Synthesis and Characterization of Well-Defined Lactic Acid–PEG Cooligomers and Its Tricarbonyl Rhenium Conjugates

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ABSTRACT: This article describes the synthesis and characterization of hydroxyl tailored, molecularly defined biodegradable cooligomers capable of chelating rhenium for potential radiopharmaceuticals. New insights were gained during the synthesis of lactide based on dimethylaminopyridine-catalyzed transesterification. © 2011 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 49: 1745–1752, 2011

KEYWORDS: cooligomer; lactic acid; polyethylene glycol (PEG); rhenium; transesterification

INTRODUCTION Applications such as targeted drug delivery or the development of various diagnostic tools will benefit from the availability of defined macromolecules and biocompatible materials bearing multiple functional groups that allow easy drug payload attachment, cell targeting, delivery, and tracking.[1] Polylactic acids or polylactides (PLAs) are a class of FDA-approved biodegradable polymers or oligomers that are widely used in biomedical and biomaterial research.[2] Polyethylene glycol (PEG) is another class of commonly used biocompatible hydrophilic polymers that are nontoxic and nonimmunogenic with little interaction with blood components.[3]

Covalently linking PLA (block A) to PEG (block B) results in amphiphilic block copolymers with AB, ABA, and BAB architectures.[4] The effect of particle size and PEG coating density on the transport of PLA–PEG particles across nasal mucosa has been studied.[5] Although there is growing academic and industrial interest in PLA, PEG, or their copolymers (PLA–PEG), literatures on the synthesis of well-defined PLA oligomers have been scarce except for two recent reports by Hawker and coworkers.[6] Preparation of monodisperse PLA oligomers would enable a wide range of structural studies for better understanding and prediction of properties, such as the degradation, and drug loading for these materials.

The medically useful radionuclides, ^{99m}Tc and $^{186/188}$Re, are attractive for developing molecular imaging and molecular radio therapeutics due to their similar coordination and physical decay characteristics. Alberto et al. developed a particularly stable and kinetically inert $[M(CO)_3]^+$ core (M = ^{99m}Tc, $^{186/188}$Re),[7] which can form complexes with various ligands including the bis(picolyl)amine moiety.[8]

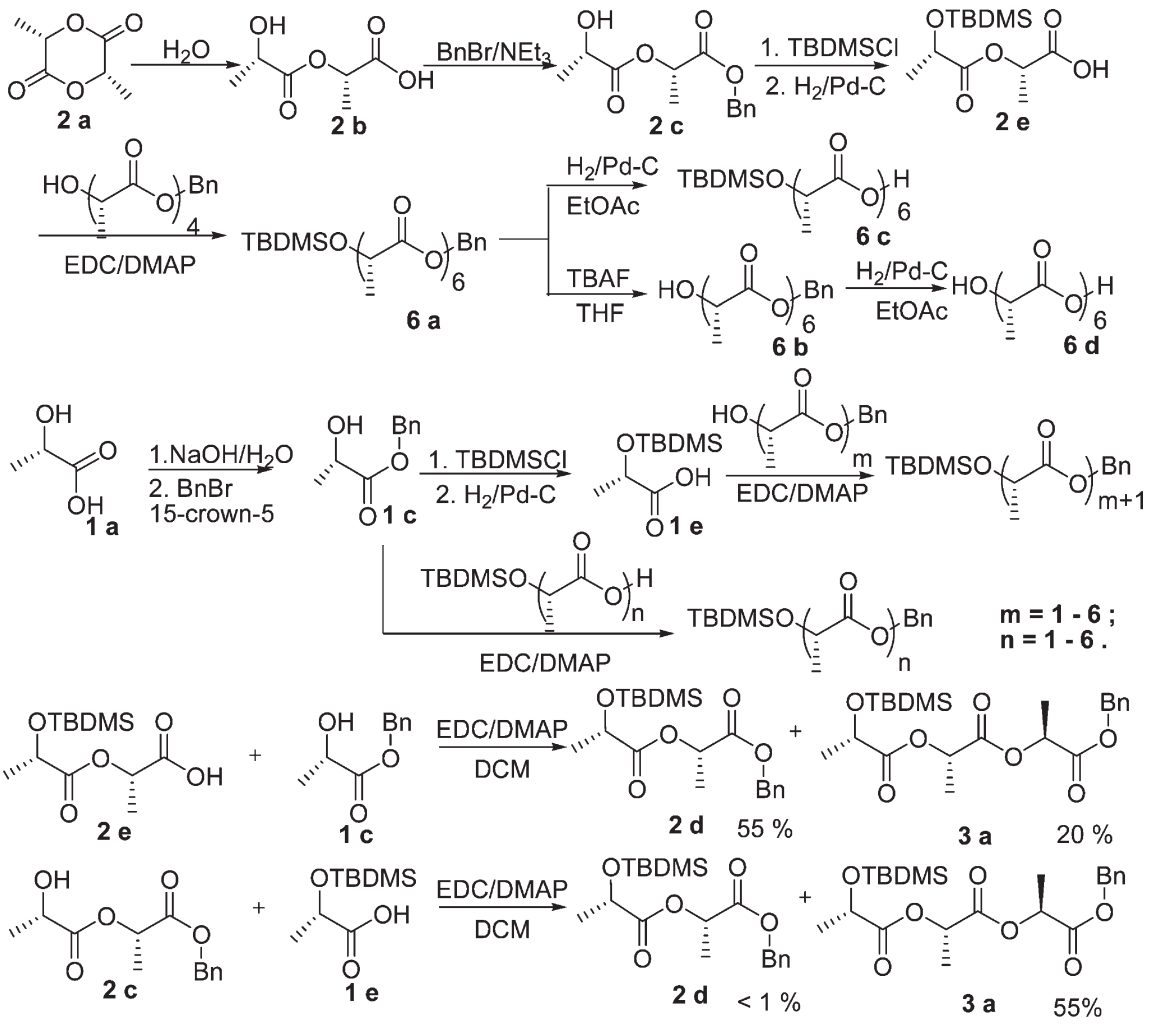
The aim of this work was to design and synthesize length controllable and biodegradable cooligomers with a custom-tailored end group to coordinate the metal ions of choice.[9] During the synthesis, we observed a new phenomenon on dimethylaminopyridine (DMAP)-catalyzed transesterification. Although it is well known that ion-exchange resins can catalyze transesterification,[10] we believe our unexpected finding may provide new insights into DMAP-prompted acylation or transesterification reactions.

CHEMICAL SYNTHESIS

Synthesis of Lactide Oligomers

The synthesis of PLA oligomers relies on the availability of orthogonal protecting groups for the hydroxyl and carboxylic acid group, respectively. In brief, *t*-butyldimethylsily (TBDMS) ether and benzyl (Bn) ester were selected to protect hydroxyl and carboxyl groups. On the basis of the work reported by Hawker and coworkers, we adopted the method shown in Scheme 1. Dimer **2b** was obtained nearly quantitatively by extraction from the reaction mixture. The hydroxyl-protected dimer **2c**, which was prepared from **2b** by BnBr/NEt_3 treatment, could also be obtained by acid-catalyzed ring opening of **2a** with 1.2 equiv of benzyl alcohol.[11] Treating **2c** with TBDMSCl led to **2d** in >95% yields. Removing the benzyl group of **2d** by hydrogenolysis gave the carboxylic

Additional Supporting Information may be found in the online version of this article. Correspondence to: Y.-M. Shen (E-mail: ymshencsu@yahoo.com)



SCHEME 1 Synthetic strategy for well-defined (L)-lactic acid from monomer to heptamer.

acid **2e** almost quantitatively. The synthesis of PLAs consisting of even numbers of lactide residues involved direct esterification reaction, which turned out to be the best choice. For the preparation of hexamer such as **6a**, the coupling and deprotecting steps were reproducible and resulted in high yields (more than 80%). Hexamer **6d**, which carries a free hydroxyl and a carboxyl group, was prepared from **6b**.

Although the synthesis of **1c** was successful, attempts to prepare oligomers consisting of odd-numbered residues with both of their termini protected failed. The reactions led to mixtures containing various byproducts. For instance, direct coupling of **1c** with **2e** gave **3a** in low yields (20%), along with byproduct **2d** (Scheme 1 and Table 1) as the major component due to transesterification.

Nevertheless, alternative strategies were successfully developed with optimized conditions. With the new method (Scheme 1 and Supporting Information), compound **1e** was obtained in high yield (90%).

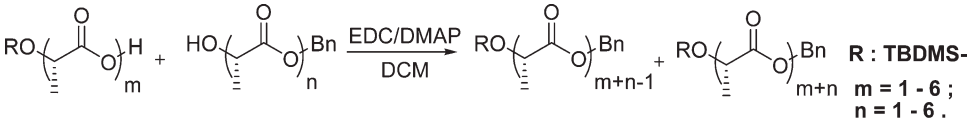
For best results, freshly prepared **1e** should be used for the next step because it was unstable. In the synthesis of oligomers with odd numbers of residues, the coupling reaction of **1e** with the corresponding acid was found to be highly efficient. From trimer **3a**, the coupling and deprotecting steps, catalyzed by EDC/DMAP, were reproducible and resulted in high yields, leading up to the heptamer (Scheme 1 and Table 1).

Synthesis and Coordination of Biodegradable Oligomers

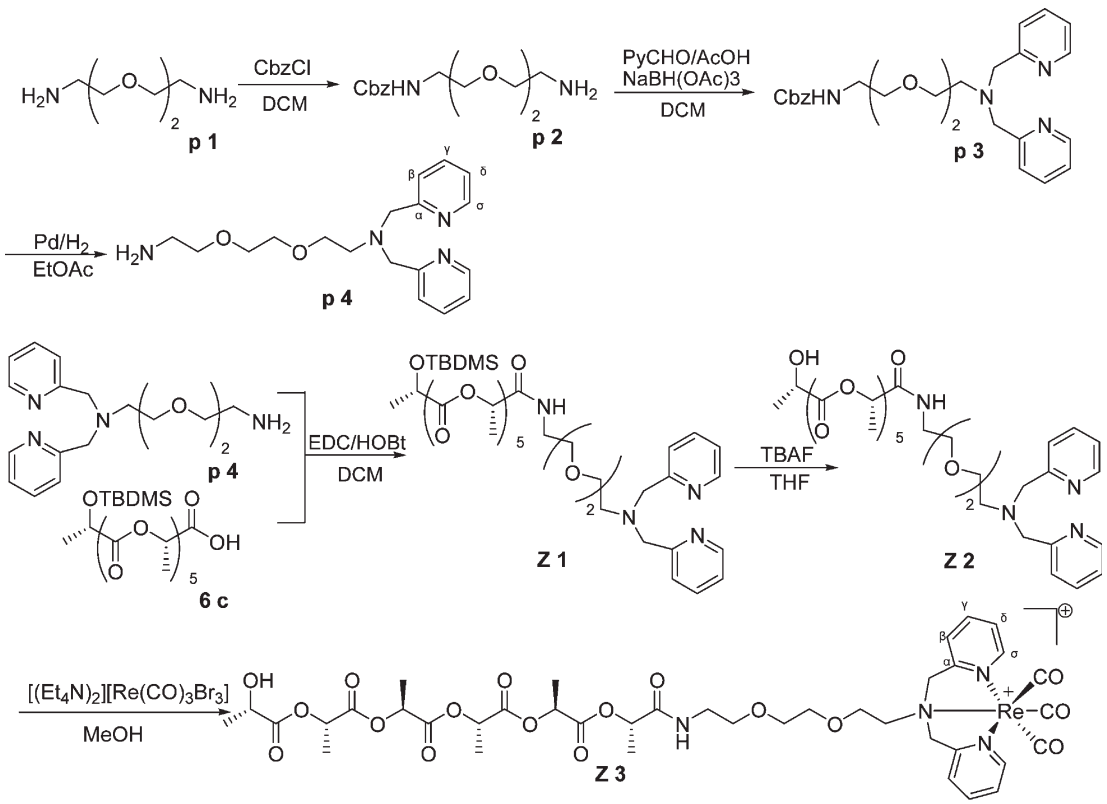
As the successful synthesis of molecularly defined lactide oligomers, there are a number of reports on the preparation of tridentate chelating systems with variable spacer groups comprising terminal, primary amine.[12] Here, we present a new procedure to synthesize compounds such as **p3** (Scheme 2). Mono-Cbz-protected bis(2-aminoethyl) ether **p2** was treated with 2 equiv of pyridine-2-carbaldehyde. A slight excess of sodium borohydride triacetate was added for the *in situ* reduction of the generated imine.

Cbz-deprotection of **p3** was achieved by hydrogenolysis (Pd/C, H_2) or in 2 M NaOH solution leading to compound **p4**. Intermediate **p4** and 2,2′-dipicolylamine were coupled with the carboxyl-functionalized lactic acid (LA)-hexamer **6c** by

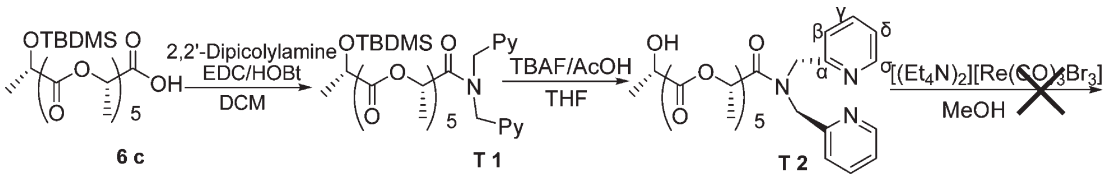
TABLE 1 Lactide Esterification and Transesterification Reactions Catalyzed by DMAP (12 h, r.t.)



Acid	Alcohol	Transesterification (Isolated Yield %)	Esterification (Isolated Yield %)
1e, $m = 1$	**2c**, $n = 2$	NA (-)	**3a** (55)
1e, $m = 1$	**3b**, $n = 3$	NA (-)	**4a** (45)
1e, $m = 1$	**4b**, $n = 4$	NA (-)	**5a** (35)
1e, $m = 1$	**6b**, $n = 6$	NA (-)	**7a** (25)
2e, $m = 2$	**1c**, $n = 1$	**2d** (55)	**3a** (20)
2e, $m = 2$	**2c**, $n = 2$	NA(-)	**4a** (78)
2e, $m = 2$	**4b**, $n = 4$	NA (-)	**6a** (65)
3c, $m = 3$	**1c**, $n = 1$	**3a** (50)	**4a** (15)
3c, $m = 3$	**2e**, $n = 2$	NA (-)	**5a** (55)
3c, $m = 3$	**3b**, $n = 3$	NA (-)	**6a** (70)
3c, $m = 3$	**4b**, $n = 4$	NA (-)	**7a** (55)
4c, $m = 4$	**1c**, $n = 1$	**4a** (50)	**5a** (10)
4c, $m = 4$	**2c**, $n = 2$	NA (-)	**6a** (55)



SCHEME 2 Synthetic strategy for metal coordinated with lactide conjugates.



SCHEME 3 Attempted synthesis of "naked" lactide conjugates.

standard peptide coupling reagents (EDC/HOBt) to form the corresponding intermediate **Z1**, respectively, in good yield (Scheme 2). Based on the general procedure described above for the deprotection of TBDMS groups, the biodegradable ligand-cooligomer **Z2** was isolated with good yield.

The tricarbonyl rhenium(I) $[Et_4N]_2[Re(CO)_3Br_3]$ complex was prepared from $[Bu_4N][ReO_4]$ based a method reported in the literature.[13] **Z3** was synthesized from **Z2** and $[Et_4N]_2[Re(CO)_3Br_3]$ after stirring in MeOH at room temperature. The crude product **Z3** was purified via flash chromatography and further recrystallized from $CHCl_3$ and hexane as a light yellow solid.

Attempted Synthesis of Lactic Acid's Tricarbonyl Rhenium Conjugates

The TBDMS-protected, tridentate chelating system-functionalized LA oligomer, **T1**, was prepared using the general procedure described earlier for synthesis of **Z1**, starting from **6c** and 2,2′-dipicolylamine (Scheme 3). The crude product was then purified via flash column chromatography to yield **T1** (80% yield) as a colorless oil. The hydroxyl end-capped, tridentate chelating LA oligomer **T2** was prepared with a procedure similar to the synthesis of **Z2**. The crude product was then purified via flash column chromatography to yield **T2** (82% yield) as a colorless oil.

A total of 76.0-mg (0.12 mmol) **T2** was dissolved in 2-mL menthol followed by the addition of 85 mg (0.11 mmol) $(Et_4N)_2[Re(CO)_3Br_3]$ and then stirred for 2 h at room temperature and at 50 °C for 3 h. We did not detect "naked" HO-LA-Re complex by TLC at either temperature. Neither was HO-LA-Re complex observed when we changed the solvent to acetone or acetonitrile under similar conditions.

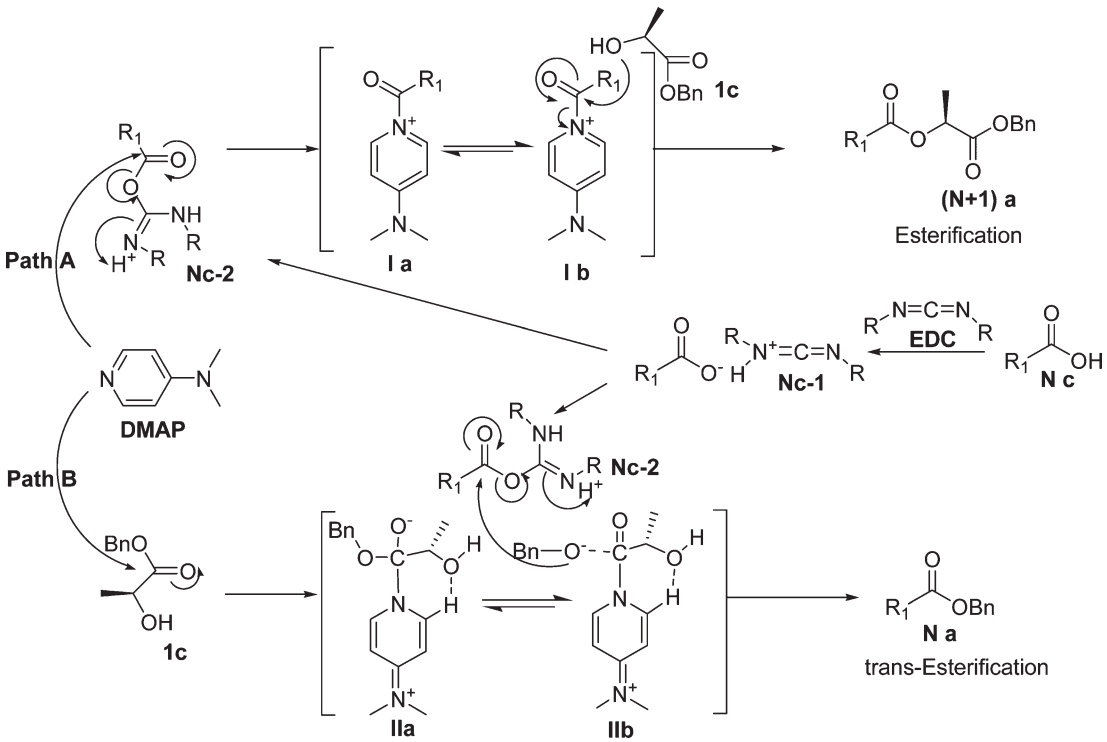
RESULTS AND DISCUSSION

Synthesis of Molecularly Defined Biodegradable Oligomers

Based on the synthetic approach described above for the preparation of well-defined lactide oligomers, molecularly defined biodegradable oligomer was produced from FDA-approved lactide acids using the commercially available EDC/DMAP as the coupling reagents in high yield.

Mechanism

As shown in Table 1, we observed a new phenomenon on DMAP-catalyzed transesterification. DMAP has been widely used for many reactions including acylation, alkylation,



SCHEME 4 Proposed mechanism for DMAP-catalyzed esterification and transesterification reactions.

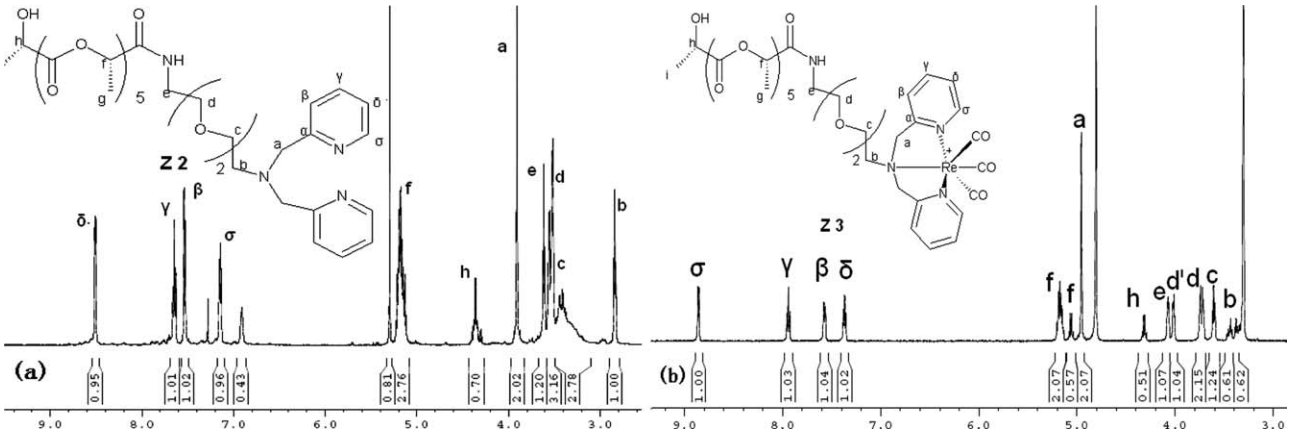


FIGURE 1 (a) ^{1}H NMR of **Z2** and (b) **Z3**.

silation, phosporylation, condensation, and transesterification and has proven to be an extremely efficient catalyst.[14] However, the exact mechanism involving DMAP remains to be elucidated.[15] In Scheme 4, we propose a possible catalytic cycle for our systems.

In such a mechanism, a carbodiimide molecule first reacts with a proton to form the carbocation **Nc-1**, which then reacts with an ionized carboxyl group to form the **Nc-2** (*O*-acylisourea).[16] In path A, DMAP, being a stronger nucleophile than a alcohol, reacts with **Nc-2** more easily, leading to the reactive amide **Ib** (active ester). This intermediate does not form side products. Instead, it reacts rapidly with alcohols and subsequently gives the corresponding esterification compound **(N+1)a**.[17]

In path B, the addition of DMAP to acyl donor **1c** forms the tetrahedral intermediate **IIa**. Because of the influence of steric effects and conjugation, the resultant **IIa**, with an ion-pair structure, is rather stable. In such a structure, the acyl group is essentially transferred to the nitrogen atom of DMAP, and the negatively charged exocyclic oxygen atom is engaged in weak hydrogen-bonding interaction. Subsequently, the reversible formation of *N*-acylpridinium salt **II**[18] was followed by the irreversible nucleophilic addition of the benzyloxy anion to **Nc-2** with concomitant electron transfer. Finally, the compound **Na** was generated on transesterification.[19] In these steps, DMAP acts as a bifunctional catalyst for acyl transfer. The activation of alcohol by DMAP (Scheme 2, path A) was energetically less favorable compared with the nucleophilic activation of the monomer (Scheme 2, path B).

However, as the alcohol becomes sterically hindered, path B would become less favorable, which is consistent with our experimental observation (Table 1). The sterically hindered compounds (**2e**, **3c**, and **4c**) reacted with **1c** result in the esterification compound and transesterification compound as well.

Metal Coordination

The tricarbonyl rhenium(I) complex $[Et_4N]_2[Re(CO)_3Br_3]$ was prepared from $[Bu_4N][ReO_4]$. Because of the custom design of oligomer, metallation of ligand-oligomer was expected to be simple. **Z3** was synthesized form **Z2** and $[Et_4N]_2[Re(CO)_3Br_3]$ by stirring in MeOH at room temperature. The "naked" tridentate chelating system-functionalized LA oligomer **T2** did not form a complex with the corresponding rhenium compound as we had hoped. On the basis of the information from NMR (Figure 7 and Supporting Information), we speculate that the rigidity of the L-lactide backbone prevents coordination between nitrogen and tricarbonyl rhenium.

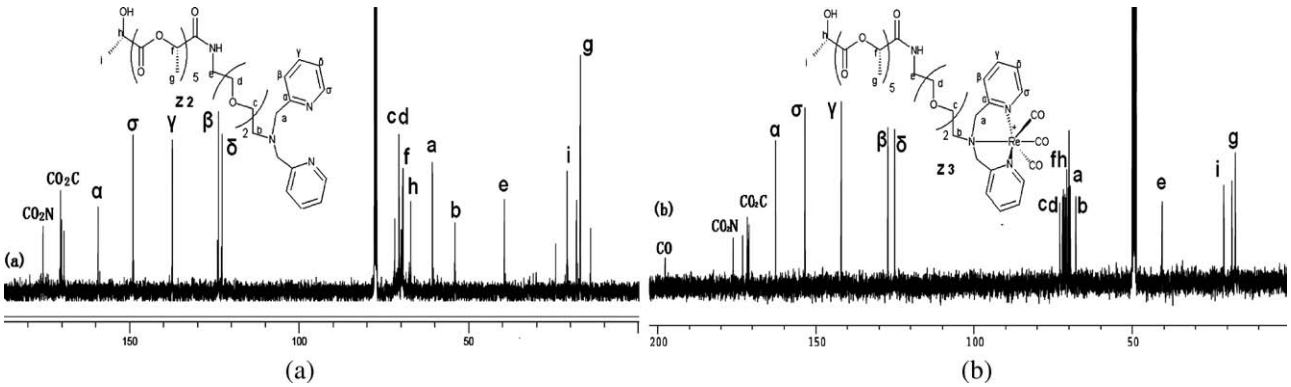


FIGURE 2 (a) ^{13}C NMR of **Z2** and (b) **Z3**.

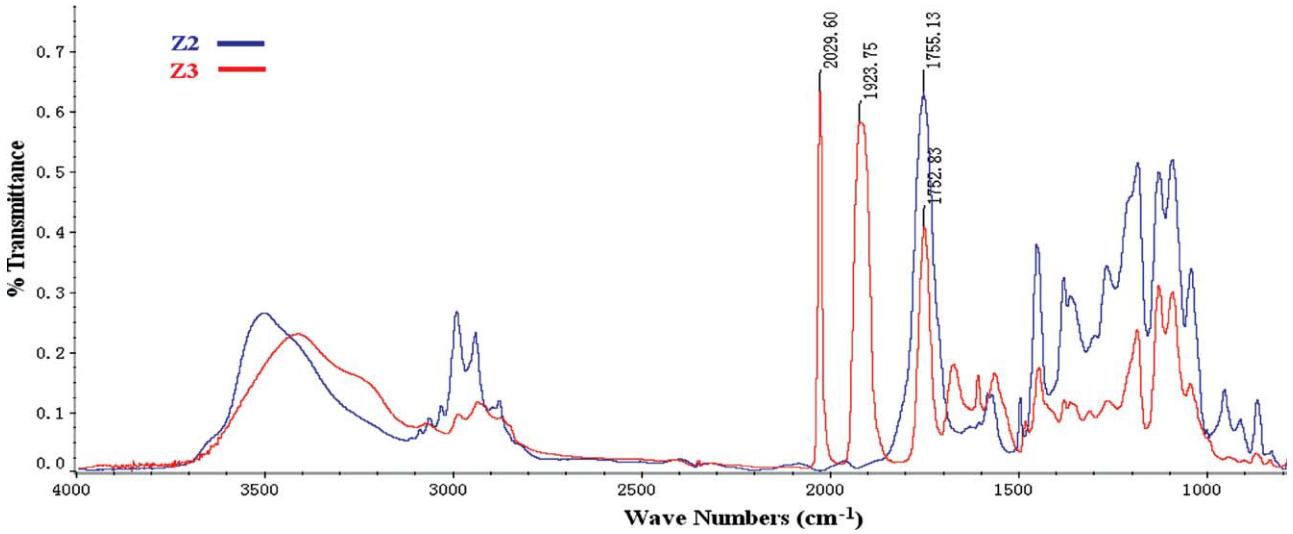


FIGURE 3 IR spectra of **Z2** and its corresponding $[Re(CO)_3]^+$ compound **Z3**.

CHARACTERIZATION

It was critical to fully characterize and determine the purity of these materials for further applications in both polymer chemistry and molecular imaging science. All lactide derivatives (without the reconjugates or change to all lactide oligomer ligands) are colorless viscous liquid and are soluble in halogenated solvents, methanol, or ethyl acetate. They were mostly purified by silica gel chromatography using hexane and ethyl acetate as an eluent. Elemental analysis showed agreements with expected values. Because of the used method for recrystallization, there was various amount of residual solvent (CH_2Cl_2) left on the surface of the crystal. Inductively coupled plasma-mass spectrometry (ICP-MS) was used as a quantitative analysis to prove the presence of rhenium in the reconjugates (**Z3**).

^{1}H NMR and ^{13}C NMR of all ligand oligomers shows PLA–PEG backbone with an excellent turnover of the starting monomer. ^{1}H NMR spectra of the hydroxyl-protected oligomers showed unique resonances for three single TBDMS terminal methyl group with chemical shifts at 0.90, 0.11, and 0.08 ppm. The small quartet at 4.38 ppm, due to the unique CH group next to the TBDMS chain end (or HO chain end), also functions as a quantitation reference peak to monitor the number of repeat units. Although the peaks in ^{13}C spectra were not integrated, their numbers do give a good indication of repeat unit numbers too (*vide infra*). Analytical data (IR, ^{1}H NMR, ^{13}C NMR, and ESI-HRMS) for **2b** and **7a** are given in the electronic Supporting Information.

Figure 1 shows the ^{1}H NMR spectra of **Z3** and the unbound oligomer ligand **Z2**. The assignments in Figure 1(b) were confirmed by 2D HSQC and HMBC (Supporting Information). The CH_2 signal on the PEG chain right next to the tertiary amine N (b) have different chemical shifts due to different chemical environments. Protons at position a moved

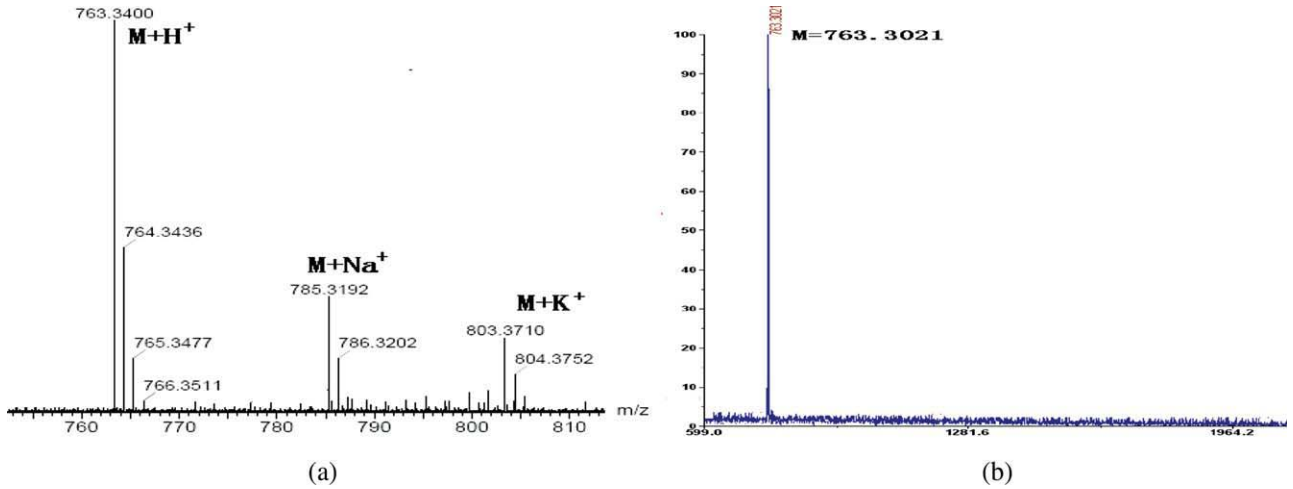


FIGURE 4 (a) ESI-HRMS and (b) MALDI mass spectra for **Z2**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

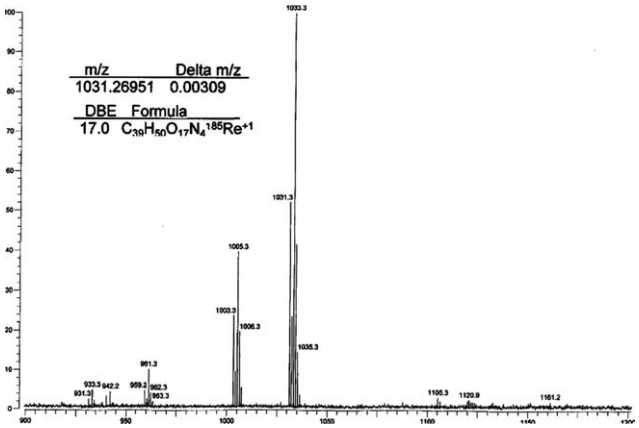


FIGURE 5 MALDI-HRMS analysis of **Z3**.

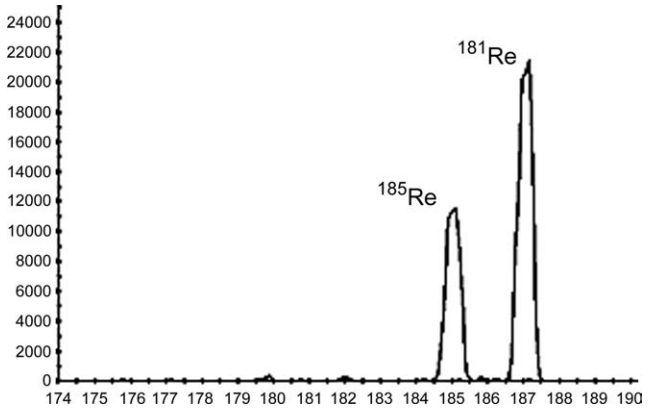


FIGURE 6 ICP-MS analysis of **Z3**.

downfield significantly due to metal binding. The oligomers backbone has produced an asymmetric effect on the compound.[20] The Py—CH_2— protons (a) of ligand **Z2** shows a single peak downshift from 3.91 to 4.96 ppm on coordination of the tertiary amine N to rhenium metal ion, and a downshift is also observed for the proton resonances in the bis(picolyl)amine group.

In Figure 2, signals for the ^{13}C NMR spectrum of rhenium complexes **Z3** show chemical shifts of carbonyl peaks among exhibiting in the range of 195.0–196.0 ppm. So many proton signals show a downfield shift compared with **Z2**. The ^{13}C chemical shifts for the PLA backbone and the ligand end cap are quite similar to those reported in the literature,[20] whereas many proton signals from the ligand show downfield shifts, presumably as a result of binding to the $[Re(CO)_3]^+$ core.

Infrared spectroscopy was also used to study these metal-coordinated oligomers. Figure 3 shows the IR spectra of **Z2** and **Z3**. **Z3** exhibits a sharp, strong band in the 1800–2200 cm^{-1} range and two broad, intense absorption at 1923 and 2029 cm^{-1}, which we attributed to ν(C—O) of the *fac*-$Re(CO)_3$ unit. The absorptions are significantly blue shifted compared with the starting material $[Re(CO)_3Br_3]^{2-}$ (1871, 1998 cm^{-1}).[21] All these features are indicative of N3 ligand-binding mode.

The molecular weights and associated purity for all of the lactide oligomers were investigated by ESI-TOF, ESI-HRMS, and MALDI-TOF mass spectrometry. For example, the ESI-TOF for HO-Hexamer-PEG-Tri (**Z2**) shows the molecular ion $M+H^+$ as well as Na^+ and K^+ adducts. HRMS analysis of $M+H^+$ and $M+Na^+$ ions was also found to be consistent with the anticipated molecular formulas [Fig. 4(a)]. MALDI-TOF mass spectrometry is also an excellent technique to determine the true MW of the lactide oligomer because it shows a fingerprint of oligomer chain and involves no referencing; the numbers are actual mass.[22] The high degree of purity for **Z2** is also reflected in the MALDI mass spectra.

MALDI-TOF mass spectra of all metal complexes show expected MWs (oligomer + $Re(CO)_3^+$). For an example, Figure 5 shows such as a mass spectrum for **Z3**. HRMS clearly shows the M^+ ion (m/z = 1033.3, 1031.3) and some dissociation of one carbonyl group (m/z = 1005.3, 1003.3) was found. The isotope pattern of rhenium complex is also a perfect match to the simulation signal (Fig. 6).

Following the same procedure, however, we did not see conclusive evidence for the formation **T2** complex with rhenium. Although $M+H^+$ and $M+Na^+$ were abundantly seen, we did not detect any ions for M+ $Re(CO)_3^+$. We speculate that steric hindrance may have prevented the metal binding. The steric

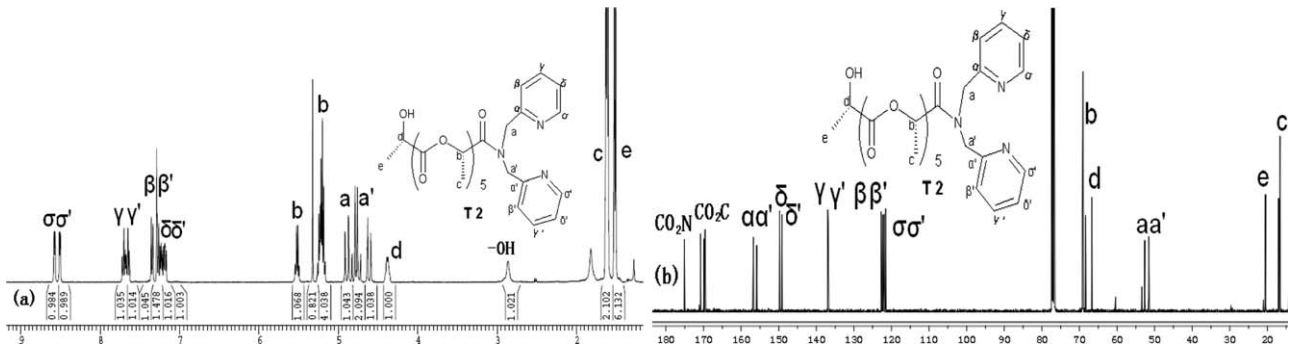


FIGURE 7 (a) ^1H NMR and (b) ^{13}C NMR of **T2**.

hindrance is supported by the ^{1}H and ^{13}C spectra of **T2**. In Figure 7, we generally see doubling peaks for most chemical equivalent germinal or ring protons. Specifically, the two methylene groups adjacent to pyridine rings show different chemical shifts. Moreover, two protons of the same methylene group have different chemical shifts. As a comparison, a singlet is observed for those protons at bis(picolylamine) chelator ligand system. Two pyridine rings have different proton chemical shifts too, and similar effects were observed in the ^{13}C NMR spectra. We believe the "doubling" of the otherwise equivalent protons is caused by the rigidity of the L-lactide backbone. As such, **T2** or its likes do not form complex with $[Re(CO)_3]^+$ core.

CONCLUSIONS

The successful synthesis of well-defined oligomers of (L)-LA and LA–PEG cooligomer is expected to provide new insights into the design of systems on drug payload and controlled release. A range of substrates were explored for DMAP-catalyzed transesterification. The coordination of *fac*-$[Re(CO)_3]^+$ by these oligomers opens up an avenue to creating reagents for applications in SPECT image or chemotherapy using these biocompatible oligomers. In fact, failure of **T2** complex implies that we have to consider steric effects in designing those biocompatible oligomers. Further research and related evaluation on oligomers labeled with radioactive nuclides such as ^{99m}Tc and $^{186/188}Re$ is in progress and will be reported in due course.

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