Block Copolymers

International Edition: DOI: 10.1002/anie.201511793
German Edition: DOI: 10.1002/ange.201511793

Block Copolymerization of Lactide and an Epoxide Facilitated by a Redox Switchable Iron-Based Catalyst

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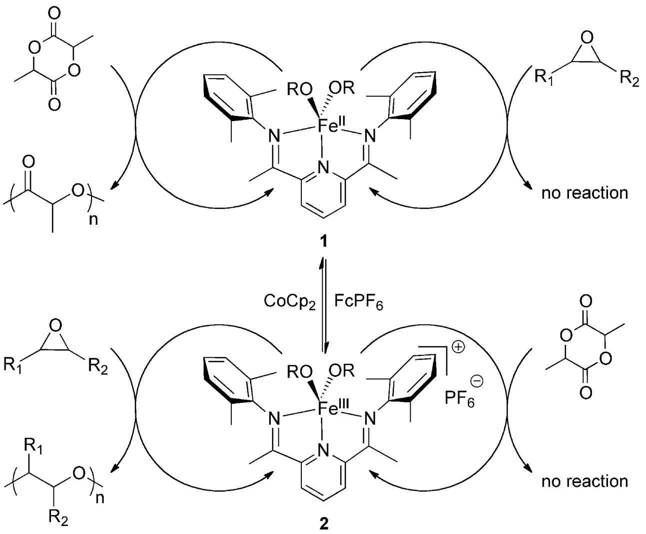
Abstract: *A cationic iron(III) complex was active for the polymerization of various epoxides, whereas the analogous neutral iron(II) complex was inactive. Cyclohexene oxide polymerization could be "switched off" upon in situ reduction of the iron(III) catalyst and "switched on" upon in situ oxidation, which is orthogonal to what was observed previously for lactide polymerization. Conducting copolymerization reactions in the presence of both monomers resulted in block copolymers whose identity can be controlled by the oxidation state of the catalyst: selective lactide polymerization was observed in the iron(II) oxidation state and selective epoxide polymerization was observed in the iron(III) oxidation state. Evidence for the formation of block copolymers was obtained from solubility differences, GPC, and DOSY-NMR studies.*

Recently, several reports have emerged that describe the ability to reversibly activate and deactivate chemical reactions with the addition of exogenous redox reagents, which have applications in sequence controlled polymerization reactions, chemical sensing, chemotherapy, information storage, and for coatings technologies.[1] The ability to control lactide ring-opening polymerization by oxidizing and reducing catalysts that are either supported by redox active ligands[2,3] or that utilize redox-active metals[4,5] as catalytically active species has been particularly successful. In 2013, we reported a bis(imino)pyridine iron complex (**1**) that undergoes lactide polymerization in the iron(II) oxidation state but is dormant in the iron(III) oxidation state (Scheme 1).[4] Sequential catalyst oxidation and reduction resulted in the ability to deactivate and activate polymerization, respectively, without evidence for detrimental side reactions.

Inspired by pioneering work from Diaconescu and co-workers,[3] we hypothesized that the different reactivity of iron(II) and iron(III) complexes would be amenable to developing a chemoselective block copolymerization with a second monomer that has orthogonal reactivity to lactide. In this report, we disclose that epoxides have such reactivity and describe how the complementary reactivity of epoxides and lactide were used for the synthesis of block copolymers. In these reactions, iron(II) serves as the active oxidation state for lactide polymerization, while iron(III) is the active oxidation state for epoxide polymerization. The exceptional chemoselectivity of the iron catalysts employed enabled the synthesis of a diblock copolymer whose composition was dictated by a fully redox-switchable polymerization catalyst. This synthetic methodology provides rapid access to block copolymers that are promising candidates for drug delivery devices[6] and as biodegradable thermoplastic elastomers.[7]



Scheme 1. Iron-based redox-switchable polymerization catalysis.

During exploratory investigations into the reactivity of iron complexes with various monomers, we discovered the cationic iron(III) alkoxide **2** was active for the polymerization of various epoxides (Table S1 in the Supporting Information). The catalyst was particularly active for the polymerization of cyclohexene oxide (CHO), which required the use of chlorobenzene as a solvent to mitigate the significant exotherm observed during neat epoxide polymerization reactions. Importantly, when CHO was treated with the iron(II) catalyst **1**, no polymerization occurred.

The redox-switchable polymerization of CHO was next demonstrated (Figure 1). A CHO polymerization in chlorobenzene was allowed to proceed to 40% conversion, at which time cobaltocene (Cp_2Co) was added to the reaction to reduce the catalyst to the inactive iron(II) state. The polymerization immediately stopped upon addition of Cp_2Co, and after 40 minutes, the reaction was reinitiated by oxidizing the catalyst with ferrocenium hexafluorophosphate ($FcPF_6$). After oxidation, the reaction proceeded at a similar rate ($k_{obs} = 1.23 \times 10^{-4}\ s^{-1}$) as initially observed ($k_{obs} = 2.54 \times$

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Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201511793.

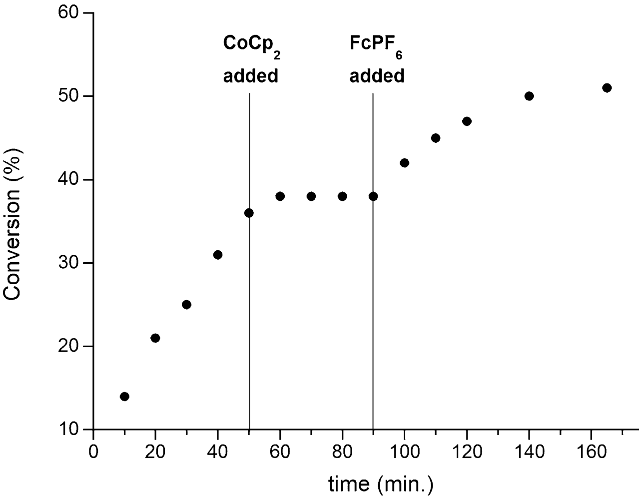


Figure 1. Redox-controlled polymerization of cyclohexene oxide in PhCl (0.91 м) with **2** (2 mol%).

10^{-4} s^{-1}), which suggested the catalyst was dormant when in the iron(II) oxidation state.

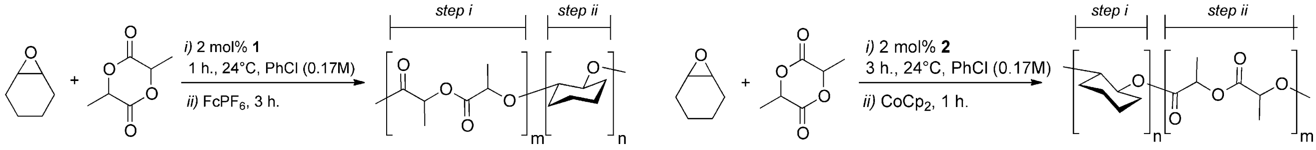
Previously reported bond metrics obtained from an X-ray crystal structure of **2** suggest that the redox reactions reported here occur at the metal center rather than at one of the two potentially redox active ligands.[4] With regard to the mechanism for epoxide polymerization, the ability to control the reaction by altering the oxidation state of catalyst suggests a coordination-insertion mechanism catalyzed by iron rather than a cationic polymerization mechanism initiated by iron, because oxidation/reduction of the metal center in the latter case would not effect polymer propagation (Scheme S1).

Currently, the epoxide polymerization reactions do not demonstrate characteristics of a living polymerization (Table S2), but the complementary reactivity of CHO and lactide made redox-switchable block copolymerization reactions possible. Satisfyingly, when a 1:1 mixture of CHO and lactide in chlorobenzene at 24 °C was exposed to **1**, clean polymerization of lactide was observed without any incorporation of CHO (entry 1, Table 1). The chemoselectivity of the reaction was apparent from the absence of polyether resonances in the ^{1}H NMR spectrum (Figure S1d).[8] The molecular weight obtained from this reaction was identical to the molecular weight of poly(lactic acid) (PLA) in the absence of CHO.[9] However, a slower reaction rate was observed (Figure S2), which likely arises from competitive binding of CHO and lactide to the iron catalyst.

Oxidation of the catalyst to iron(III) with $FcPF_6$ led to clear evidence for the formation of poly(CHO) in the ^{1}H NMR spectrum (Figure S1e). Molecular weight analysis of the resulting polymer by gel permeation chromatography (GPC) revealed a broad polydispersity ($M_w/M_n = 2.2$, Table S3), which led us to believe the copolymer contained some polyether homopolymer. Fortunately, separation of the copolymer from the polyether homopolymer was possible through sequential polymer precipitations in acetone and hexanes (SI).[10] This procedure resulted in 70% yield of copolymer based on the mass of recovered polymer products. GPC analysis of the isolated copolymer showed a single peak with a polydispersity of 1.5, but a decrease in molecular weight was also observed when the copolymer was analyzed using a refractive index (RI) detector calibrated relative to polystyrene standards (entry 1, Table 1). The significantly different hydrodynamic volume expected for the block copolymers compared to polystyrene may explain this result. Therefore, GPC analysis using a light scattering (LS) detector was carried out, which showed comparable values with the RI detector for PLA, but higher molecular weight for the copolymer product ($M_n = 37.5$ kg mol^{-1}).[11] These results are consistent with the formation of a diblock copolymer.[12]

Control experiments indicated that epoxides are inert to hexafluorophosphate anion, and while ferrocenium can serve as an initiator for the polymerization of epoxides, they do so at a much slower rate, with lower molecular weights, and broader molecular weight distributions (Supporting Information, Table S6). To further demonstrate that electron transfer

Table 1: Redox-controlled diblock copolymerization of (*rac*)-lactide (L) and cyclohexene oxide (CHO) (1:1).



	After step *i*				After step *ii* and precipitation[a]					
	M_n[b]	M_w/M_n	%CHO[c]	%L[c]	M_n[b]	M_w/M_n	%CHO[c]	%L[c]	m:n[d]	%Copolymer[e]
1	11.9	1.2	0	98	10.2 (37.5)	1.5	69	98	7:1	67
2[f]	11.2 (12.1)	1.2	0	98	9.2 (27.2)	1.5	89	98	7:1	65
3[g]	10.0	1.2	0	99	3.5 (20.1)	1.4	71	98	5:1	23
4[h]	4.5	1.3	0	35	1.7 (27.0)	2.0	32	36	4:1	68
5	1.2 (22.8)	1.9	22	0	10.6 (30.9)	1.4	22	97	9:1	95
6[i]	7.4	1.8	42	0	12.5 (20.5)	1.4	42	98	9:1	84
7[g]	1.2	2.0	50	0	5.8 (34.6)	1.4	51	99	3:1	53
8[g,j]	2.2	2.4	21	0	11.6 (30.1)	1.4	22	98	3:1	48

[a] Isolated by precipitation from acetone then hexanes. [b] kg mol^{-1}, detected by GPC using RI detector relative to polystyrene standards; values in parentheses from LS detector. [c] % conversion detected by ^{1}H NMR. [d] Detected by ^{1}H NMR. [e] Detected from mass of isolated copolymer/mass of total polymer. [f] Epoxide added in step *ii* after $FcPF_6$. [g] [CHO]:[L] = 5:1 ([CHO] = 0.80 м). [h] Step *i* carried out for 15 min. [i] Lactide added in step *ii* after $CoCp_2$. [j] Step *i* carried out for 30 min.

is faster than epoxide polymerization from the oxidant, the copolymerization was carried out via sequential addition of monomers, which ensures catalyst oxidation occurs prior to epoxide polymerization. This experiment resulted in polymers of similar molecular weights and composition to the one-pot reaction (entry 2, Table 1), indicating negligible contribution from the oxidant as a polymerization catalyst.

When the copolymerization was carried out with a 5:1 ratio of CHO:L, higher incorporation of CHO into the copolymer was observed (entry 3, Table 1), albeit with lower yields of isolated copolymer. To further demonstrate the chemoselectivity of the redox switch, the lactide polymerization was carried out to partial completion (35 %) prior to catalyst oxidation. As expected, catalyst oxidation led to CHO polymerization with no further incorporation of lactide (entry 4, Table 1).

After demonstrating an effective switch from lactide to epoxide polymerization, the reverse order was then investigated. Complementing the results just disclosed, a 1:1, a mixture of the monomers underwent selective polymerization of CHO upon exposure to iron(III) complex **2** (entry 5, Table 1). We were pleased to find that reduction of **2** with $CoCp_2$ led to the rapid consumption of lactide without any further conversion of epoxide. GPC analysis (RI and LS) after copolymer precipitation revealed one peak that increased in molecular weight and decreased in molecular weight distribution when $CoCp_2$ was added to the reaction (entry 5, Table 1). This observation was once again consistent with the production of a block copolymer; the decrease in polydispersity of the copolymer being attributed to the high percentage of narrow dispersity PLA in the copolymer. Successive precipitation of the copolymer in acetone and hexanes to remove residual homopolyether[10] resulted in 95 % yield of the copolymer.

Sequential polymerization of epoxide followed by lactide proceeded in a similar fashion as the one pot reaction with the only significant difference being higher conversion of the epoxide (entry 6, Table 1). At the expense of lower copolymer yields, significant increase in ether content could be achieved by using higher concentrations of CHO (entry 7, Table 1). Finally, the chemoselectivity of the iron(III) to iron(II) switch was demonstrated by carrying out reactions to lower conversions prior to catalyst reduction (entry 8, Table 1), which led to full lactide conversion without any further epoxide polymerization upon catalyst reduction. Although beyond the scope of this communication, these results combined with those shown for the iron(II) to iron(III) switch make it theoretically possible to carry out a multiblock copolymerization reaction involving multiple redox switches.

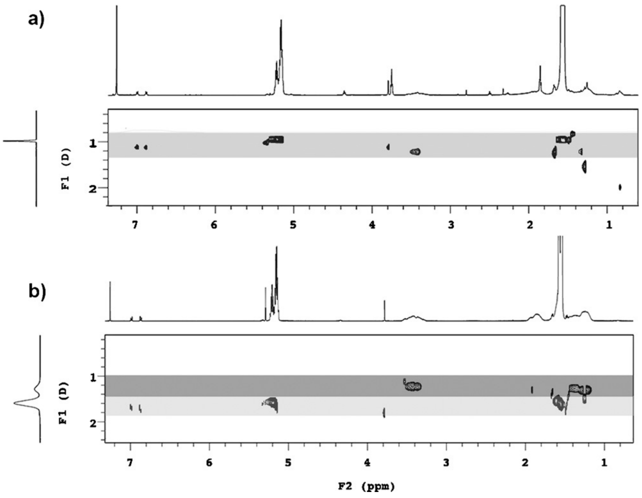


Figure 2. DOSY-NMR spectra in $CDCl_3$ of a) block copolymer (Table 1, entry 1) and b) blend of homopolymers with similar M_n and [PLA]:[PCHO].

In addition to GPC data and solubility,[10] DOSY-NMR was used to distinguish the possibility of forming block copolymers from a blend of homopolymers.[13] Consistent with the formation of block copolymers, DOSY-NMR of the polymers isolated from the iron(II) to iron(III) redox switch displayed a single peak with resonances assigned to the polyester and polyether having the same diffusion coefficient ($D = 9.5 \times 10^{-11}\ m^2 s^{-1}$, Figure 2). Likewise, DOSY-NMR for polymers formed from the iron(III) to iron(II) redox switch demonstrated similar behavior ($D = 1.1 \times 10^{-10}\ m^2 s^{-1}$, Figure S3). In contrast, DOSY-NMR of a blend of PLA and poly(CHO) homopolymers of similar molecular weights (Table S4) showed two distinct diffusion coefficients at 1.6 and $1.3 \times 10^{-10}\ m^2 s^{-1}$, which are correlated to resonances assigned to the polyester and polyether, respectively (Figure 2). Thus, the observation of one rather than two peaks in the DOSY-NMR of the polymers produced in the redox-switchable reactions is further evidence for the formation of block copolymers.

In conclusion, cationic iron(III) bis(alkoxide) complex **2** was found to be an active catalyst for epoxide polymerization, while complexes in the iron(II) oxidation state were completely inactive. This trend is opposite to what was observed previously for lactide polymerization.[4] To rationalize the switch in chemoselectivity, we hypothesize that lactide polymerization reactions benefit from nucleophilic activation of the alkoxides that are characteristic of a more electron rich iron(II) center, whereas epoxide polymerizations benefit more from electrophilic activation that is more prevalent from the electron deficient iron(III) center. While further mechanistic studies are needed to test this hypothesis, this report demonstrates for the first time that changes in oxidation state of a catalyst can lead to a complete change in the chemoselectivity of a chemical reaction. Previously, the Diaconescu group disclosed that the composition of a polyester copolymer could be altered with the redox-controlled block copolymerization of lactide and ε-caprolactone (CL).[3] Despite orthogonal redox control observed in homopolymerization reactions, the corresponding copolymerization reactions did not result in completely chemoselective reactions. Similar complications do not exist in the present system, thereby leading to formation of block copolymers with compositions that mimic sequential polymerization techniques and that feature different functional groups for each block (i.e. ester and ether).

So as to make the redox-switchable copolymerization reactions more amenable to the production of multiblock copolymers, future work will be directed towards improving the fidelity of the epoxide polymerization reaction through mechanistic studies. In parallel, rapid redox-switching techniques will be explored along with the investigation of alternative monomers.

Acknowledgements

The authors thank Dr. John Boylan for help with DOSY-NMR spectroscopy. This research was financially supported by the NSF-CAREER (1454807) and an NSF-GRF for A.B.B.

Keywords: block copolymers · iron · redox chemistry · redox-switch · ring-opening polymerization

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 5251–5254
Angew. Chem. **2016**, *128*, 5337–5340

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[8] Reactions in neat epoxide also demonstrated only lactide polymerization.

[9] Higher M_n than theoretical value (7.2 $\mathrm{kg\,mol^{-1}}$) was obtained due to a small amount of the catalyst being inactive.

[10] Unlike the polymer produced in these reactions, homopolymer blends could be separated by sequential precipitations in acetone and hexanes (Table S5).

[11] Aliquots removed in the first step were too dilute to analyze by LS, but PLA analyzed independently showed similar molecular weights by RI and LS detectors.

[12] Number-averaged molecular weight (M_n) of the copolymers were also measured by end group analysis using NMR spectroscopy (SI). While these data were also consistent with the formation of block copolymers, M_n of the copolymers was found to be significantly smaller than measured using the LS detector.

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Received: December 21, 2015
Revised: February 1, 2016