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Mechanistic Studies of Redox Switchable Copolymerization of Lactide and Cyclohexene Oxide by a Zirconium Complex

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Supporting Information Placeholder

ABSTRACT: Several aspects of the copolymerization of L-lactide (LA) and cyclohexene oxide (CHO) by a redox switchable zirconium catalyst, (salfan)Zr(O'Bu)₂ (salfan = 1,1'-di(2-*tert*-butyl-6-*N*-methylmethylenephenoxy)ferrocene), were examined such as the mechanism of cyclohexene oxide polymerization, the reactivity of [(salfan)Zr(O'Bu)₂][BAR^F] (BAR^F = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) toward lactide, and co-monomer effects on polymerization rates. Experimental methods and DFT calculations indicate that the likely mechanism of CHO polymerization by [(salfan)Zr(O'Bu)₂][BAR^F] is coordination insertion and not a cationic pathway, as employed by the majority of cationic catalysts. Furthermore, DFT calculations showed that the polymerization of LA by [(salfan)Zr(O'Bu)₂][BAR^F] is not thermodynamically favored, in agreement with experimental results. Lastly, we found that the conversion times of CHO or LA from block to block correlate with the amount of monomer left from the previous block rather than other factors.

INTRODUCTION

Biodegradable polymers are an increasing percentage of the global plastic production.¹ They have many uses in biomedical devices and disposable utensils.²⁻⁴ However, replacing petroleum-derived polymers remains a challenge because of the wide range of applications that traditional plastics have. In order to expand the physical properties of biodegradable polymers, one can incorporate blocks of other polymers to make block copolymers. Altering the length, number of blocks, or microstructure of the block copolymer provides a number of ways to tune the material's properties.⁵⁻⁷

Switchable catalysis⁸⁻³¹ has emerged over the past few years as an increasingly viable method toward achieving controlled block copolymer synthesis.²⁵⁻³³ Redox switches for polymerization reactions are particularly useful and have shown good applicability.^{25-27, 33} In 2014, our group reported a one-pot synthesis of a polylactide-polycaprolactone (PLA-PCL) diblock copolymer using a (thiolan*)Ti(O'Pr)₂, thiolan* = 1,1'-di(2-*tert*-butyl-6-thiophenoxy)ferrocene).²⁶ This compound polymerized L-lactide (LA) in its reduced state, then, after an in situ redox switch, polymerized ϵ -caprolactone (CL) in its oxidized state. Although this represented a proof of concept, the catalyst could only polymerize 17% of CL in the oxidized state before lactide, present in solution, began to polymerize as well.

In 2016, concurrently with Byers et al., who used a bis(imino)pyridine iron complex, Fe(PDI)(4-methoxyphenoxy)₂, PDI = 2,6-(2,6-Me₂-C₆H₃N=CMe)₂C₅H₃N,³³ the monomer scope of redox switchable polymerization was expanded beyond cyclic esters to include cyclic ethers. The copolymerization of cyclohexene oxide (CHO) and LA was achieved with a zirconium complex, (salfan)Zr(O'Bu)₂, salfan = 1,1'-di(2-*tert*-butyl-6-*N*-methylmethylenephenoxy)ferrocene,²⁵ as well as the iron complex.

Several diblock (AB, BA) and triblock copolymers (ABA and BAB) of LA and CHO were synthesized and characterized.²⁵

While studying the redox switchable polymerization of LA and CHO by (salfan)Zr(O'Bu)₂, there were a number of mechanistic questions that required more investigation. The mode of CHO polymerization by the oxidized precatalyst, [(salfan)Zr(O'Bu)₂][BAR^F] (BAR^F = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate), was not obvious. In addition, [(salfan)Zr(O'Bu)₂][BAR^F] showed some reactivity toward LA at elevated temperatures after performing the polymerization of CHO. Furthermore, the polymerization rates of LA or CHO differed depending on whether the monomer was being polymerized in the first, second, or third block. Herein, we report our findings regarding these questions and our interpretation of results based on experimental methods and DFT calculations.

RESULTS AND DISCUSSION

Mechanism of CHO polymerization. The polymerization of epoxides often occurs via an anionic or cationic mechanism,³⁴⁻³⁵ therefore, we considered the possibility that CHO polymerization by [(salfan)Zr(O'Bu)₂][BAR^F] might occur by the latter. We observed that, in the presence of both CHO and LA, [(salfan)Zr(O'Bu)₂][BAR^F] polymerized 83% of CHO in one hour and then began to polymerize LA, reaching 50% in 4 hours (Figure 1). When [(salfan)Zr(O'Bu)₂][BAR^F] was instead reduced after 1 hour, LA polymerization reached 96% in 3 hours (Figure 1). The polymerization of LA after CHO by [(salfan)Zr(O'Bu)₂][BAR^F] was unusual because [(salfan)Zr(O'Bu)₂][BAR^F] cannot polymerize LA alone (Figure 1). If a cationic mechanism was in place, the positive charge would be moved away from the metal center, thereby decreasing its electrophilicity to a state close to that of the reduced compound (Figure 2, path B).

Figure 1. Polymerization of LA and CHO by [(salfan)Zr(O^tBu)₂][BAR^F].

To consider this possibility, DFT calculations for the coordination insertion and cationic ring opening mechanism of CHO polymerization were performed (Figure 2) with the GAUSSIAN 09 program package.³⁶ The calculations employ a model, replacing O^tBu with OMe groups and ^tBu groups on the benzene rings with H atoms for simplicity. Although both pathways are energetically favorable overall, intermediate **III^{ox}-CHO**, on the coordination insertion pathway, was found to be 26 kcal/mol lower in energy than intermediate **V^{ox}-CHO**, found on the cationic pathway. Likewise, **TS2^{ox}-CHO**, corresponding to the second insertion during the first mechanism, was 18 kcal/mol lower in energy than **TS3^{ox}-CHO**, which corresponds to the second insertion during the latter mechanism. Therefore, path A, a coordination insertion mechanism, seems to be favored. A similar mechanism was proposed by Byers et al.,³³ although a detailed mechanistic study has not been reported.

It is important to mention that the accepted mechanism for the ring opening polymerization of epoxides is a bimolecular pathway, also known as the Vandenberg mechanism.³⁷⁻³⁹ Although we do not discard the possibility that a bimolecular mechanism is possible in the present case, we would like to point out the following:

1. The Vandenberg mechanism was initially supported by studies from Okuda and coworkers on aluminum complexes that required the presence of a nucleophile in order to generate an ate compound, which would react with another neutral molecule to form a bimetallic intermediate.⁴⁰ Recent advances in stereoselective epoxide polymerization also support a bimetallic mechanism but feature the presence of nucleophiles as well.⁴¹⁻⁴⁵ However, in the present case, the species catalyzing the reaction are cationic. Furthermore, the counterion used, BAR^F, is known as a weakly coordinating anion that is unlikely to act as a nucleophile. Nevertheless, we carried out natural bond order charge calculations that show that the difference between the charge of the methoxy oxygen atom in **I^{ox}** and **II^{ox}-CHO**, the two species that would generate a dinuclear intermediate, is small and insignificant.

2. From the space filling model of (salfan)Zr(O^tBu)₂ (Figure 3), it is obvious that zirconium is well protected by the *t*-butoxide groups and the phenoxide donors. While this does not necessarily preclude the formation of a dinuclear intermediate, it is important to note that such a compound would also have to accommodate at least one molecule of coordinated CHO. Although the studies performed by Jacobsen and

coworkers were conducted with chromium salen (salen = N,N'-ethylenesalicylimine) complexes,⁴²⁻⁴⁴ therefore the supporting ligands are similar to those reported herein, in the present case, the ferrocene backbone is rigid and less likely to accommodate a dizirconium structure. Dinuclear examples, i.e., the two metals are different than iron from ferrocene, reported by us involving ferrocene chelating ligands feature the dissociation of one of the ligand arms.¹⁴

Table 1. NBO charge distribution.

	Zr	Fe	O _{OMe}	O _{CHO}
I^{ox}	2.09	0.22	-0.86	N/A
II^{ox}-CHO	2.05	0.19	-0.83	-0.58

Figure 3. Space filling model of (salfan)Zr(O^tBu)₂.

In addition, we examined the one-pot copolymerization activity of [(salfan)Zr(O^tBu)₂][BAR^F] at different temperatures. At room temperature, the copolymerization of LA and CHO showed only a 3% conversion of LA after 18 hours (Figure 1). At 100 °C, however, the conversion of LA rose to 81.5% in the same amount of time (Figure 1). Without CHO, at 100 °C, LA polymerization reached 8 percent after 25 hours (Figure 1). Therefore, the polymerization of LA by [(salfan)Zr(O^tBu)₂][BAR^F] seems to require both high temperatures as well as the presence of CHO to proceed at a significant rate. This may be explained by the coordination of CHO to the oxidized complex to form the low energy intermediate **III^{ox}-CHO**, which allows the polymerization of LA more easily than **I^{ox}-CHO**.

To verify this theory, we calculated the energy barriers for the polymerization of LA (Figure 4). For the reduced catalyst, the first insertion of LA is favorable. The final product **V^{red}-LA** has a similar structure to the initial catalyst **I^{red}-LA** and is more stable by 8.9 kcal/mol. Therefore, the propagation step should have a similar energy barrier as the initiation step and LA polymerization should proceed smoothly, as observed experimentally.

For the oxidized catalyst, after the insertion of LA, the carbonyl group coordinates to Zr tightly, making the five-membered ring structure **IV^{ox}-LA** the favored product. Product **V^{ox}-LA** is less stable by 7.1 kcal/mol than **IV^{ox}-LA**, making the following propagation thermodynamically unfavorable. Furthermore, the energies corresponding to the propagation step for the oxidized catalyst are all positive, including those for product formation. Therefore, it is likely that the insertion of CHO decreases the energy of the LA polymerization product in agreement with the calculations shown for the initiation step (Figure 4).

Figure 2. Potential energy surfaces of the ROP of CHO by [(salfan)Zr(O'Bu)₂][BARF].

Table 2. LA and CHO diblock copolymers synthesized by redox switchable catalysis.

Entry	Polymer	Conversion 1 st block (%) ^a	Conversion 2 nd block (%) ^a	Time 1 st block (h)	Time 2 nd block (h)	M _{n, theo} ^b	M _{n, GPC} ^c	Đ ^d
1	LA ₅₀ -CHO ₅₀	90	73	7	19	11.5	13.0	1.22
2	CHO ₅₀ -LA ₅₀	91	90	6	4	12.9	13.8	1.53
3	LA ₅₀ -CHO ₅₀ [*]	94	79	3	21	11.7	13.6	1.29
4	CHO ₅₀ -LA ₅₀ [*]	90	95	3	2	13.2	15.5	1.26
5	LA ₂₅ -CHO ₂₅	90	84	5	20	5.2	7.4	1.20
6	CHO ₂₅ -LA ₂₅	90	88	6	3	5.9	8.7	1.23
7	LA ₁₂ -CHO ₁₂	88	58	3	21	2.6	3.8	1.06
8	CHO ₁₂ -LA ₁₂	89	90	1	3	4.4	8.8	1.17
9	LA ₂₅ -CHO ₂₅ - LA ₂₅ -CHO ₂₅	91 95	86 98	5 2	20 20	 12.9	 12.1	 1.31
10	CHO ₂₅ -LA ₂₅ - CHO ₂₅ -LA ₂₅	89 75	89 95	5 20	2 2	 9.6	 9.7	 1.16

Conditions: [M]/[I] = 100, [I] = 0.01 mM, 100 °C in reduced state, 25 °C in oxidized state, (4:1) benzene-d₆: 1,2-difluorobenzene as solvent, 1,3,5-trimethoxybenzene as an internal standard, ^{Ac}FcBARF as oxidant, CoCp₂ as reductant. LA = L-lactide, CHO = cyclohexene oxide. M_n values are reported in 10³ g/mol. ^a Conversion calculated by integration of polymer and monomer peaks versus internal standard in ¹H NMR spectra. ^b Determined by integration of PLA methine region and PCHO versus internal standard in ¹H NMR spectra. ^c Determined by GPC MALS. ^d Đ = M_w/M_n. * Concentration was doubled.

Block dependent polymerization rates. Since the presence of CHO showed an effect on the polymerization of LA by [(salfan)Zr(OⁱBu)₂][BAR^F], we decided to investigate the influence of one monomer on the other's polymerization. Previously, we had observed different polymerization rates of LA and CHO depending on whether the reaction started with LA or CHO.²³ To probe whether changes in the rate of polymerization were concentration, block length, or switch dependent, we synthesized a series of diblock copolymers under different conditions (Table 1).

Figure 5. Comparison of polymerization rates of LA by (salfan)Zr(OⁱBu)₂ (top) and CHO by in situ generated [(salfan)Zr(OⁱBu)₂][BAR^F] (bottom) with and without the presence of the other monomer.

We found that LA was polymerized more quickly as a second block than as a first block (Table 2, entries 1 and 2, Figure S1), while CHO was polymerized more slowly as a second block than as a first block (Table 2, entries 1 and 2, Figure S1). Increasing the concentration of the reaction made the polymerizations faster, but did not change the relative increases or decreases in time to achieve full conversion for the second block (Table 2, entries 3 and 4, Figure S1). Similarly, decreasing the number of equivalents from 100 to 50 (Table 2, entries 5 and 6, Figure S1) did not significantly change the relative rates of polymerization. Decreasing the number of equivalents to 25 (Table 2, entries 7 and 8, Figure S1) shortened the polymerization times of the first blocks and significantly increased the polymerization time of CHO as a second block. An additional two redox switches with two more copolymer blocks (Table 2, entries 9 and 10), showed that the increases and decreases in CHO and LA polymerization time established in the second blocks continued to further blocks, but did not change apprecia-

bly. To visualize these results, the changes in percent conversion were plotted against time (Figure 5). The polymerization of LA changed from 5 hours for 90% conversion in the first block to 2 hours for 89% conversion in the second block, 2 hours for 95% conversion in the third block and 2 hours for 95% conversion in the fourth block. For CHO, it took 5 hours to reach 89% conversion in the first block, 20 hours to reach 86% conversion in the second block, 20 hours to reach 75% conversion in the third block, and 20 hours to reach 98% conversion in the fourth block. These polymerization rates did not reveal a trend of polymerization time relative to position in the tetrablock copolymer, however, the rates seem to correlate with the percentage of monomer left from the previous block, i.e., the more monomer is left unreacted, the higher the influence on the rate of polymerization of the next monomer.

CONCLUSIONS

The redox switchable copolymerization mechanism of (salfan)Zr(OⁱBu)₂ was examined using experimental methods and DFT calculations. [(salfan)Zr(OⁱBu)₂][BAR^F] was found to polymerize CHO using an unusual mechanism for epoxides, coordination insertion. The polymerization of LA by [(salfan)Zr(OⁱBu)₂][BAR^F] was found to be thermodynamically unfavorable by DFT calculations, but experimentally possible at 100 °C following the polymerization of CHO. We explained these results on the basis that the initiation step for LA ring opening, a step similar to the polymerization of LA after CHO, is thermodynamically favorable, while the propagation step is not. Thus, the polymerization of LA by [(salfan)Zr(OⁱBu)₂][BAR^F] does not occur when LA is present alone in the system, but it becomes possible after the polymerization of CHO.

The influence of one monomer on the polymerization of another was also investigated by studying the different conversion times of LA and CHO as a function of the block number, i.e., whether the switchable polymerization starts with LA or with CHO. In those experiments, LA is polymerized more quickly after CHO, while CHO is polymerized more slowly after LA. These relative changes occurred regardless of monomer concentration or number of equivalents and correlated with the amount of leftover monomer in solution from the synthesis of the previous block.

The present study highlights system effects encountered in redox switchable polymerization, most importantly that the presence of the other monomer can greatly influence the catalyst response even though the switchable catalyst shows orthogonal activity in the two oxidation states toward two different monomers.

EXPERIMENTAL SECTION

General considerations. All experiments were performed under a dry nitrogen atmosphere using standard Schlenk techniques or an MBraun inert-gas glovebox. Solvents were purified using a two-column solid-state purification system by the method of Grubbs⁴⁶ and transferred to the glove box without exposure to air. NMR solvents were obtained from Cambridge Isotope Laboratories, degassed and stored over activated molecular sieves prior to use. ¹H NMR spectra were recorded on Bruker 300, Bruker 400 or Bruker 500 spectrometers at room temperature in C₆D₆ or CDCl₃. Chemical shifts are reported with respect to internal solvent, 7.16 ppm (C₆D₆) and 7.26 ppm

(CDCl₃) for ¹H NMR spectra. Cyclohexene oxide and 1,2-difluorobenzene were distilled over CaH₂ and brought into the glove box without exposure to air. L-lactide and 1,3,5-trimethoxybenzene were recrystallized from toluene at least twice before use. 2,4-di-*tert*-butylphenol, *n*-BuLi, cobaltocene, and Zr(O^{*i*}Bu)₄ were purchased from Sigma Aldrich and used as received. [AcFc][BAR^F]₄⁴⁷ and (salfan)Zr(O^{*i*}Bu)₂²⁶ were synthesized following previously published procedures. Molecular weights of the polymers were determined by GPC-MALS instrument at UCLA. GPC-MALS uses a Shimadzu Prominence-i LC 2030C 3D equipped with an autosampler, two MZ Analysentechnik MZ-Gel SDplus LS 5 μm, 300 x 8mm linear columns, Wyatt DAWN HELEOS-II and Wyatt Optilab T-rEX. The column temperature was set at 40 °C. A flow rate of 0.70 mL/min was used and samples were dissolved in chloroform or THF. dn/dc values were calculated for PLA and PCHO by making 5 solutions of increasing concentration (0.1 - 1.0 mg/mL), directly injecting them into the RI detector sequentially, and using the batch dn/dc measurement methods in the Astra software. The dn/dc value for PLA and PCHO were calculated to be 0.024 mL/g and 0.086 mL/g over three trials.

DFT calculations. All calculations were carried out with the GAUSSIAN 09 program package.³⁶ Geometry optimizations were performed with B3LYP.⁴⁸⁻⁵⁰ The LANL2DZ basis set⁵¹⁻⁵³ with ECP was used for Fe, and the 6-31G(d) basis set⁵⁴⁻⁵⁶ was used for other atoms. Frequency analysis was conducted at the same level of theory to verify that the stationary points are minima or saddle points. The single point energies and solvent effects in benzene were computed with PBE1PBE/⁵⁷SDD-6-311+G(d,p) basis sets⁵⁸ by using the PCM solvation model.⁵⁹ The D3 version of Grimme's dispersion was applied for the dispersion correction.⁶⁰ All enthalpies and the Gibbs free energies are given in Hartree.

General procedure for the polymerization of LA and CHO by [(salfan)Zr(O^{*i*}Bu)₂][BAR^F] followed by reduction with CoCp₂. To a C₆D₆ (0.15 mL) solution of (salfan)Zr(O^{*i*}Bu)₂ (4.6 mg, 5 μmol) in a J-Young NMR tube, a solution of 1,3,5-trimethoxybenzene (16.8 mg, 50 μmol) in C₆D₆ (0.15 mL), 0.10 mL of *o*-F₂C₆H₄ and a solution of AcFcBAR^F (5.5 mg, 5 μmol) in *o*-F₂C₆H₄ (0.10 mL) was added and the reaction was left at room temperature for 2 h. A solution of cyclohexene oxide (49.0 mg, 0.5 mmol) in C₆D₆ (0.10 mL) and L-lactide (72.0 mg, 0.5 mmol) was added. After one hour, a solution of CoCp₂ (5.5 mg, 5 μmol) in C₆D₆ (0.10 mL) was then added and the reaction was left at room temperature for 2 h. The reaction was heated to 100 °C and monitored by ¹H NMR spectroscopy. At the end, the reaction was dissolved in CH₂Cl₂ and poured into cold methanol; a white solid precipitated briefly and was filtered.

Copolymerization of LA and CHO by (salfan)Zr(O^{*i*}Bu)₂ (red-ox). To a C₆D₆ (0.15 mL) solution of (salfan)Zr(O^{*i*}Bu)₂ (4.6 mg, 5 μmol) in a J-Young NMR tube, a solution of 1,3,5-trimethoxybenzene (16.8 mg, 50 μmol) in C₆D₆ (0.15 mL), 0.20 mL of *o*-F₂C₆H₄, 0.50 mL C₆D₆ and L-lactide (72.0 mg, 0.5 mmol) were added. The reaction was heated to 100 °C and removed from the oil bath every hour to be analyzed by ¹H NMR spectroscopy until about 90% conversion occurred. A solution of AcFcBAR^F (5.5 mg, 5 μmol) in *o*-F₂C₆H₄ (0.10 mL) was then added and the reaction was left at room temperature for 2 h. The volume of the solution was reduced to 0.90 mL and a solution of cyclohexene oxide (49.0 mg, 0.5 mmol) in C₆D₆ (0.10 mL) was added. The reaction was left at room temperature and ana-

lyzed by ¹H NMR spectroscopy until about 90% conversion occurred. At the end, the reaction mixture was dissolved in CH₂Cl₂ and poured into cold methanol; a white solid precipitated briefly and was filtered.

Copolymerization of LA and CHO by [(salfan)Zr(O^{*i*}Bu)₂][BAR^F] (ox-red). To a C₆D₆ (0.15 mL) solution of (salfan)Zr(O^{*i*}Bu)₂ (4.6 mg, 5 μmol) in a J-Young NMR tube, a solution of 1,3,5-trimethoxybenzene (16.8 mg, 50 μmol) in C₆D₆ (0.15 mL), 0.4 mL C₆D₆, 0.10 mL F₂C₆H₄ and a solution of AcFcBAR^F (5.5 mg, 5 μmol) in *o*-F₂C₆H₄ (0.10 mL) was added and the reaction was left at room temperature for 2 h. A solution of cyclohexene oxide (49.0 mg, 0.5 mmol) in C₆D₆ (0.10 mL) was added. The reaction was monitored at room temperature by ¹H NMR spectroscopy until about 90% conversion occurred. A solution of CoCp₂ (5.5 mg, 5 μmol) in C₆D₆ (0.10 mL) was then added and the reaction was left at room temperature for 2 h. The volume of the solution was reduced to 1.0 mL and L-lactide (72.0 mg, 0.5 mmol) was added. The reaction was heated to 100 °C and removed from the oil bath every hour to be analyzed by ¹H NMR spectroscopy. At the end, the reaction was dissolved in CH₂Cl₂ and poured into cold methanol; a white solid precipitated briefly and was filtered.

When using 50 equivalents or 25 equivalents, the volume of the overall solution was scaled down from 1.00 mL to 0.50 mL or 0.25 mL. When doubling the concentration, the overall concentration was scaled down to 0.50 mL. A solvent ratio of 4:1 *o*-F₂C₆H₄ : C₆D₆ was maintained in all trials.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

¹H NMR spectra, GPC traces, and data from computational studies for LA and CHO copolymerization (PDF)

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Notes

The authors declare no competing financial interest.

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