formation (vide supra). The reaction of **3** with the commercially available  $Pd(CH_3CN)_4^{2+} 2BF_4^{-}$  gave the catalyst **4** in a quantitative yield. The  ${}^{31}P{}^{1}H$  NMR spectrum of **4** in DMSO-*d*<sub>6</sub> gives rise to a signal at 14.5 ppm, which is in the area expected for Pd(II) complexes bearing a similar monomeric or dendritic ligand.<sup>[11]</sup> Polymer 4 can be easily solubilized in water, much faster than the free ligand. The formation of micelles of 4 in the aqueous phase was verified by complexation of pyrene using the fluorescence technique<sup>[12]</sup> giving the critical micelle concentration (CMC) for the micelle formation of 0.09 mg mL<sup>-1</sup>. The micelle formation was also confirmed by transmission electron microscopy (TEM) imaging, which showed spherical micellar particles of approximately 30-50 nm in diameter (Figure 1).

The catalytic activity of 4 was tested in the hydrogenation of acetophenone in pure water (Scheme 2). Ketone hydrogenations in pure water are difficult reactions and usually require a high pressure of hydrogen and elevated temperatures to achieve good vields.<sup>[13,14]</sup> We found that at 7 atm of hydrogen pressure, acetophenone was completely converted to 1phenylethanol within six hours, which was an optimal time for this reaction, at room temperature with the



Figure 1. TEM image of micelles of 4 on carbon.



Scheme 2. Catalytic hydrogenation of acetophenone in pure water.

| Entry | Catalyst                             | Conversion [%]          | Product   |
|-------|--------------------------------------|-------------------------|---|
| 1     | 4                                    | 100 (1st cycle)         | 1-phenylethanol                                 |
| 2     | 4                                    | 100 (2nd cycle)         | 1-phenylethanol                                 |
| 3     | 4                                    | $100 (3rd cycle)^{[b]}$ | 1-phenylethanol                                 |
| 4     | 4                                    | $100 (4th cycle)^{[c]}$ | 1-phenylethanol                                 |
| 5     | $[(CH_{3}CN)_{4}Pd]^{2+}2BF_{4}^{-}$ | 100                     | ethylbenzene                                    |
| 6     | 5% Pd/C                              | 100                     | 60% 1-cyclohexylethanol and 40% 1-phenylethanol |
| 7     | 5a                                   | 5                       | 1-phenylethanol                                 |
| 8     | 5b + 20% SDS                         | 100                     | 1-phenylethanol                                 |
| 9     | 5b + 20% SDS                         | 42 <sup>[b]</sup>       | 1-phenylethanol                                 |
| 10    | <b>5b</b> + $1/8$ equiv. of <b>2</b> | 100                     | 1-phenylethanol                                 |
| 11    | <b>5b</b> + $1/8$ equiv. of <b>2</b> | 47                      | 1-phenylethanol                                 |
| 12    | 5b + 1/8 equiv. of 2                 | 12 <sup>[b]</sup>       | 1-phenylethanol                                 |

**Table 1.** Catalytic hydrogenation of acetophenone.<sup>[a]</sup>

<sup>[a]</sup> *Conditions:* acetophenone (0.43 mmol), catalyst (0.9% per Pd), hydrogen (7 atm), water (3 mL), time (6 h). All the experiments were performed at room temperature.

<sup>[b]</sup> After 12 h.

<sup>[c]</sup> After 6 h.

catalyst loading as low as 0.9% per Pd (Table 1). Importantly, no Pd ion leaching occurs during the reaction, as under the identical conditions, free  $Pd(CH_3CN)_4^{2+} 2BF_4^-$  gave ethylbenzene as the reaction product (Table 1, entry 5). Furthermore, 5% Pd on charcoal gave 1-cyclohexylethanol as the major reaction product under the same conditions (Table 1, entry 6). In addition to the high activity, polymer 4 could easily be recycled. After the product extraction with diethyl ether and removal of organic solvent under a stream of nitrogen, polymer 4 showed no decrease in catalytic activity compared with the first run (Table 1, entry 2). Longer reaction times did not lead to catalyst decomposition, as evidenced from entries 3 and 4 in Table 1.

Attachment of catalytically active metal complexes to water-soluble polymers is an important technique to achieve a high degree of catalyst recycling.<sup>[15]</sup> In most cases, the catalyst remains soluble in the aqueous phase without the formation of micelles. Thus, the reactions often require organic co-solvents or are limited in the substrate scope.

To verify that the formation of micelles is essential for the catalytic hydrogenation with **4**, we prepared the ligand which has the same diphosphine ligating group but lacks the hydrophobic polypeptide block. Polymer **5a**, in which the metal catalyst is attached directly to the PEG chain (Scheme 3), showed considerable solubility in water, however, formed no micelles in the aqueous solution according to the pyrene fluorescence method. Also, no evidence for micelle formation was obtained from the TEM analysis. Consequently, only 5% of conversion was observed when **5a** was used as catalyst in the hydrogenation of acetophenone under the conditions reported in Table 1. Thus, micelle formation is indeed crucial for the high catalytic activity shown by polymer **4**, as the reaction





Scheme 3. Preparation of the non-micellar analogues of catalyst 4.

most likely proceeds in the hydrophobic core of the block copolymer micelle.

As active micellar catalysts can be prepared using various surfactants, we also verified the effect of our ligand design on the catalyst recycling. To this end, we synthesized complex 5b (Scheme 3), a simple monomeric analogue of 4, which shares the same ligand features in the proximity to the metal center. Using 5b in combination with 20% of sodium dodecyl sulfate (SDS) in the hydrogenation of acetophenone under our standard conditions resulted in 100% conversion to 1-phenylethanol. However, only 42% of the product after 12 h was obtained during the recvcling experiment (Table 1, entries 8 and 9). Similarly, a mixture of 5b with 1/8 of equivalent of block copolymer 2 provided a catalyst that converted acetophenone to 1-phenylethanol in a 100% yield after 6 h. The yield dropped to 47% in the second cycle and 12% (after 12 h) in the third one (Table 1, entries 10-12). Therefore, although good conversions can be achieved using the combination of an organic catalyst and a surfactant, the chemical attachment of the catalyst units to the micelle core provides the benefits of the efficient recycling. Using a mixture of polymer 5a and 20% SDS gave no hydrogenation product as the catalyst and surfactant remained in different phases during the reaction.



Scheme 4. Synthesis of the micellar ROMP catalyst 7.

Potential benefits of the block copolymer design of the micellar catalyst were further explored in the ring-opening metathesis polymerization (ROMP) reactions. The Ru-catalyzed ROMP is a very important reaction that is rarely performed in an aqueous media.<sup>[16]</sup> In most cases, water-soluble catalysts and soluble or partly soluble monomers were used to maintain polymer solubility during the polymerization, the reactions often requiring very low pH.<sup>[17]</sup> Alternatively, a large excess of a surfactant was employed.<sup>[18]</sup> Polymer-supported catalysts were also reported.<sup>[5d,19]</sup> Considering the stability of block copolymer micelles compared with micelles formed by regular surfactants, we thought that our system may provide considerable solubility for the growing polymeric chains. This would allow us to obtain high molecular weight polymers with low polydispersity even for hydrophobic monomers. It was recently reported that an  $RN(CH_2PCy_2)_2$  chelating ligand attached to a dendrimer can be used to promote the Ru carbine-based ROMP of norbornene.<sup>[20]</sup> We, thus, prepared 6 (Scheme 4), a bis(dicyclohexyl)phosphine analogue of 3, using the protocol similar to the one shown in Scheme 1. Reaction with the commerically available 1<sup>st</sup> generation Hoveyda–Grubbs catalyst [dichloro(oisopropoxyphenylmethylene)(tricyclohexylphosphine)ruthenium(II)] resulted in the ruthenium coordination to the diphosphine fragment of the lysine backbone with concomitant liberation of free PCy<sub>3</sub>. The <sup>31</sup>P NMR spectrum of the new compound **7** showed a signal at 36.6 ppm, while the carbene hydrogen atom gave rise to a broad singlet at 17.0 ppm in the <sup>1</sup>H NMR spectrum. The observed chemical shifts are in agreement with the data reported by Astruc et al.<sup>[20]</sup> Interestingly, similar to what was observed in the dendritic system, the <sup>1</sup>H NMR spectrum of a solution of 7 in CDCl<sub>3</sub> showed additional signals for the carbene hydrogen atom at 15.6 and 17.1 ppm. Likewise, the <sup>31</sup>P NMR spectrum of **7** in CDCl<sub>3</sub> exhibited two additional signals at 41.5 and 34.2 ppm. The additional signals were assigned to the monomer-dimer equilibrium between the ruthenium carbene complexes.<sup>[20]</sup>

The ROMP of norbornene catalyzed by 7 (1% per Ru) in water was complete after 2 h at 50°C (Scheme 5). The resulting poly(norbornene) con-



Scheme 5. ROMP of norbornene in water using catalyst 7.

tained *ca.* 74% of the *trans*-alkene and showed a very high molecular weight with a low polydispersity  $(M_n = 157 \text{ kDa}, \text{PDI} = 1.3)$ . Such higher than theoretical values of the molecular weight are common for reactions in the aqueous media<sup>[18]</sup> and result from incomplete catalyst consumption. The importance of the micelle formation was also observed in the ROMP reaction. Attaching the  $-N(CH_2PCy_2)_2$  chelate directly to the PEG fragment (similar to **5a**), followed by the Ru complexation resulted in the water-soluble complex which showed sluggish catalytic activity in the ROMP of norbornene.

Using the 1<sup>st</sup> generation Hoveyda–Grubbs catalyst alone provided the polymer with a low molecular weight and large PDI. Interestingly, a high molecular weight unmodified hydrocarbon polymer was obtained in pure water without organic cosolvents with only a small amount of an amphiphilic block copolymer. This contrasts the reactions utilizing small molecule surfactants where a large excess of the amphiphilic reagent was utilized.<sup>[16a,18]</sup>

In summary, we have reported the first examples of an amphiphilic block polypeptide-based metal systems for efficient catalysis in pure water. The catalysts operate under mild reaction conditions and can often be recycled several times without loss of activity. The micelle formation is essential for the high catalytic activity, as similar water-soluble catalysts showed very low activity under the same reaction conditions. We are currently exploring the scope of the new catalytic systems.

## **Experimental Section**

#### **General Experimental Procedures**

All reactions were performed in ultrapure water ( $\Omega$  18 MOhm, <10 ppb TOC) obtained using Barnstead EASYpure II UF water purification system. Use of regular deionized water gave comparable results. The reagents were purchased from Sigma–Aldrich or Strem and used as received. Complete experimental procedures are reported in the Supporting Information.

#### **Conditions for Acetophenone Hydrogenation**

All experiments were carried out in a 100-mL Fischer-Porter high pressure glass reactor. The catalyst (0.9% mol) was dissolved in ultrapure water (3 mL) and 0.43 mmol (50 µL) of acetophenone was added. The reactor was evacuated and hydrogen gas introduced. The pressure was adjusted to 7 atm and the reaction mixture was stirred at room temperature for six hours. The product was extracted with diethyl ether and analyzed by <sup>1</sup>H NMR:  $\delta$ =7.37–7.25 (m, phenyl, 5H), 4.86 (q, *J*=6.5 Hz, CH-OH, 1H), 2.36 (s, OH, 1H), 1.46 (d, *J*=6.5 Hz, CH<sub>3</sub>, 3H). The reported yields are the average of at least two runs using different catalyst batches.

#### **Conditions for ROMP of Norbornene**

To a Schlenk flask, containing norbornene (64.0 mg, 0.68 mmol) the catalyst (1%) in 5 mL of degassed water was added *via* syringe. The reaction mixture was stirred at 50 °C for 2 h. The flask was opened to air and the polymerization was terminated by adding an excess of ethyl vinyl ether (100 equiv.). The contents were dissolved in THF and precipitated twice in water. The solids were filtered, washed with water (20 mL), methanol (20 mL) and dried under vacuum to yield poly(norbornene). The polymer was analyzed by <sup>1</sup>H NMR spectroscopy and size exclusion chromatography (THF) using polystyrene as reference.

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