Polymerization

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Bioinspired Iron-Based Catalyst for Atom Transfer Radical Polymerization**

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Atom transfer radical polymerization (ATRP) provides well-defined polymers with predetermined molecular weight and narrow molecular weight distributions and precisely controlled architecture.[1] Copper-based ATRP catalysts are the most efficient for the preparation of a broad range of well-defined polymers.[2] However, the development of new transition-metal-based catalysts remains of great interest in order to extend the range of polymers that can be prepared by ATRP.[3] Consequently, iron-mediated ATRP has been widely investigated because of its low toxicity and biocompatibility, especially advantageous when targeting biological applications.[4] Despite these potential benefits of iron-based catalysts, their application in ATRP is quite limited because of their lower activity and selectivity. Therefore, the design and development of new iron-based catalysts comparable in activity to traditional catalysts and able to polymerize a broader range of monomers is critical for progress in this field.

ATRP is typically performed in organic solvents, but performing ATRP in aqueous media provides several advantages. Water is an environmentally benign solvent, enabling direct polymerization of water-soluble monomers, faster reactions, and polymerization in the presence of biomolecules.[5] Several methods for well-controlled Cu-based ATRP in water have been developed, but in the majority of reports a limited number of catalytic systems and narrow range of monomers are used.[6] Difficulties with control of ATRP in aqueous media are associated with some side reactions including catalyst and chain-end instabilities, as well as a large equilibrium constant responsible for significantly increased rates of reaction.[7] Our group has recently reported the synthesis of protein–polymer hybrids by ATRP under biologically relevant conditions, which were designed to sustain the structure of a protein during polymerization as well as provide good control.[8] In this system, a protein served as an initiator, but recent publications by Bruns[9] and diLena[10] show that certain proteins/enzymes can also serve as catalysts for ATRP. Protein-based catalysts, so called ATRPases, with iron heme centers, such as horseradish peroxidase (HRP), catalase or hemoglobin (Hb) act as ATRP catalysts and can produce high molecular weight (MW) polymers with molecular weight distributions (MWDs) close to 1.5, indicative of some limited control. These catalytic systems can potentially expand the range of polymerizable monomers because of a different catalyst structure and tolerance to pH variation. However, a major drawback of using proteins for catalysis is their sensitivity to reaction conditions and high molecular weight.[11] Therefore, the development of synthetic analogs that can reproduce or enhance the properties of native catalytic proteins without the need for such stringent conditions and high mass loading of the catalyst would allow for broader application of these bioinspired catalytic systems.[12]

Application of the naturally occurring hematin, the structure of which is similar to the prosthetic group of HRP, Hb, or catalase, for catalysis of radical polymerization reactions of vinyl monomers showed that it can successfully replace HRP.[13] Indeed, some iron porphyrins can induce an atom transfer process, as in ATRP, and even provide a certain level of control indicated by a linear increase of molecular weight with conversion and moderate dispersity values ($M_w/M_n < 2$; M_w = weight average molecular weight and M_n = number average molecular weight.[14] Poly(*N*-isopropylacrylamide), poly(NIPAAm), prepared in the presence of alkyl halide initiator and hematin had relatively high M_w/M_n values (1.8–2.1). These results indicate that iron porphyrins can act as catalysts for ATRP, but significant improvements are needed to prepare well-defined materials.

Hemin was chosen for initial testing as an iron-based catalyst for ATRP. Hemin is a ferric form of heme with a chloride ligand instead of hydroxyl group as in hematin.[15] Hemin was used to catalyze activators generated by electron transfer (AGET) ATRP of oligo(ethylene oxide) methyl ether methacrylate ($OEOMA_{475}$, average MW 475)[16] in aqueous media with ascorbic acid as reducing agent (see Scheme S1 in the Supporting Information). This method allows in situ generation of Fe^{II} species, thereby preventing the irreversible formation of μ-oxo bisiron(III) complexes that can occur between two iron(II) porphyrins in the presence of oxygen.[15,17] However, this catalyst has low halidophilicity,[18] low solubility in water, and can itself polymerize because of the presence of vinyl moieties.[19] Therefore, we developed a second generation of hemin-inspired catalysts that addressed these issues and provided significantly improved performance in the preparation of well-defined polymers (Scheme 1).

We first attempted to improve the reported earlier catalase catalytic system,[10b] by addition of NaCl, yielding

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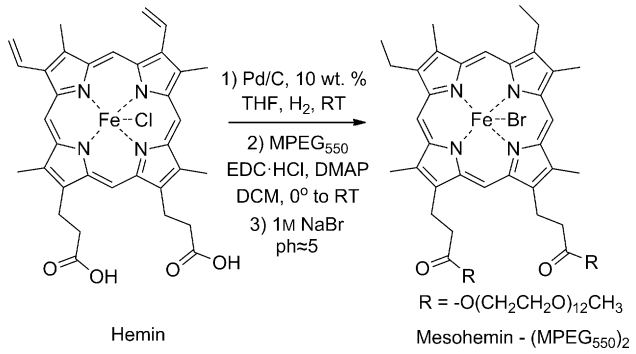

Scheme 1. Hemin and its modification to mesohemin-$(MPEG_{550})_2$.

polymers with a higher MW and narrower MWD (Table 1, entry 1 and Figure S1). Since the ATRPase catalytic systems had limited halidophilicity, an additional halide salt was necessary for faster deactivation and controlled polymerization. This strategy was also applied to the next series of experiments with hemin.

A set of polymerizations was conducted to determine if the prosthetic group, hemin, can be used alone to catalyze ATRP without the entire protein. Initial results demonstrated that hemin can be reduced in situ by ascorbic acid and catalyze ATRP; however the deactivation rate was slow, resulting in rapid but poorly controlled polymerization (Table 1, entry 2). The polymerization reached a conversion of 60% of the monomer in 1 h and stopped after that time, forming a polymer with high values of $M_w/M_n = 1.65$. Macroinitiator residue in gel permeation chromatography (GPC) traces indicated a low initiation efficiency (Figure S2). To determine if the low halidophilicity of hemin caused the poor control over the polymerization, reactions were conducted in the presence of excess halide salts (Table 1, entry 3–4). Addition of KBr resulted in more linear kinetic plots and improved the initiation efficiency (Figure 1 and Figure S3A). Addition of NaCl led to a slower polymerization and higher M_w/M_n (Figure 1 and Figure S3B), indicating that the presence of extra bromide ions shifts the equilibrium towards stable Fe^{III}-X species, increasing the deactivation efficiency. Bromide salt enhances both the polymerization rate and the initiation efficiency, compared to chloride salt. Therefore, further polymerizations were conducted in the presence of excess bromide salt to enhance the deactivation and initiation efficiencies.

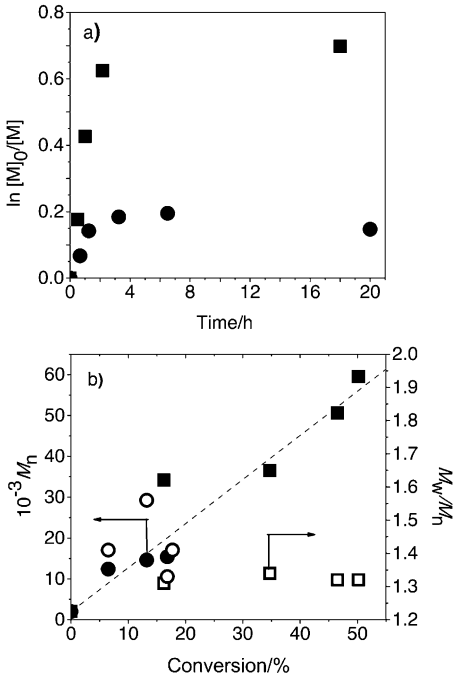

Figure 1. a) First-order kinetic plots, b) evolution of M_n and M_w/M_n with conversion. Entries 3 (■) and 4 (●). $[OEOMA_{475}]_0 = 0.45$ M; $[OEOMA_{475}]/[I]/[Asc.\ A]/[Hemin] = 227/1/10/1$, 100 mM NaCl/KBr, water, 30°C (OEOMA = oligo(ethylene oxide) methyl ether methacrylate, I = initiator, and Asc. A = ascorbic acid).

Although the initiation efficiency was improved by addition of the extra halide salt, complete consumption of the macroinitiator required more than 1 h, according to the GPC traces (Figure S3A). The slow initiation led to a MW higher than predicted and a broader MWD, plausibly because of the limited solubility of the hemin catalyst in the aqueous media. It was reported that hematin with attached poly(ethylene glycol), PEG, chains can be used in aqueous media without cosolvents or pH adjustments.[13b] Therefore, to determine if modification of hemin with water-soluble moieties can improve the catalytic performance, the hemin carboxyl groups were esterified with PEG_{1000} (Scheme S2).

Table 1: Experimental conditions and results of ATRP of OEO(M)A (M = monomer, I = initiator, RA = reducing agent, and Cat = catalyst).[a]

	M/I/RA/Cat[a]	Catalyst	Salt	Solvent	t [h]	Conv. [%]	$M_{n,theo}$ [10^{-3}][f]	$M_{n,GPC}$ [10^{-3}][g]	M_w/M_n
1	78/1/15/0.007[b]	catalase	NaCl	H_2O	16	49	20	47	1.19
2	227/1/10/1[c,d]	hemin	–	H_2O	1	60	67	178	1.65
3	227/1/10/1[c,d]	hemin	KBr	H_2O	18	50	56	60	1.32
4	227/1/10/1[c,d]	hemin	NaCl	H_2O	20	14	17	27	3.26
5	227/1/10/1[c,e]	hemin-$(PEG_{1000})_2$	KBr	H_2O	5	78	86	116	1.32
6	227/1/1/1[c,e]	hemin-$(PEG_{1000})_2$	KBr	H_2O	6	47	53	103	1.72
7	227/1/10/1[c,e]	mesohemin-$(MPEG_{550})_2$	KBr	H_2O	5.5	75	83	101	1.30
8	227/1/5/1[c,e]	mesohemin-$(MPEG_{550})_2$	KBr	H_2O	6	65	72	86	1.28
9	227/1/1/1[c,e]	mesohemin-$(MPEG_{550})_2$	KBr	H_2O	6	60	66	63	1.19
10	227/1/1/1[c]	mesohemin-$(MPEG_{550})_2$	TBABr	anisole	6	54	61	94	1.22

[a] 30°C, 20% [M] (v/v). [b] $[I] = [PEG_{2000}BBr] = 5$ mM, $M = OEOA_{480}$. [c] $[I] = [PEG_{2000}BPA] = 2$ mM, $M = OEOMA_{475}$. [d] 20% dimethyl formamide, DMF, (v/v). [e] 6% DMF (v/v). [f] $M_{n,theo} = ([M]_0/[I]_0) \times conversion \times M_{monomer}$. [g] Universal calibration.

The initial experiments using hemin-$(PEG_{1000})_2$ instead of hemin resulted in a well-controlled polymerization (Table 1, entry 5), as evidenced by linear semilogarithmic kinetic plots up to high conversion, linear increase of the MW with conversion, and a narrow MWD, with $M_w/M_n \approx 1.3$ (Figure 2).

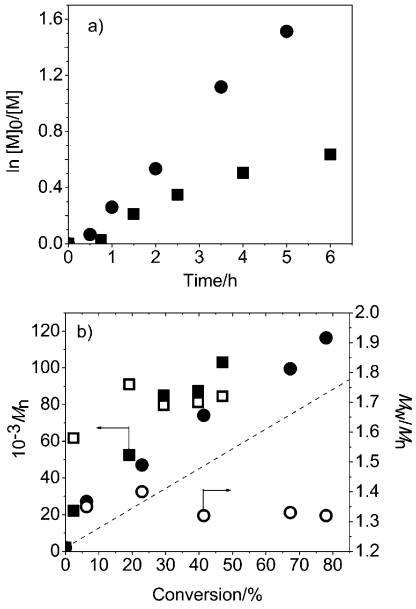

Figure 2. a) First-order kinetic plots, b) evolution of M_n and M_w/M_n with conversion, GPC traces. Entries 5 (●) and 6 (■). $[OEOMA_{475}]_0 = 0.45$ M; $[OEOMA_{475}]/[I]/[Asc.\ A]/[Hemin\text{-}(PEG_{1000})_2] = 227/1/1n/1$, where $n = 1$, 10; water, 30 °C, 100 mM KBr.

Another indication of enhanced control was a significant reduction of the macroinitiator residues in the GPC traces, already after 30 minutes (Figure S4). These results suggested that in addition to excess bromide salt, PEG tails improve the performance of the catalyst because of better solubility and stability of the catalyst.[4g] However, a 10-fold excess of ascorbic acid was required for successful polymerization. With only one equivalent, poor control was observed and the MWD broadened to $M_w/M_n \approx 1.7$ (Table 1, entry 6). This limited control could be due to a possible copolymerization of hemin through its vinyl bonds (Figure 2). Indeed, the precipitated polymers had a brown color and UV/Vis analysis revealed spectra typical for metal porphyrins (Figure S5).[20]

To exclude the possibility of copolymerization of the catalyst, hemin was converted to mesohemin by hydrogenation, and then esterified with methoxy PEG_{550}, $MPEG_{550}$ (Scheme 1). The resulting modified iron porphyrin preserved its structure, as confirmed by the presence of the characteristic Soret band at 437 nm and Q bands in the visible region of UV/Vis spectra in $CHCl_3$ (Figure S6). The structure of the complex was characterized by electrospray ionization mass spectrometry (ESI-MS) with a $[mesohemin\text{-}(MPEG_{550})_2]^+$ species at m/z ranging from 1266.1 to 1927 with an interval of 44 because of the distribution present in $MPEG_{550}$[21] and $[mesohemin\text{-}(MPEG_{550})_2]^{2+}$ species at m/z ranging from 584.8 to 1064 with an interval of 22 (Figure S7). Cyclic voltammetry (CV) analysis of mesohemin-$(MPEG_{550})_2$ showed the presence of two reduced states ($E_{pc} = -0.73$ and -0.94 V versus ferrocene, $Fc^{0/+}$; Figure S8), probably because of iron center interaction with side PEG groups. However, upon addition of 10 equivalents of NaBr only one cathodic peak ($E_{pc} = -0.89$ V versus $Fc^{0/+}$) suggested formation of mesohemin-$(MPEG_{550})_2$Br species. The cyclic voltammogram indicated a quasi-reversible reaction. The half-wave potential ($E_{1/2}$) was slightly more negative for mesohemin-$(MPEG_{550})_2$Br than for hemin-Br (-0.78 and -0.75 V vs. $Fc^{0/+}$, respectively). Upon addition of initiator (ethyl α-bromophenylacetate), the cyclic voltammogram showed an increase of the cathodic current and a decrease of the anodic current, because of a reaction of electrochemically produced Fe^{II} species with the alkyl halide, that is, a regeneration of Fe^{III} species (Scheme S3).

This optimized second-generation catalyst, consisting of hydrogenated hemin (mesohemin) with $MPEG_{550}$ tails, performed significantly better than original hemin or hemin-$(PEG_{1000})_2$ (Table 1, entries 7–10). Polymerizations using mesohemin-$(MPEG_{550})_2$ as a catalyst were fast, providing initially linear first-order kinetic plots, linear evolution of MW with conversion and M_w/M_n values close to 1.2 (entry 7). However, after approximately 60% conversion, the rate of polymerization decreased, plausibly because of the excessive amount of ascorbic acid. A decrease of the molar ratio of ascorbic acid to mesohemin-$(MPEG_{550})_2$ from 10/1 to 5/1 to 1/1 resulted in more linear kinetic plots, linear increase of the MW with conversion, and a narrower MWD (see Figure 3). When the ratio of ascorbic acid to mesohemin-$(MPEG_{550})_2$ was 1/1, the experimental MW correlated well with theoretical values. Mesohemin cannot copolymerize and become incorporated into the polymer chain. Thus, it shows an enhanced performance because a catalyst incorporated into a polymer chain cannot efficiently participate in atom transfer reactions. Indeed, essentially colorless polymers were prepared with mesohemin-based catalyst (Figure S5).

To show the versatility of the mesohemin-based catalyst for ATRP, a polymerization was performed in organic media (Table 1, entry 10). An AGET ATRP of OEOMA475 in anisole was activated by addition of tin(II) 2-ethyl hexanoate as a reducing agent and displayed close to linear first-order kinetic plots and a linear MW evolution with conversion (Figure S9). A slow initiation was indicated by slight curvature during the initial stage of polymerization in the semilogarithmic kinetic plot and experimental MW higher than theoretically predicted. Dispersities stayed low throughout the course of polymerization.

In conclusion, a bioinspired iron porphyrin-based complex was designed and successfully used as a new ATRP catalyst. Mesohemin-$(MPEG_{550})_2$, prepared from naturally occurring hemin, performs significantly better than hemin itself or previously reported hematin. This can be attributed to its increased solubility because of the PEG tails and hydrogenated vinyl bonds, preventing copolymerization and allowing for faster deactivation in the presence of excess bromide salt. Mesohemin-$(MPEG_{550})_2$ can be used for ATRP of methacrylates in both organic and aqueous media. This new, environmentally benign ATRP catalyst is very promising and its further modifications are under investigation.

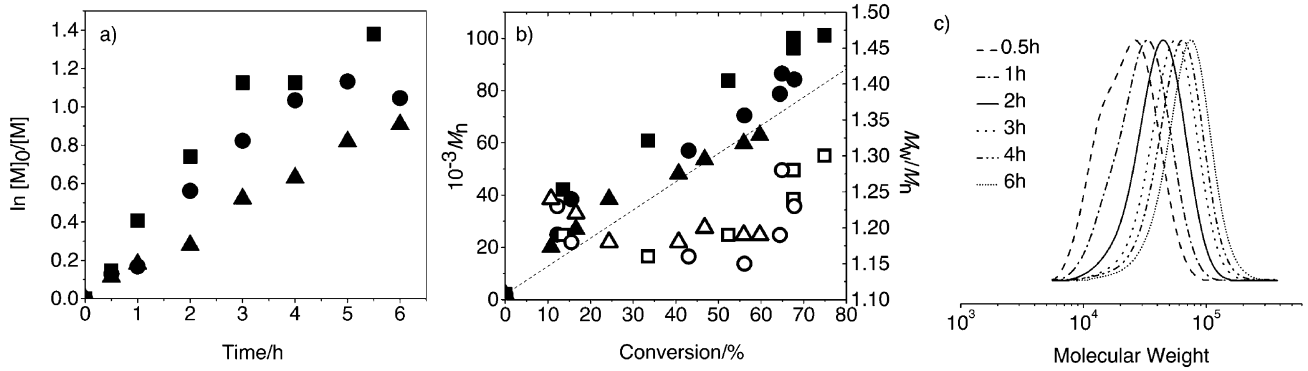

Figure 3. a) First-order kinetic plots, b) evolution of MW and MWD with conversion, and c) GPC traces with conversion for entry 9. Entries 7 (■), 8 (●), and 9 (▲) $[OEOMA_{475}]_0 = 0.45$ M; $[OEOMA_{475}]/[I]/[Asc.\ A]/[Mesohemin\text{-}(MPEG_{550})_2] = 227/1/1n/1$, where $n = 1$, 5, 10; water, 30 °C, 100 mM KBr.

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