Ring Opening Polymerization of α-Amino Acid *N*-Carboxyanhydrides Catalyzed by Rare Earth Catalysts: Polymerization Characteristics and Mechanism

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ABSTRACT: Five rare earth complexes are first introduced to catalyze ring opening polymerizations (ROPs) of γ-benzyl-L-glutamate *N*-carboxyanhydride (BLG NCA) and L-alanine NCA (ALA NCA) including rare earth isopropoxide ($RE(OiPr)_3$), rare earth tris(2,6-di-*tert*-butyl-4-methylphenolate) ($RE(OAr)_3$), rare earth tris(borohydride) ($RE(BH_4)_3(THF)_3$), rare earth tris[bis(trimethylsilyl)amide] ($RE(NTMS)_3$), and rare earth trifluoromethanesulfonate. The first four catalysts exhibit high activities in ROPs producing polypeptides with quantitative yields (>90%) and moderate molecular weight (MW) distributions ranging from 1.2 to 1.6. In $RE(BH_4)_3(THF)_3$ and $RE(NTMS)_3$ catalytic systems, MWs of the produced polypeptides can be controlled by feeding ratios of monomer to catalyst, which is in contrast to the systems of $RE(OiPr)_3$ and $RE(OAr)_3$ with little controllability over the MWs. End groups of the polypeptides are analyzed by MALDI-TOF MS and polymerization mechanisms are proposed accordingly. With ligands of significant steric hindrance in $RE(OiPr)_3$ and $RE(OAr)_3$, deprotonation of 3-NH of NCA is the only initiation mode producing a *N*-rare earth metallated NCA (**i**) responsible for further chain growth, resulting in α-carboxylic-ω-aminotelechelic polypeptides after termination. In the case of $RE(BH_4)_3(THF)_3$ with small ligands, another initiation mode at 5-CO position of NCA takes place simultaneously, resulting in α-hydroxyl-ω-aminotelechelic polypeptides. In $RE(NTMS)_3$ system, the protonated ligand hexamethyldisilazane (HMDS) initiates the polymerization and produces α-amide-ω-aminotelechelic polypeptides. © 2011 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 50: 1076–1085, 2012

KEYWORDS: α-amino acid *N*-carboxyanhydride; biopolymers; end group functionalized polypeptides; rare earth catalysts; ring-opening polymerization

INTRODUCTION Peptide polymers have many advantages over conventional synthetic polymers, as they are able to self-assemble into stable ordered conformations (coils, α-helix, and β-sheet) and hierarchical structures (tertiary and quaternary structures), which arise from their stereoregularity and precisely arranged sequence of the amino acid. This ability is the foundation of the biological activity of proteins, which provide life-giving function.[1] Polypeptides are a class of attractive biomimetic materials. Recently, there has been interest in developing synthetic routes for preparation of the natural polymers for applications in biotechnology.[2] As a biomaterial with a lot of interesting properties resulting from well-defined conformational and hierarchical structures,[3–5] polypeptides are used in drug delivery,[6] tissue engineering,[7] biomineralization,[8] and nanoscale self-assembly.[9,10] Although these applications are in their infancy period, great potential is manifested.

The synthetic methodology of polypeptide has been explored over the past decades. Among the methods for polypeptide synthesis, ring opening polymerization (ROP) of amino acid *N*-carboxyanhydride (NCA) is the most used one.[11] Ever since the amino acid NCA monomer is discovered by Leuchs, great efforts have been made to explore the catalysts to polymerize them. Amines (primary amines, secondary amines, and tertiary amines), alcohols, water, and thiols[12] are a class of metal-free catalysts, among which primary amines and tertiary amines are the most widely used for their convenience and nontoxic nature. Generally, primary amines produce polypeptides with low molecular weights (MWs), which can be controlled by the monomer to catalyst ratio, whereas tertiary amines yield much higher ones but show little controllability over them. The molecular weight distributions (MWDs) of the two catalytic systems are usually broad.[13,14] Besides, a lot of metal salts and organometallic compounds are used to catalyze the ROP of NCA including solution of lithium chloride in *N*,*N*-dimethylformamide (DMF), sodium carbamate, 9-fluorenyl potassium, sodium hydride, sodium acetate, sodium methoxide, diethylzinc, tributylaluminum,

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diethylcadmium, tributyltinmethoxide, and so on.[15,16] The MWDs of the polypeptides obtained in these systems are usually broad arising from the multiple propagation active centers, heterogeneous character of reaction system and a variety of side reactions. After 1997, Deming and Lin reported living ROPs of NCAs by zero-valent nickel and platinum complexes. The MWDs of the polypeptides are quite narrow (MWD < 1.2) and block polypeptides can be conveniently synthesized by sequential addition of the two monomers.[17–19] In 2007, Cheng et al. reported hexamethyldisilazane (HMDS) a controlled polymerization catalyst for NCA. The MWs of the polypeptides obtained were the expected ones and the products exhibited low MWDs (MWD = 1.19–1.26).[20] HMDS and its derivatives are further successfully applied to prepare functionalized polypeptides with narrow MWDs (MWD < 1.3).[21,22] Besides, supramolecular polymerization is achieved by this catalyst.[23] Great efforts were also made to improve the traditional primary amine catalytic system and some approaches were elaborated including: high vacuum techniques,[24–26] lowering the reaction temperature[27–29] or the pressure,[30] and treating the primary amine with hydrochloride.[31] These methods had the unique advantage to allow preparation of copolymers composed of polypeptide and nonpolypeptide blocks with well-defined microstructures, as amino-terminated polymers are easily accessible.

Reaction mechanisms of ROP of NCA have received great attention in the past few years. Two mechanisms, that is, the normal amine mechanism (NAM) and the activated monomer mechanism (AMM), have been proposed to ROP of NCA. Depending on the relative nucleophilicity and basicity, the catalyst can selectively participate in one of the mechanisms in a polymerization. Generally, primary amine takes the NAM route, whereas tertiary amine leads to the AMM.[1,32] With the highlight of the chain end structures, many groups have carried out extensive mechanism studies. Kricheldorf et al.[33–38] revisited the polymerization mechanism of the polypeptides prepared by traditional catalysts by means of MALDI-TOF MS. A variety of the chain structures have been identified, complementing the polymerization mechanisms and dispelling any doubts with any of the NCA issues before. Messman and coworkers[39] rigorously characterized and compared the end-groups of the poly(*O*-benzyl-L-tyrosine) prepared under high-vacuum conditions and glovebox by means of MALDI-TOF MS, NALDI-TOF MS, and ^{13}C NMR spectroscopy, demonstrating the advantage of high-vacuum techniques for preparation of well-defined polypeptides. Using nonaqueous capillary electrophoresis, Giani and coworkers concluded that in primary amine catalytic system, the NAM is the only possible initiation pathway and "dead" polymers resulted from side reactions of the propagating chain ends with DMF or the NCA. The fractions of the living chains can be greatly enhanced by decreasing the reaction temperature to 0 °C.[27,28,40,41]

In the past few years, rare earth compounds have been successfully applied to the catalysis of the polymerization of various monomers including ethyne, isoprene, propylene oxide, ε-caprolactone, lactide, cyclic carbonates, and so on.[42] In ROP of NCA, investigations on organometallic catalysts have been mainly focused on alkali metals, alkaline-earth metals, and late-transition metals with rare earth metals being largely overlooked. To the best of our knowledge, only one paper reported the polymerization of γ-stearyl-L-glutame NCA using tri-component catalyst of neodymium acetylacetonate [$Nd(acac)_3$]- or neodymium tris(2-ethylhexylphosphanate) [$Nd(P_{204})_3$]- with triethylaluminum and water. Relatively high MW ($M_w = 8.4 \times 10^4$ Da) polyglutamates with narrow MWD of 1.22 are produced.[43] The promising result encouraged us to further explore the polymerization behavior in rare earth catalytic systems.

This work investigates ROPs of γ-benzyl-L-glutamate NCA (BLG NCA) and L-alanine NCA (ALA NCA) catalyzed by five rare earth catalysts, that is, rare earth isopropoxide ($RE(OiPr)_3$), rare earth tris(2,6-di-*tert*-butyl-4-methylphenolate) ($RE(OAr)_3$), rare earth tris(borohydride) ($RE(BH_4)_3(THF)_3$), rare earth trifluoromethanesulfonate ($RE(OTf)_3$), and rare earth tris[bis(trimethylsilyl) amide] ($RE(NTMS)_3$). They are all high efficient catalysts for polymerizations of ester monomers such as ε-caprolactone, lactide, and trimethylene carbonate.[44–50] Their ligands are different in sizes and bond types including rare earth–oxygen bond (RE—O), rare earth–borohydride hydrogen bond ($RE—HBH_3$), and rare earth–nitrogen bond (RE—N). Their reaction activities toward ROP of NCA are investigated and discussed in comparison.

EXPERIMENTAL

Materials

BLG (99.0%, Shanghai Hanhong Chemical, China), L-alanine (98.5%, Sinopharm Chemical Reagent, China), sodium bis(trimethylsilyl)amide (95%, Sigma-Aldrich), sodium borohydride (96.0%, Sinopharm Chemical Reagent, China), and trifluoromethanesulfonic acid (98%, Shanghai Jingchun, China) were used as received. 2-Propanol was dried by sodium metal and distilled. Tetrahydrofuran (THF), hexane, and benzene were refluxed over potassium/benzophenone ketyl before use. Ethyl acetate was stirred over CaH_2 and distilled. DMF was purified by drying over a mixture of 3 Å and 4 Å molecular sieves followed by vacuum distillation.

Catalysts Preparation

All catalysts were prepared in Schlenk tubes using vacuum-line techniques under purified argon. Anhydrous rare earth chlorides were prepared by heating the mixture of hydrated rare earth chloride and ammonium chloride under reduced pressure.[51]

$RE(OiPr)_3$, $RE(OAr)_3$, $RE(BH_4)_3(THF)_3$, and $RE(OTf)_3$ were prepared according to our previous reports.[44,45,52,53] $RE(NTMS)_3$ was synthesized according to a reported literature.[54] In a typical example, YCl_3 (0.651 g, 3.33 mmol) was suspended in 25 mL of THF. Then, a THF solution (10 mL) of sodium bis(trimethylsilyl)amide (1.932 g, 10.0 mmol) was added dropwise over a period of an hour. This reaction was stirred at room temperature for 24 h and centrifuged separated. The liquid part was evaporated and then extracted

with 30 mL of hexane. The hexane solution was concentrated and allowed to crystallize. $Y(NTMS)_3$ was obtained as white needle-like crystals form with a yield of 62%.

Synthesis of γ-Benzyl-L-glutamate *N*-Carboxyanhydride and L-Alanine *N*-carboxyanhydride

In a typical procedure, BLG (10.1 g, 42.2 mmol) was suspended in 100 mL of anhydrous THF under argon atmosphere. Triphosgene (4.60 g, 15.5 mmol) in 20 mL of THF was added dropwise over half an hour. The mixture was allowed to stir for further 2 h and a clear solution was obtained. The solution was concentrated and precipitated by anhydrous hexane. After purification by recrystallization four times from ethyl acetate and hexane, white BLG NCA crystals (10.37 g, yield = 83%) were obtained. ALA NCA (yield = 53%) was synthesized in a similar way.

Polymerizations of BLG NCA and ALA NCA

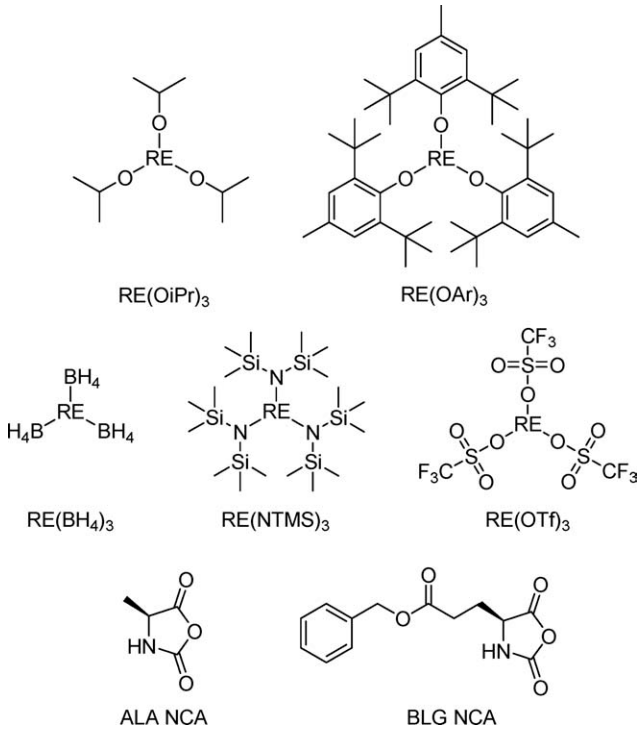
All polymerizations were performed in Schlenk tubes under argon. In a typical example, BLG NCA (0.396 g, 1.51 mmol) was dissolved in 3 mL of DMF. Then THF (0.32 mL) solution of $Y(OiPr)_3$ (0.093 mol/L) was added by syringe. The tube was sealed and placed in a 40 °C oil bath for 24 h. The polymer was isolated by precipitation from methanol containing 5% HCl, washed with methanol, and dried in vacuum (yield > 95%). Polymerizations of ALA NCA were carried out in THF for 3 days and precipitated from diethyl ether (yield > 95%).

Measurements

MWs and MWDs were determined by gel permeation chromatography/multiangle laser light scattering (GPC/MALLS). The GPC system consisted of a Waters 1515 isocratic high performance liquid chromatograph pump, two columns of Styragel (HT3 and HT4), a Wyatt DAWN DSP MALLS detector, and a Wyatt Opitlab DSP interferometric refractometer. DMF containing 0.1 mol/L LiBr was used as the eluent with a flow rate of 1.0 mL/min at 60 °C. Viscosity average molecular weights ($M_{v,LS}$s) were obtained from reduced specific viscosity using the relationship formulated by Doty et al.[55] This method was reported to be reproducible and had an error within ±10%. The viscosities were determined at the concentration of 0.2 g/100 mL in dichloroacetic acid in Ubbelohde viscometers at 25 °C. The MALDI-TOF mass spectra were measured on an Applied Biosystems Voyager System 4350 with a nitrogen laser (l = 337 nm). All mass spectra were recorded in the reflection mode with an acceleration voltage of 20 kV. The irradiation targets were prepared from trifluoroacetic acid solutions with 2,5-dihydroxybenzoic acid as matrix and potassium trifluoroacetate as dopant.

RESULTS AND DISCUSSION

$RE(OiPr)_3$, $RE(OAr)_3$, $RE(BH_4)_3(THF)_3$, $RE(NTMS)_3$, and $RE(OTf)_3$ are five typical complexes reported to catalyze ROP of lactone monomers with different activities due to their electronic and steric effects of the ligands.[44–50] Their chemical structures are shown in Scheme 1. $RE(OiPr)_3$ and $RE(OAr)_3$ have bulky isopropoxy and phenoxy ligands and



SCHEME 1 Chemical structures of $RE(OiPr)_3$, $RE(OAr)_3$, $RE(BH_4)_3(THF)_3$, $RE(NTMS)_3$, $RE(OTf)_3$, ALA NCA, and BLG NCA.

rare earth–oxygen bonds (RE—O). Rare earth metals have a high affinity to the oxygen atom and tend to be coordinated by carbonyl group.[56,57] $RE(BH_4)_3(THF)_3$ is a compound with rare earth–borohydride hydrogen bonds ($RE—HBH_3$) characterized as $RE[(\mu_2\text{-}H)_3BH]_2[(\mu_2\text{-}H)_2BH_2)]$ by X-ray diffraction.[48] In contrary to the above two catalysts, this catalyst has a relatively small ligand with reduction ability. $RE(NTMS)_3$ is of special interest, as the trimethylsilyl group of the ligand can mediate the ROP of NCA.[20] Besides, $RE(NTMS)_3$ has a more basic rare earth–nitrogen bond (RE—N) than the RE—O catalysts and a hexamethyldisilazanyl ligand with considerable steric hindrance. $RE(OTf)_3$ is a Lewis acid.[58,59] Polymerization of lactones by $RE(OTf)_3$ exclusively proceeds through a cationic mechanism, differing from the coordination–insertion mechanism of the other four.[56,57]

The five catalysts are used to catalyze ROP of BLG NCA (Table 1). Except $RE(OTf)_3$, the other four catalysts are highly efficient toward the polymerization of BLG NCA producing polyBLGs (PBLGs) with high yields. The monomers are completely consumed within 24 h as shown by FTIR and ^1H NMR. At the same molar ratio of monomer to catalyst ([NCA]/[RE]), the obtained PBLGs have widely different MWs depending on the catalyst (Table 1). $Y(OiPr)_3$ and $Y(OAr)_3$ produce polypeptides with the highest weight average MWs of about 1×10^5 Da, whereas $Y(BH_4)_3(THF)_3$ yields the middle one ($\sim 7.5 \times 10^4$ Da). $Y(NTMS)_3$ gives the lowest M_w of 2.9×10^4 Da. All GPC traces of PBLGs obtained exhibit symmetrical and monomodal peaks (Fig. 1) with relatively

TABLE 1 Polymerization of BLG NCA catalyzed by single-component rare earth catalysts[a]

Run	Catalyst	Temp. (°C)	Yield (%)	$M^{b}_{v,LS}$ (10^4 Da)	$M_n{}^{c}$ (10^4 Da)	$M_w{}^{c}$ (10^4 Da)	MWD[c]
1	$Y(OiPr)_3$	40	98.5	9.02	6.86	10.36	1.5_1
2	$Y(OAr)_3$	40	93.2	9.11	6.85	10.53	1.5_4
3	$Y(BH_4)_3$	40	90.9	6.66	5.25	7.51	1.4_3
4	$Y(NTMS)_3$	40	94.3	2.97	2.29	2.86	1.2_5
5	$Y(OTf)_3$[d]	80	0	–	–	–	–
6	$Sc(OTf)_3$[d]	80	37.5	2.19	–	–	–

[a] Polymerization conditions: [BLG NCA]/[Y] = 200, [BLG NCA] = 0.5 mol/L, 24 h in DMF.
[b] Viscosity average molecular weights ($M_{v,LS}$).
[c] Determined by GPC/MALLS.
[d] Reaction time was prolonged to 3 days.

narrow MWDs (MWD < 1.6) compared to the one catalyzed by phenethylamine (MWD > 2.8).[13] $Y(NTMS)_3$ produces PBLG with the narrowest MWD of 1.25. $Sc(OTf)_3$ has low activity to ROP of BLG NCA, whereas $Y(OTf)_3$, $Nd(OTf)_3$, and $La(OTf)_3$ are not active at all. This result by $RE(OTf)_3$ is within our expectation, as the fact that neither radicals nor cations and acids can initiate ROP of NCA.[15]

Figure 2 shows the dependence of MWs of PBLGs on the [NCA]/[Y] ratio. $Y(OiPr)_3$ and $Y(OAr)_3$ produce PBLGs with the highest $M_{v,LS}$. In the $Y(OiPr)_3$ system, the MWs are totally independent on the [NCA]/[Y] ratios and the $M_{v,LS}$s are almost unchanged at the value of 9×10^4 Da. In $Y(OAr)_3$ system, the MWs are changed slightly within the range of 8×10^4–10×10^4 Da with the feeding ratios of [NCA]/[Y] varying from 50 to 1000. The polymerization features of these two catalytic systems are similar to that of the strong base catalyst such as triethylamine,[60] which catalyzes ROP of NCA via the AMM mechanism. $Y(BH_4)_3(THF)_3$ is different from $Y(OiPr)_3$ and $Y(OAr)_3$. The MWs of PBLGs can be controlled by the [NCA]/[Y] ratios. However, they are higher than the calculated ones. $Y(NTMS)_3$ produces PBLG with the lowest MW when the same [NCA]/[Y] is used and exhibits a linear relationship between $M_{v,LS}$s and [NCA]/[Y]. Also, the effect of rare earth elements is studied as shown in Figure 3. With the same ligand, rare earth metals including scandium, yttrium, lanthanum, and dysprosium exhibit similar catalytic behaviors. In $RE(BH_4)_3(THF)_3$ and $RE(NTMS)_3$ systems, yttrium complexes always produce PBLG with the highest MW than the other three corresponding Sc, La, and Dy complexes.

Figure 4 compares ROPs of BLG NCA at various reaction temperatures. In $Y(OiPr)_3$, $Y(OAr)_3$, and $Y(BH_4)_3(THF)_3$ catalytic systems, temperature is a key factor in the MW control of PBLGs. MWs increase dramatically when the reaction temperature arises from 0 to 40 °C. In the ROPs catalyzed by $Y(NTMS)_3$, however, the MWs of PBLG are almost independent with the reaction temperature in the range of 0–60 °C.

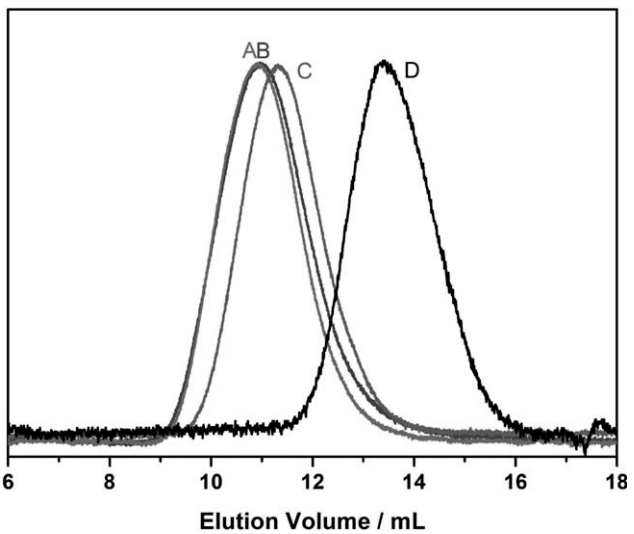


FIGURE 1 GPC/MALLS traces of PBLGs prepared by $Y(OAr)_3$ (A in red, run 2 in Table 1), $Y(OiPr)_3$ (B in blue, run 1 in Table 1), $Y(BH_4)_3(THF)_3$ (C in green, run 3 in Table 1), and $Y(NTMS)_3$ (D in black, run 4 in Table 1).

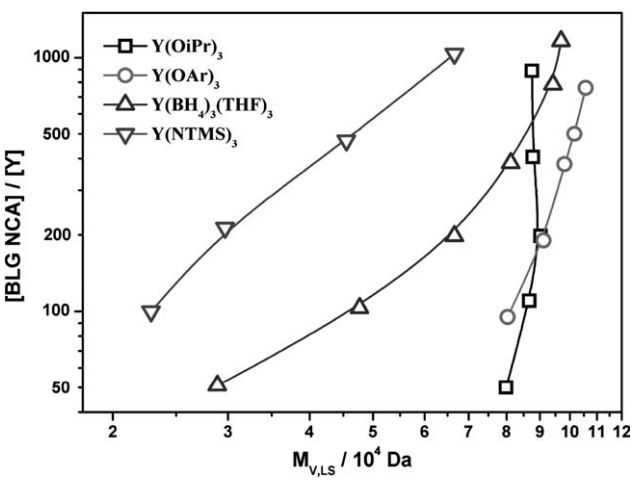


FIGURE 2 Plots of the viscosity average molecular weights ($M_{v,LS}$s) versus feeding ratios of [BLG NCA]/[Y] in the polymerizations of BLG NCA catalyzed by $Y(OiPr)_3$, $Y(OAr)_3$, $Y(BH_4)_3(THF)_3$, and $Y(NTMS)_3$.

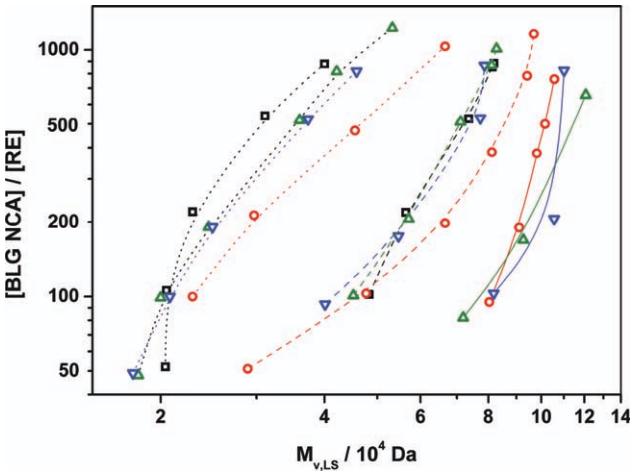


FIGURE 3 The viscosity average molecular weights ($M_{v,LS}$s) of PBLGs catalyzed by $RE(OAr)_3$ (solid lines), $RE(BH_4)_3(THF)_3$ (dash lines), and $RE(NTMS)_3$ (dotted lines), in which RE are Sc (□), Y (○), La (□), and Dy (▽).

This may be related to the coordination of the catalyst. The rare earth–nitrogen bond is much more reactive than RE—O and RE—HBH_3 bonds, and the energy barrier is relatively low, resulting in a fast initiation process and high initiation efficiency at low temperature.

Investigation on end groups of polypeptide is very powerful to reveal polymerization mechanisms of NAM or AMM. Hexylamine, a typical primary amine, is a well-known initiator for NCA polymerization by NAM mechanism producing polypeptide chain containing hexyl group of the initiator residue at one end and amino group at the other. *N*-Ethyldiisopropylamine, a tertiary amine, initiates AMM polymerization generating polypeptides with amino and carboxyl groups at each end.[34,37] In this work, MALDI-TOF MS is applied to analyze the end groups of the polypeptides prepared by the four rare earth catalysts. ALA NCA is chosen for the study instead of BLG NCA in this section because the side reaction between the amino end-group and the ester group of the last amino acid segment in BLG NCA polymerization[61] would complicate the MALDI-TOF MS results.

The MALDI-TOF mass spectrum of polyALA (PALA) prepared by $Y(OiPr)_3$ is shown in Figure 5. The major peaks of **a** and **g** correspond to a PALA chain with an amino end (NH_2) and a carboxylic end (COOH) (compound **I** in Scheme 2). $Y(OAr)_3$ catalyzed PALA shows the same patterns (Supporting Information, Fig. S1). A typical polymerization mechanism with features similar to the tertiary amine polymerization, AMM mechanism is shown in Scheme 2. A deprotonation step at 3-NH happens resulting in a *N*-rare earth metallated NCA (**i**) and a molecule of alcohol or phenol. Complex **i** attacks at the 5-CO of another ALA NCA molecule leading to a dimer (**ii**) with a highly electrophilic *N*-acyl NCA end-group and a nucleophilic carbamate end group. Further chain growth can proceed through the carbamate end by attacking at the 5-CO of another NCA or **i**, or through the electrophilic *N*-acyl NCA end attacked by **i** or the carbamate end of another **ii**. After polymerization, the carboxylic end group is generated during the precipitation into moist diethyl ester with the process of an attack at 5-CO of *N*-acyl NCA end group by water and release of a molecule of CO_2.[37] The amino end arises from hydrolysis of the active rare earth carbamate group followed by releasing CO_2. Another two structures are identified also in both MALDI-TOF spectra of PALAs catalyzed by $Y(OiPr)_3$ and $Y(OAr)_3$ catalysts. One contains an amino and a hydantoinic ends (**II** in Scheme 2) and the other contains a carboxylic and a hydantoic acid ends (**III**

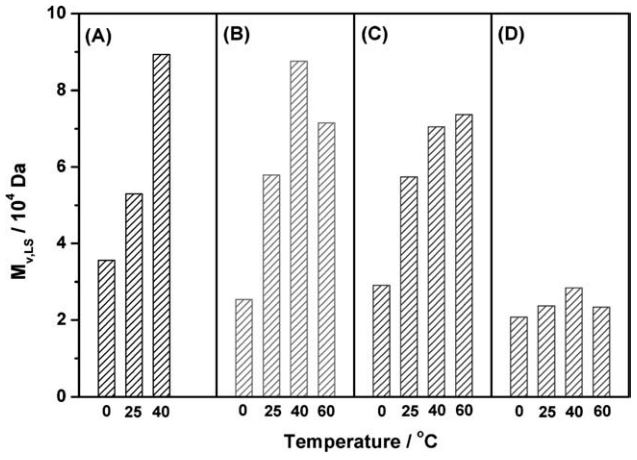


FIGURE 4 The effect of temperature to the viscosity average molecular weights ($M_{v,LS}$s) of PBLGs prepared by various rare earth catalysts: $Y(OiPr)_3$ (A), $Y(OAr)_3$ (B), $Y(BH_4)_3(THF)_3$ (C), and $Y(NTMS)_3$ (D). Polymerization conditions: [BLG NCA]/[Y] = 250, [BLG NCA] = 0.5 mol/L in DMF, 1 day.

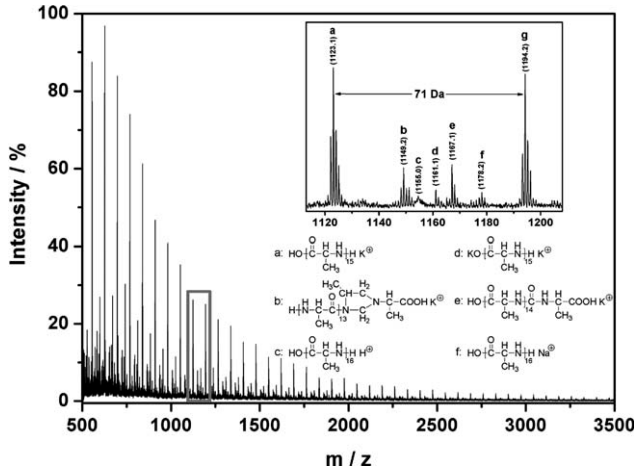
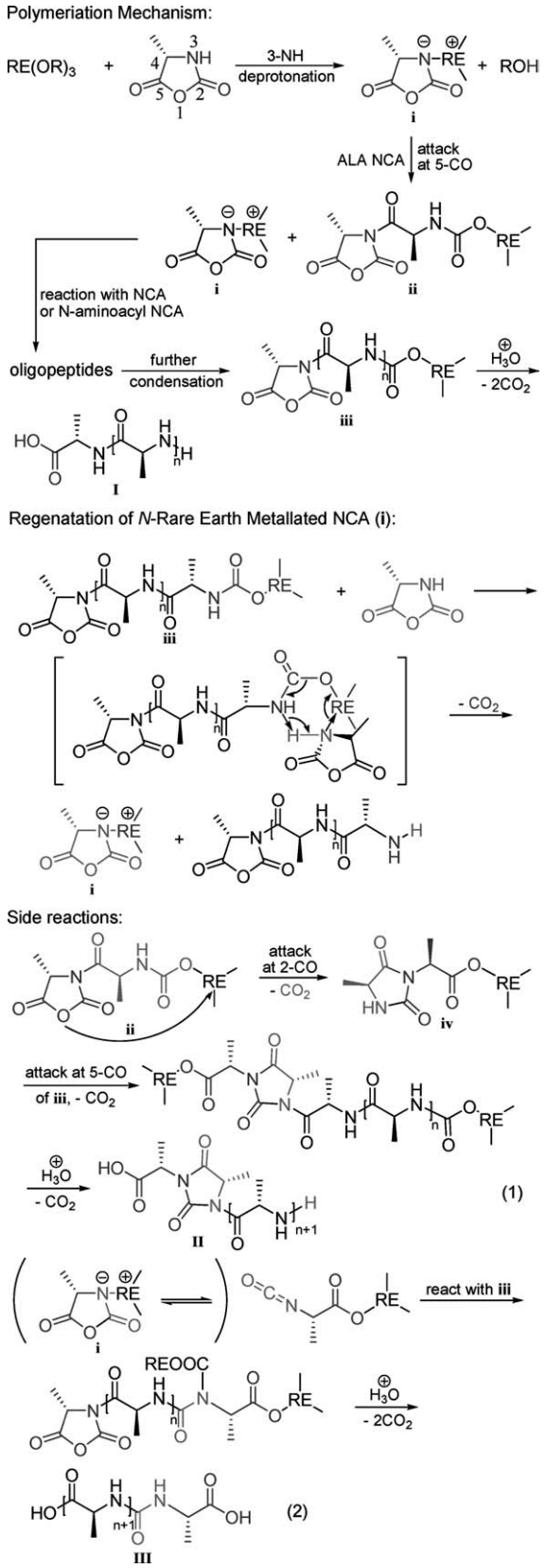


FIGURE 5 MALDI-TOF mass spectrum of PALA catalyzed by $Y(OiPr)_3$. Polymerization conditions: [ALA NCA]/[Y] = 100, [ALA NCA] = 0.87 mol/L, 25 °C in THF, 3 days.



SCHEME 2 Polymerization mechanism and side reactions of ROP of ALA NCA catalyzed by rare earth alkoxide and aryloxide ($RE(OR)_3$, R = iPr or Ar).

in Scheme 2). Product **II** is first proposed by Bamford and Block[62,63] and Hashimoto and Imanishi[64] years ago and only experimentally demonstrated by Kricheldorf et al.[37] recently. Its formation is closely related to **i**. After the dimer **ii** formed, cyclization occurs in competition with propagation. This cyclized product 3-(rare earth carboxylate) hydantoin (**iv**) attacks the 5-CO of N-acyl NCA end group of a polymer chain (**iii**) forming the product **II**. Product **III** is formed by the addition of a propagating nucleophilic carbamate end to the rare earth α-isocyanato carboxylate, which arises from the rearrangement of **i**, a well-documented process in the literature.[15] No cyclic PALA is found in our system in contrast to the tertiary amine catalytic system.

The MALDI-TOF mass spectrum of $Y(BH_4)_3(THF)_3$ catalyzed PALA is shown in Figure 6. Besides, α-carboxylic-ω-aminotelechelic PALA (**I**) [Figs. 6(b,f)] which is formed by the reaction pathway 2 (RP-2) in Scheme 3 similar to that of $RE(OiPr)_3$ and $RE(OAr)_3$, another major product is identified as α-hydroxyl-ω-aminotelechelic PALA (**IV**). It is well known that the borohydride ligand is reductive in ROP of ε-caprolactone.[48,65] Its reductive ability is also manifested in this polymerization producing a polypeptide chain containing a hydroxyl end group as shown in the reaction pathway 1 (RP-1) in Scheme 3. Attacked at 5-CO by $RE(BH_4)_3(THF)_3$, the NCA ring opens and inserts into the RE—HBH_3 bond resulting an intermediate [—RE{$OC(O)NHCH(CH_3)C(O)HBH_3$}] (**v**), in which the HBH_3 group immediately interacts with the α-carbonyl group to form the corresponding rare earth alanine carbamate derivative [—RE{$OC(O)NHCH(CH_3)CH_2(OBH_2)$}] (**vi**). Polymerization of ALA NCA by **vi** then proceeds through the rare earth carbamate attacking at the 5-CO of the monomer resulting in the (1-oxygen)−(5-acyl) bond cleavage followed by release of a molecule of CO_2. After termination, α-hydroxyl-ω-aminotelechelic PALA chains are formed. The hydroxyl end group results from the hydrolysis of the [—$NHCH(CH_3)CH_2(OBH_2)$] chain end in water termination.

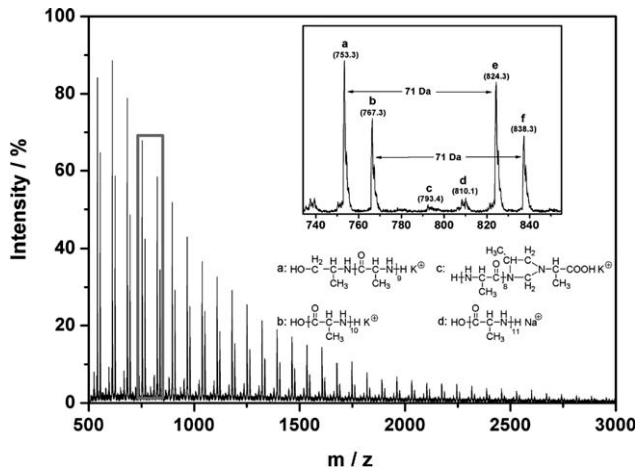
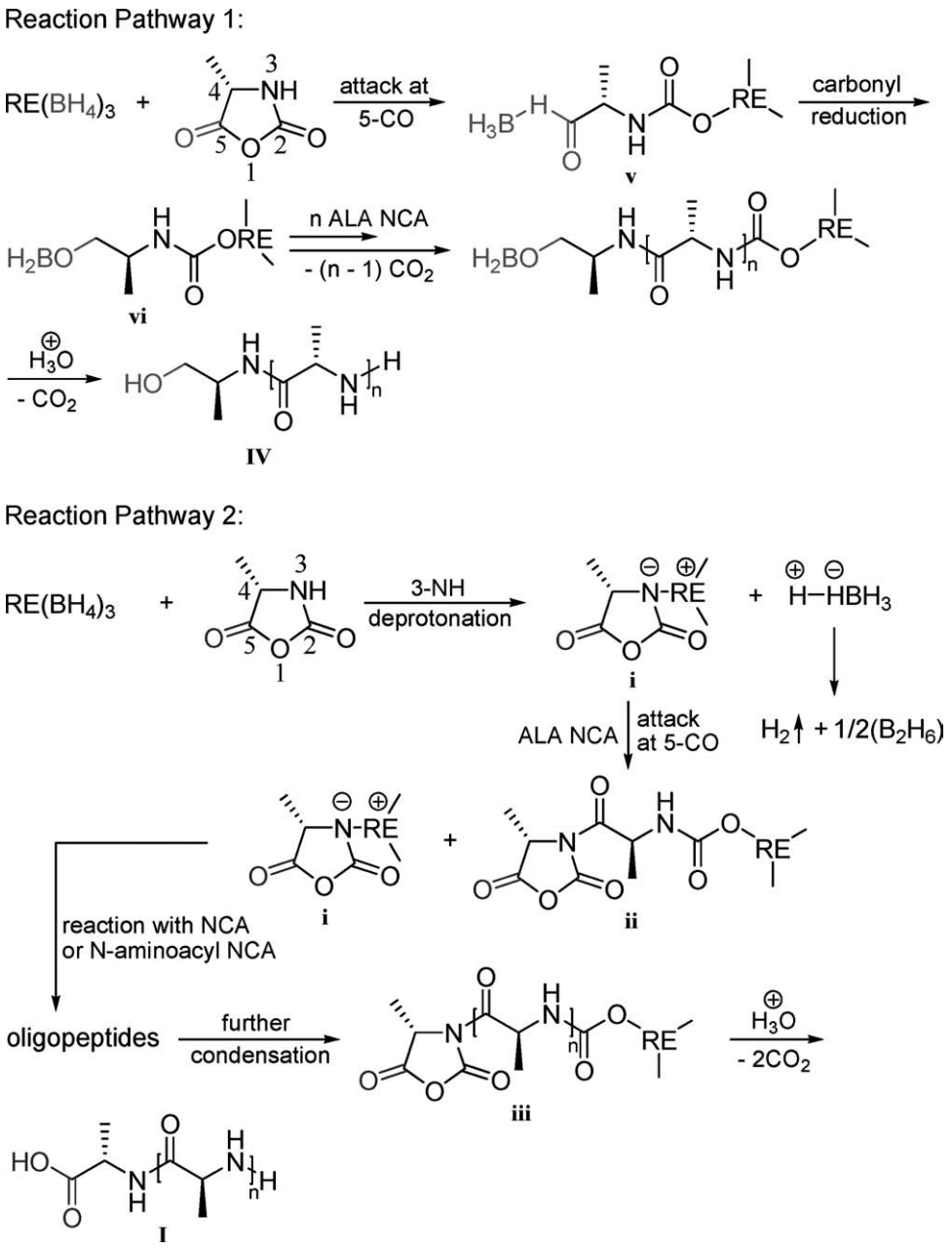


FIGURE 6 MALDI-TOF mass spectrum of PALA catalyzed by $Y(BH_4)_3(THF)_3$. Polymerization conditions: [ALA NCA]/[Y] = 100, [ALA NCA] = 0.87 mol/L, 25 °C in THF, 3 days.



SCHEME 3 Mechanism of ROP of ALA NCA catalyzed by $RE(BH_4)_3(THF)_3$.

Hydrolysis of the active rare earth carbamate group and release of CO_2 generate an amino group at the other chain end. This mechanism is similar to NAM. It needs to mention that RP-1 and RP-2 can switch back and forth, resulting in monomodal GPC traces and partial control of the MWs.

Figure 7 shows the MALDI-TOF mass spectrum of PALA prepared by $Y(NTMS)_3$. The major peaks are identified as the product **V** containing an amide end group and an amino end group. Its formation is illustrated in Scheme 4. As a strong base, deprotonation of 3-NH of ALA NCA takes place first resulting in HMDS (**vii**) and **i**. The *in situ* generated **vii** is responsible for further chain growth. Reaction of **vii** with an ALA NCA which involves the Si—N bond cleavage and the trimethylsilyl (TMS) group transfer generates **viii**, which contains an active trimethylsilyl carbamate (TMS-CBM) propagating chain end. The following propagation of polypeptide proceeds through the transfer of TMS group from the terminal TMS-CBM to the incoming NCA monomer until the monomer is completely consumed or the reaction is quenched. Amide and amino groups are formed by hydrolysis of the TMS groups. This process is studied in detail by Lu and Cheng.[20,21] Product **II** is also found in $Y(NTMS)_3$ catalyzed

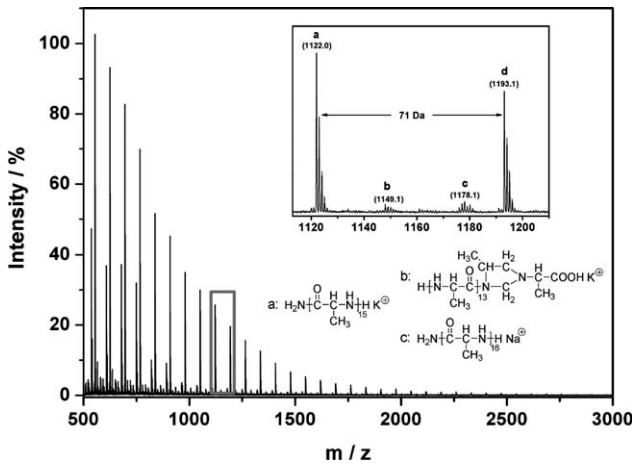


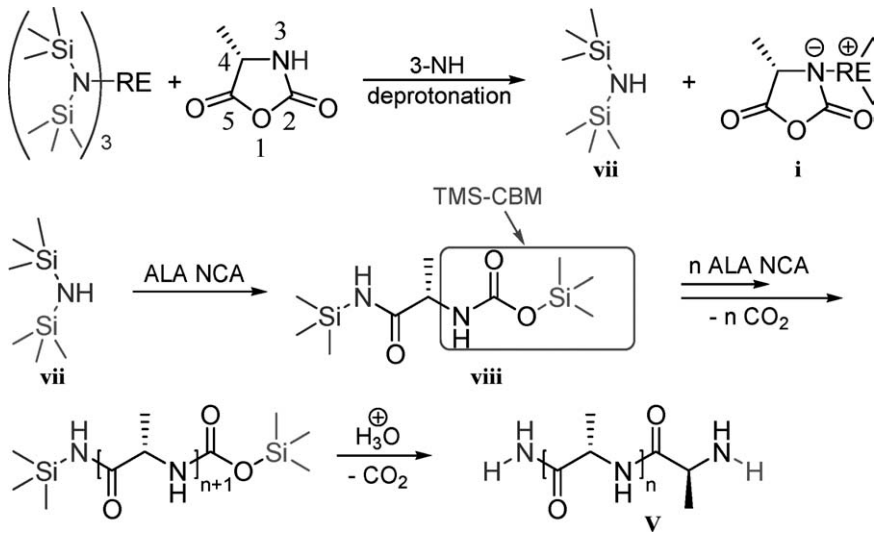
FIGURE 7 MALDI-TOF mass spectrum of PALA catalyzed by $Y(NTMS)_3$. Polymerization conditions: [ALA NCA]/[Y] = 100, [ALA NCA] = 0.87 mol/L, 25 °C in THF, 3 days.

polymerization indicating **i** is formed. Its formation process is the same with that of $Y(OiPr)_3$ and $Y(OAr)_3$ catalytic systems (side reaction (2) in Scheme 2). $Y(NTMS)_3$ system exhibits good MW controllability and narrow MWD of polypeptide as shown in Table 1 and Figure 1. Block polypeptides can be also synthesized by sequential addition of NCA monomers (data not shown).

In NCA ROPs by the four rare earth catalysts, mechanism similar to AMM always exists. It arises from the strong basicity of the rare earth–ligand bonds, and thus, deprotonation of 3-NH of NCA is inevitable. Depending on the steric hindrance of the ligand, mechanism similar to NAM is selectively chosen. In the case of the bulky ligand, isopropyl (OiPr) and 2,6-di-*tert*-butyl-4-methylphenyl (OAr) ligands, for example, the polymerization proceeds exclusively through mechanism similar to AMM. For a small ligand of HBH_3 in $RE(BH_4)_3(THF)_3$, its nucleophilicity is manifested and a polymerization mechanism similar to NAM takes place in parallel resulting polypeptides containing hydroxyl end groups. Bis (trimethylsilyl)amido (NTMS) ligand represents a special case. The *in situ* generated HDMS (**vii**) rather than *N*-rare earth metallated NCA (**i**) initiates most of the monomers producing a polypeptide chain containing amide end group.

CONCLUSIONS

Five rare earth complexes, that is, $RE(OiPr)_3$, $RE(OAr)_3$, $RE(BH_4)_3(THF)_3$, $RE(NTMS)_3$, and $RE(OTf)_3$, are used as single component catalyst for the ROP of NCAs. The first four show high catalytic activities toward the polymerizations and the produced polypeptides are in high yields (>90%) with relatively narrow MWDs ranging from 1.2 to 1.6. In each catalytic system, rare earth elements do not exhibit great difference. Polymerization features and chain structures of these catalytic systems are studied in comparison. In $RE(OiPr)_3$ and $RE(OAr)_3$ catalytic systems, the MWs obtained are almost independent with the molar ratios of monomer to catalyst and high MW polypeptides of about 1×10^5 Da are produced. MALDI-TOF MS result indicates a α-carboxylic-ω-aminotelechelic polypeptide chain (**I**) is formed in these systems and a polycondensation mechanism (Scheme 2) is proposed accordingly. In $RE(BH_4)_3(THF)_3$ system, the MWs obtained can be controlled from 2.5×10^4 to 1×10^5 Da by the feeding ratios. By means of MALDI-TOF MS, a α-hydroxyl-ω-aminotelechelic polypeptide chain (**IV**) is found as the major product along with **I**. A nucleophilic ring opening initiation and chain growth process (RP-1 in Scheme 3) is proposed to explain its formation. In $RE(NTMS)_3$ catalytic



SCHEME 4 Mechanism for ROP of ALA NCA catalyzed by $RE(NTMS)_3$.

system, linear relationship is shown between the MWs and the molar ratios of monomer to catalyst (Figs. 2 and 3). End group analysis indicates a α-amide-ω-aminotelechelic polypeptide chain (**V**) is formed. This structure is attributed to the HMDS (**vii**) initiated polymerization as illustrated in Scheme 4. Besides, hydantoin-terminated polypeptide chain (**II**) is detected as the byproduct in all the catalytic systems.

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