Video Article

Controlled Photoredox Ring-Opening Polymerization of O-Carboxyanhydrides Mediated by Ni/Zn Complexes

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URL: <https://www.jove.com/video/56654>

DOI: [doi:10.3791/56654](https://doi.org/10.3791/56654)

Keywords: Chemistry, Issue 129, Ring-Opening Polymerization, O-Carboxyanhydride, Photoredox, Poly(α -hydroxy acids), Polyester, Living polymerization

Date Published: 11/21/2017

Citation: Feng, Q., Tong, R. Controlled Photoredox Ring-Opening Polymerization of O-Carboxyanhydrides Mediated by Ni/Zn Complexes. *J. Vis. Exp.* (129), e56654, doi:10.3791/56654 (2017).

Abstract

Here, we describe an effective protocol that combines photoredox Ni/Ir catalysis with the use of a Zn-alkoxide for efficient ring-opening polymerization, allowing for the synthesis of isotactic poly(α -hydroxy acids) with expected molecular weights (>140 kDa) and narrow molecular weight distributions ($M_w/M_n < 1.1$). This ring-opening polymerization is mediated by Ni and Zn complexes in the presence of an alcohol initiator and a photoredox Ir catalyst, irradiated by a blue LED (400 - 500 nm). The polymerization is performed at a low temperature (-15 °C) to avoid undesired side reactions. The complete monomer consumption can be achieved within 4 - 8 hours, providing a polymer close to the expected molecular weight with narrow molecular weight distribution. The resulted number-average molecular weight shows a linear correlation with the degree of polymerization up to 1000. The homodecoupling ¹H NMR study confirms that the obtained polymer is isotactic without epimerization. This polymerization reported herein offers a strategy for achieving rapid, controlled O-carboxyanhydrides polymerization to prepare stereoregular poly(α -hydroxy acids) and its copolymers bearing various functional side-chain groups.

Video Link

The video component of this article can be found at <https://www.jove.com/video/56654/>

Introduction

Poly(α -hydroxy acid) (PAHA) is an important class of biodegradable and biocompatible polymers with applications ranging from biomedical devices to packaging materials.^{1,2} Although PAHAs can be prepared directly by polycondensation of α -hydroxy acids, the molecular weights (MWs) of the resulting PAHAs are generally low.³ Ring-opening polymerization (ROP) of lactones (e.g., lactide and glycolide) is an alternative synthetic approach that provides the better control on MWs and molecular weight distribution ($\bar{D}$) than polycondensation. However, the lack of side-chain functionality in PAHAs and in lactones limit the diversity of physical and chemical properties and their applications.^{4,5} Since 2006, 1,3-dioxolane-2,4-diones, so-called O-carboxyanhydrides (OCAs), which can be prepared with a rich variety of side-chain functionalities,^{6,7,8,9,10,11,12,13} have emerged as an alternative class of highly active monomers for polyester polymerization.^{14,15}

Catalytic systems for the ROP of OCAs can be categorized into organocatalysts,^{8,12,16,17} organometallic catalysts^{12,18,19,20,21} and biocatalysts.²² Generally, the ROP of OCAs promoted by organocatalyst proceeds in a more or less uncontrolled manner, such as epimerization (i.e., lack of stereoregularity) for OCAs bearing electron-withdrawing groups,^{8,17} unpredictable MWs, or slow polymerization kinetics.¹³ To address these problems, an active Zn-alkoxide complex was developed for the ROP of OCAs.¹² Well-controlled ROPs were achieved at a low degree of polymerization (DP) without epimerization. However, this Zn-alkoxide catalyst cannot efficiently produce polymers with a high degree of polymerization (DP $\geq$ 300).¹³

We have recently reported a promising approach that greatly improves customizability and efficiency of PAHA synthesis (**Figure 1**).¹³ We merge photoredox Ni/Ir catalysts that promote OCA decarboxylation with zinc alkoxide to mediate ring-opening polymerization of OCAs. The use of low temperature (-15 °C) and photoredox Ni/Ir catalysis synergistically accelerates ring-opening and decarboxylation of OCA for chain propagation while avoiding undesired side reactions, e.g., the formation of Ni-carbonyl.^{23,24} Upon transmetalation with Ni complex the active Zn-alkoxide is located at chain terminus for chain propagation.¹³

In this protocol, we add fresh prepared (bpy)Ni(COD) (bpy = 2,2'-bipyridyl, COD = 1,5-cyclooctadiene), Zn(HMDS)₂ (HMDS = hexamethyldisilazane),²⁵ benzyl alcohol (BnOH) and Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (**Ir-1**, dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) into the monomer **1-1** solution²⁶ in a glove box with a cold trap, in the presence of a blue LED light (400-500 nm) and a fan to maintain temperature (**Figure 1**). The temperature is kept at -15 °C $\pm$ 5 °C during the polymerization. The conversion of OCA is monitored by Fourier-transform infrared spectroscopy. The resulting polymer MWs and $\bar{D}$ s is characterized by a gel permeation chromatography (GPC). The homodecoupling ¹H NMR study determines whether the obtained polymer is

isotactic or not. As most chemicals are highly sensitive to moisture, the detailed video protocol is intended to help new practitioners avoid pitfalls associated with the photoredox ROP of OCAs.

Protocol

Caution: Please consult all relevant materials safety data sheets (MSDS) before use. Many chemicals used in the synthesis are acutely toxic and carcinogenic. Please use all appropriate safety practices when performing reaction including the use of engineering controls (fume hood and glovebox) and personal protective equipment (safety glasses, gloves, lab coat, full-length pants, closed-toe shoes, blue-light blocking safety goggles). Following procedures involve standard air-free handling techniques in a glove box. All solutions are transferred using pipette.

1. Preparation of Catalyst and Initiator

NOTE: The whole process is conducted in a glove box with a cold trap. All chemicals are dried or purified before moving into the box.¹³ All vials and glassware are dried and heated in the oven before moving into the box.

1. Preparation of (bpy)Ni(COD) solution

NOTE: (bpy)Ni(COD) should be freshly prepared *in situ*. It should be stored in the glove box freezer (-35 °C) and used within one week. All other catalysts and initiator solutions can be stored in the glove box freezer over 1 month.

1. Weigh Ni(COD)₂ (3.5 mg, 12.7 μmol, 1.0 eq) into a 7-mL scintillation vial.
2. Weigh 2,2'-bipyridine (5.9 mg, 37.8 μmol) into a 7-mL scintillation vial.
3. Dissolve the 2,2'-bipyridine in 1 mL of anhydrous tetrahydrofuran (THF).
4. Add resulting 2,2'-bipyridine solution (337 μL) into the vial containing Ni(COD)₂.
5. Dilute the mixture in 1 mL of anhydrous THF.
6. Cap the vial and place the reaction mixture at room temperature for 2 h.

NOTE: Ni(COD)₂ is not soluble in THF, whereas (bpy)Ni(COD) is soluble in THF. There should be no precipitation in the purple solution after 2 h.

7. Store the (bpy)Ni(COD) in the -35 °C freezer.

2. Preparation of Zn(HMDS)₂ solution

1. Add Zn(HMDS)₂ (3.3 mg, 4 μL, 8.5 μmol) to a 7-mL scintillation vial.
2. Dissolve the Zn(HMDS)₂ in 1 mL of anhydrous THF.
3. Store Zn(HMDS)₂ solution in the -35 °C freezer.

3. Preparation of BnOH solution

1. Add BnOH (4.0 mg, 4 μL, 37.0 μmol) to a 7-mL scintillation vial.
2. Dissolve the BnOH in 4 mL of anhydrous THF.
3. Store the BnOH solution in the -35 °C freezer.

4. Preparation of Ir-1 solution

1. Turn off the glove box light.
Caution: It is necessary to turn off the glove box light to avoid deactivation of Ir-1 before polymerization.
2. Add Ir-1 (2.9 mg, 2.6 μmol) to a 7-mL scintillation vial.
3. Dissolve the Ir-1 in 3 mL of anhydrous THF.
4. Store the Ir-1 solution in the -35 °C freezer.

2. Photoredox ring-opening polymerization of I-1

NOTE: The whole process is conducted in a glove box with a cold trap. All OCA monomers are recrystallized in the glove box before use.¹³ Here we give the example of the polymerization at DP=500 ([I-1]/[(bpy)Ni(COD)]/[Zn(HMDS)₂]/[BnOH]/[Ir-1] = 500/1/1/1/0.1). Polymers at different DPs can also be prepared by adjusting the monomer mass accordingly.

1. Preparation of I-1 solution for polymerization

1. Add I-1 (72.2 mg, 375.7 μmol) to a 7-mL scintillation vial.
2. Dissolve the I-1 in 722 μL of anhydrous THF.
3. Add 200 μL of I-1 solution into another 7-mL scintillation vial equipped with a stir bar.
4. Add 100 μL of anhydrous THF into the 7-mL scintillation vial.
5. Cap the vial and place the I-1 solution in the cold trap.
6. Turn off the glove box light.
Caution: It is necessary to turn off the glove box light to avoid deactivation of Ir-1 before polymerization.

2. Cooling down the cold trap

1. Inside the box, put a thermometer into the cold trap.
2. Outside of the box, add ca. 500 mL of ethanol into the dewar flask.
3. Add liquid nitrogen into the dewar flask.
4. Load the KGW dewar flask to the cold trap.
5. Cool the cold trap to -50 °C.
6. Put a stir plate underneath the cold trap (see Figure 1).

3. Perform the photoredox ring-opening polymerization

NOTE: Before starting the polymerization, place safety goggles that block blue light within reach. All catalyst system solutions are immediately taken out from the freezer and added successively into the 7-mL scintillation vial containing 20 mg of I-1 without pause or disruption over 30 s.

1. Add (bpy)Ni(COD) solution (16.4 μ L, 0.208 μ mol) into the 7-mL scintillation vial containing I-1 (prepared in 2.1).
2. Add Zn(HMDS)₂ solution (24.4 μ L, 0.208 μ mol) into the vial.
3. Add BnOH solution (22.5 μ L, 0.208 μ mol) into the vial.
4. Add Ir-1 solution (24.2 μ L, 0.0208 μ mol) into the vial and cap the vial.
5. Wear safety goggles blocking blue LED light.

Caution: As blue LED light with a relative high intensity is used, wear safety goggles during the whole process.

6. Turn on the blue LED light (34 W) and the fan to dissipate the heat generated by the LED light. Direct the light towards the vial in the cold trap. (Figure 1)
7. Turn on the stirrer.
8. Cover the cold trap with aluminum foil.
9. Keep the reaction temperature at -15 ± 5 °C and add liquid nitrogen every 15-20 minutes.

NOTE: The maintenance of reaction temperature is important for polymerization and MW control.

3. Monitor the monomer conversion by Fourier-transform infrared spectra

NOTE: Fourier-transform infrared spectra (FTIR) are recorded on an FT-IR spectrometer equipped with Diamond ATR and Transmission sampling accessory.

1. At specific time points, add a small aliquot of polymer solution (20 μ L) into a 7-mL scintillation vial, and capped.
2. Remove the vial out of the glove box.
3. Immediately drop the solution (3 μ L) onto the FTIR-ATR diamond sampler. The solution forms a film within 10 s for the spectrum measurement.
4. Measure the FTIR spectrum of the sample.

NOTE: The monomer conversion was determined by the intensity ratio between 1760 cm^{-1} and 1805 cm^{-1} : $\text{conversion\%} = I_{1760}/(I_{1760} + I_{1805})$ (Representative results in Figure 2). Generally, the polymerization takes about 1-8 h for DP ranging from 200 to 1000 (detailed kinetics are discussed in reference¹³).

4. The measurement of polymer's molecular weight by gel-permeation chromatography

NOTE: Gel-permeation chromatography (GPC) experiments are performed on a system equipped with an isocratic pump with degasser, multiangle laser light scattering (MALS) detector (GaAs 30 mW laser at $\lambda = 690$ nm), and differential refractive index (DRI) detector with a 690-nm light source. Separations are performed using serially connected size exclusion columns (100 Å, 500 Å, 10³ Å, and 10⁴ Å columns, 5 μ m, 300 $\times$ 4.6 mm) at 35 °C using THF as the mobile phase at a flow rate of 0.35 mL/min. The polymer molecular weight (MW) and molecular weight distribution ($\bar{D}$) are determined using the Zimm model fit of MALS-DRI data. The presence of metal complex in the polymer does not affect the GPC measurement results.

1. Remove a small aliquot of polymer solution (50 μ L) out of the glove box.
2. Add 100 μ L of THF into the vial.
3. Inject the sample into the GPC sampler.
4. Analyze the result once the GPC run is completed.

NOTE: The polymer should be monodispersed with narrow $\bar{D}$ (Representative results in Figure 3). The polymer (20 mg) can be dried and washed by 1 mL diethyl ether containing 1% HOAc and 1 mL methanol, which can remove 87% of Ni and 50% of Zn complexes, determined by inductively coupled plasma mass spectrometry (ICP-MS).

Representative Results

The conversion of OCA is monitored by Fourier-transform infrared spectroscopy, as shown in Figure 2. The peak at 1805 cm^{-1} is assigned as the anhydride bond stretch in OCA; the peak at 1760 cm^{-1} corresponds to the formation of the ester bond in the polymer. Once the monomer's peak at 1805 cm^{-1} completely disappears, the polymerization is finished.

The MW and $\bar{D}$ of the resulting polymer is characterized by a gel permeation chromatography. Figure 3 shows controlled photoredox ring-opening polymerization of OCAs with DP ranging from 200 to 1000. Increasing the monomer feed ratio ([I-1]/[Zn(HMDS)₂]) ratio leads to an increased and expected M_n of the resulting polymer. Besides, M_n of the polymers increases linearly with initial [I-1]/[Ni]/[Zn]/[Ir-1] ratio up to 1000/1/1/0.1, and all of the $\bar{D}$ values are < 1.1.

The NMR studies measure the stereochemistry of obtained polymer. The ROP of OCAs mediated by organocatalyst such as dimethylaminopyridine can induce epimerization on the α -methine for OCAs bearing electron-withdrawing groups.^{8,17} The homodecoupling ¹H NMR of these polymers exhibited multiple peaks in α -methine region, indicating the loss of the stereoregularity in the polymerization. Using our method, the homodecoupling ¹H NMR study shows single peak at α -methine region (5.0 - 5.3 ppm), indicating that the obtained polymer is isotactic without epimerization (Figure 4).

Figure 1. Scheme of Ni/Zn-mediated photoredox ROP of I-1. The photoredox polymerization is conducted in a glove box with cold trap, irradiated by LED light with a cooling fan to maintain the temperature. [Please click here to view a larger version of this figure.](#)

Figure 2. FTIR spectra of (a) I-1 and (b) the reaction mixture during the photoredox polymerization. [Please click here to view a larger version of this figure.](#)

Figure 3. (a) Plots of M_n and molecular weight distribution (M_w/M_n) of poly(I-1) versus $[I-1]/[Zn(HMDS)_2]$ ratio ($[(bpy)Ni(COD)]/[Zn(HMDS)_2]/[BnOH]/[Ir-1] = 1/1/1/0.1$). (b) Representative gel-permeation chromatography (GPC) traces of the photoredox polymerization reaction in panel (a). [Please click here to view a larger version of this figure.](#)

Figure 4. NMR spectra of poly(l-1). (a) ^1H NMR spectrum; (b) ^1H homodecoupling NMR spectrum. [Please click here to view a larger version of this figure.](#)

Discussion

The critical step within the protocol is maintaining the reaction temperature at $-15 \pm 5^\circ\text{C}$. All catalysts solutions and OCA monomers have to be stored in a glove box freezer at -35°C before the polymerization. The reaction vials have to be pre-cooled in the cold trap. During the reaction, because the LED light dissipates heat, it is necessary to monitor the reaction every 15 - 20 minutes. Once the temperature is raised up to -10°C , liquid nitrogen should be added into the dewar to cool the trap. The reason for the low temperature is the formation of the $\text{Ni}(\text{CO})$ complex at room temperature, which is detrimental to the controlled photoredox polymerization and affects the MW and $\bar{D}$.¹³

Synthesis attempts from O-carboxyanhydrides with pendent functional groups by organocatalysts have been plagued by uncontrolled polymerization including epimerization, which hampers the preparation of stereoregular high-MW polymers. This photoredox controlled ROP polymerization can successfully prepare stereoregular high-MW polymers with DP reaching 1000 for various OCA monomers, which are documented in reference¹³. The copolymerization of different OCA monomers by sequential addition is also undemanding using our methods. However, for L-mandelic OCA monomers, the MW control has not been achieved at high DPs. We are currently investigating this methodology and trying to develop a new catalyst strategy for the polymerization.

In conclusion, our Ni/Zn-mediated photoredox polymerization protocol offers a strategy for achieving rapid, controlled OCA polymerization to prepare stereoregular poly(α -hydroxy acids) and their copolymers bearing various functional side-chain groups. We expect that our new strategy allows for the generation of new polyesters with desirable macroscopic properties such as rigidity, elasticity, and biodegradability. This method also can be useful for new fabrication techniques such as light-cured nanoimprinting lithography.

Disclosures

The authors declare no competing financial interests. A provisional patent (U.S. Patent Application No: 62/414,016) has been filed pertaining to the results presented in this paper.

Acknowledgements

This work was supported by start-up funding from Virginia Polytechnic Institute and State University. Q.F. acknowledges support from National Natural Science Foundation of China (21504047), Natural Science Foundation of Jiangsu Province (BK20150834), Nanjing University of Posts and Telecommunications Scientific Foundation NUPTSF (NY214179).

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