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Synthesis, Characterization, and Hydrolytic Degradation of Polylactide-Functionalized Polyoxanorbornenes

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ABSTRACT: This paper describes the synthesis of polylactide-functionalized polyoxanorbornenes and their hydrolytic degradation behavior. Macromonomers with one or two *exo*-PLA chains as well with two *endo,exo* chains were prepared using tin(II) 2-ethylhexanoate as a catalyst in the presence of mono- or dialcohol derivatives of oxanorbornene. The well-characterized macromonomers were then subjected to ROMP by first, second, and modified second generation Grubbs ruthenium initiators. Investigation of these graft copolymers by SEC and NMR spectroscopy showed the presence of some uncapped PLA homopolymer, formed as a side product during the ROP of lactide. The degradation behavior showed that the presence of PLA homopolymer impurities in the graft copolymers significantly increases the rate of degradation of the final material. Therefore, a convenient procedure of graft copolymers purification to remove PLA homopolymer from the samples was developed. The degradation studies of graft copolymers with the same oxanorbornyl backbone length and different length of PLA grafts indicated that the degradation rate increased with increasing length of PLA grafts. The degradation behavior of material depends also on configuration of PLA side chains on polyoxanorbornene backbone chain. The fastest degradation was observed in the case of graft copolymers with one *exo*-PLA side chain.

Introduction

Biodegradable polymers and copolymers prepared from cyclic esters, such as glycolide (GL), lactide (LA), or ϵ-caprolactone (CL), have been widely used as sutures, drug delivery carriers, and implants to ensure a temporary mechanical or therapeutic function as well as cell scaffolds in tissue engineering.[1−4] These polymers decompose via hydrolysis of the ester bonds in an aqueous environment and give readily absorbable degradation products.[4] All the practical uses of these materials involve their biodegradable character, and thus their decomposition profile has to be practically matched to the requirements of the application. The degradation rate of the polymeric material depends on many factors, including the polymer composition, molecular weight distribution, the presence of catalysts, and the geometry of the device.[2,5−7] As a consequence, there is increasing interest in methods that allow for the preparation of polymers which degrade in a controlled fashion. In this respect the preparation of tailored macromolecular architectures remains an important challenge in biodegradable materials. Various materials based on polyhydroxy acids with a broad range of properties have been obtained by copolymerization of different comonomers,[8,9] ring-opening polymerization (ROP) with multifunctional initiators,[10] and also a combination of different polymerization techniques.[11−15]

In this paper the synthesis of well-defined degradable graft copolymers with polylactide (PLA) side chains and oxanorbornene backbones is reported. The method, in which PLA macromonomers with oxanorbornene end groups were subjected to ring-opening metathesis polymerization (ROMP), was chosen so that the properties of the arms could be evaluated prior to the synthesis of copolymers. We chose an oxanorbornene-based group for three reasons. First, the ROMP of substituted norbornenes is a well-established methodology for the synthesis of structurally precise polymers. Second, ruthenium Grubbs catalysts **I**−**III** (Figure 1) are the most widely used initiators for ROMP because of their excellent functional group tolerance.[16−18] However, the synthesis of polymers containing bulky side chains requires the use of ruthenium initiators which are more active than **I**.[14,15] Finally, it is to be expected that the presence of the oxygen in the 7-position makes the backbone more hydrophilic[19] and hence increases the probability of biocompatibility of the backbone. The side chains in this polymer are definitely biodegradable, but the biostability of the main chain is unknown and may well be a function of the degree of polymerization (DP) of the backbone. This feature needs careful evaluation when considering possible therapeutic applications.[20]

Herein, we describe the synthesis of oxanorbornene-based macromonomers with either one (*exo*-) or two (*exo,exo*- or *endo,exo*-) PLA chains of variable length. Subsequently, the ROMP reactions of these well-characterized macromonomers catalyzed by three well-defined Grubbs initiators, **I**−**III,** with different activity were investigated. Finally, the hydrolytic degradation behavior of the graft copolymers was studied in detail with particular regard to the variables affecting degradation of these materials, such as the nature of the ROMP fragment, the length and composition of the degradable PLA side chain, the side-chain density of the polymer, and the impurities present in the copolymers.

Experimental Section

General Procedures. The ROP and the ROMP were carried out under nitrogen using the conventional vacuum/nitrogen line or glovebox techniques.

NMR spectra were recorded using a Varian Mercury 400 or a Varian Inova 500 spectrometer. Chemical shifts are reported in ppm with respect to the internal reference tetramethylsilane.

Size exclusion chromatography (SEC) data were obtained using a Viscotek TDA 302 equipped with 2 × 300 mm PLgel 5 μm mixed

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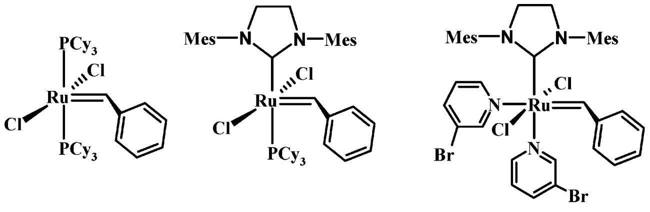


I II III

Figure 1. Well-defined Grubbs ruthenium initiators.

C columns. Tetrahydrofuran (THF) was used as the eluent at a flow rate of 1.0 mL/min at 30 °C. Polystyrene standards were used for calibration.

Materials. DL-Lactide (LA) (Aldrich) was recrystallized twice in toluene and subsequently dried overnight under vacuum and stored in a fridge in the glovebox. Stannous octoate, $Sn(Oct)_2$, and $[RuCl_2(=CHPh)(PCy_3)(IMesH_2)]$ (second generation Grubbs catalyst) (**II**) were purchased from Aldrich and used as received. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene (PhMe) were dried by passage through solvent purification columns. Heptane (HPLC grade) was used without further purification. $[RuCl_2(=CHPh)(PCy_3)_2]$ (**I**) (first generation Grubbs catalyst),[16] $[RuCl_2(=CHPh)(3\text{-Br-py})_2(IMesH_2)]$ (**III**) (modified second generation Grubbs catalyst),[17] *exo*-2-hydroxymethyl-*exo*-3-methoxymethyl-7-oxabicyclo[2.2.1]hept-5-ene (**1**),[21] *exo,exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dimethanol (**2**),[21] and 7-oxabicyclo[2.2.1]hept-5-ene-2-*endo*-3-*exo*-dimethanol (**3**)[22] were prepared according to literature procedures.

General Procedure for Preparation of Macromonomers 1−3. In the glovebox 0.15 mL solution of $Sn(Oct)_2$ (0.5 mol dm^{-1}) in PhMe was added to oxanorbornene alcohol. Lactide (15 mmol, 2.16 g) was dissolved in 5 mL of THF and added to the alcohol/catalyst solution, and then the reaction was stirred at 70 °C under nitrogen for 24 h, 72 h, or 7 days depending on the alcohol and the molar ratio of lactide to alcohol (see Table 1). The PLA macromonomer was precipitated from MeOH, dried overnight under the reduced pressure, and reprecipitated twice in CH_2Cl_2/hexane to give a white material. The yield after reprecipitation was generally around 90%.

*Macromonomer **1**.* ^1H NMR (500 MHz; $CDCl_3$): 6.36 (m, 2=C*H*); 5.19 (m, C*H*, PLA), 4.82 (s, br, 1C*H*,), 4.77 (s, br, 1C*H*), 4.37 (m, C*H*, PLA and 1CH_2), 4.05 (m, 1CH_2), 3.42 (m, 2CH_2), 3.36 (s, OCH_3), 2.8 (br, O*H*, PLA), 1.96 (m, 2C*H*), 1.57 (m, CH_3, PLA), 1.49 (m, CH_3, PLA).

*Macromonomer **2**.* ^1H NMR (500 MHz; $CDCl_3$): 6.38 (s, 2=C*H*), 5.19 (m, C*H*, PLA), 4.78 (s, br, 2C*H*), 4.5 − 3.9 (m, C*H*, PLA and 2CH_2), 2.71 (br, O*H*, PLA), 2.00 (s, br, 2C*H*), 1.57 (m, CH_3, PLA), 1.48 (m, CH_3, PLA).

*Macromonomer **3**.* ^1H NMR (500 MHz; $CDCl_3$): 6.42 (m, 1=C*H*), 6.31 (pseudo t, $J_{HH} = 6.5$ Hz, 1=C*H*), 5.16 (m, C*H*, PLA), 4.88 (m, 1C*H*), 4.70 (s, br, 1C*H*), 4.33 (m, C*H*, PLA and 1CH_2), 4.05 (m, 2CH_2), 3.73 (m, 1CH_2), 2.8 (br, O*H*, PLA), 2.04 (m, 1C*H*), 1.74 (m, 1C*H*), 1.57 (m, CH_3, PLA), 1.22 (m, CH_3, PLA).

General Procedure for ROMP of PLA Macromonomers. The PLA macromonomers were polymerized in a glovebox under an atmosphere of N_2. The PLA macromonomer (0.01 mmol of **1A**−**3A**, **1B**−**3B**, and **1C**−**3C** or 0.005 mmol of **1D**−**3D**) was dissolved in 8 mL of solvent (CH_2Cl_2 or THF). The initiator (**I**, **II**, or **III**), dissolved in 2 mL of the same solvent, was added to the PLA macromonomer. The reaction was allowed to run for an appropriate time (see Tables 2−4). Next, the reaction was removed from the glovebox, and ethyl vinyl ether (1 mL) was added. The polymer was precipitated into an excess of hexane, isolated by filtration, dried, and then reprecipitated in CH_2Cl_2/hexane and dried under vacuum for 24 h. The yield of precipitated material calculated by weight was generally high (95−98%), but it was subsequently shown that this material included uncapped PLA and, in some cases, unreacted PLA macromonomer. More meaningful yields were calculated from ^1H NMR and SEC.

The crude polymer was dissolved in $CHCl_3$ and passed through a short SiO_2 column. The resulting polymer solution volume was reduced, and white or slightly yellow polymer was recovered by precipitating into hexane.

*Polymer **1**.* ^1H NMR (400 MHz; $CDCl_3$): 5.72 (br, =C*H*), 5.55 (br, =C*H*), 5.1 (m, C*H*, PLA), 4.55 (br, CH_2), 4.35 (m, C*H*, PLA), 4.14 (br, C*H* and CH_2), 3.40 (br, CH_2), 3.29 (s, br, OCH_3), 2.36 (br, C*H*), 2.25 (br, C*H*), 1.54 (m, CH_3, PLA), 1.47 (m, CH_3, PLA).

*Polymer **2**.* ^1H NMR (500 MHz; $CDCl_3$): 5.74 (br, =C*H*), 5.58 (br, =C*H*), 5.17 (m, C*H*, PLA), 4.45 (br, C*H*), 4.35 (br, C*H*, PLA), 4.22 (br, C*H*, and CH_2), 2.77 (br, C*H*), 2.42 (br, C*H*), 1.55 (m, CH_3, PLA), 1.27 (m, CH_3, PLA).

*Polymer **3**.* ^1H NMR (500 MHz; $CDCl_3$): 5.66 (br, =C*H*), 5.49 (br, =C*H*), 5.09 (m, C*H*, PLA), 4.3−3.9 (m, br, C*H*, PLA, CH_2 and C*H*), 2.67 (br, CH_2), 2.43 (br, CH_2), 1.95 (br, C*H*), 1.49 (m, CH_3, PLA), 1.20 (m, CH_3, PLA).

General Procedure for Hydrolytic Degradation of PLA Macromonomers and Graft Copolymers. The specimens were formed on glass plates by melting the PLA macromonomers or graft copolymers and then carefully pressed to obtain a smooth sample with uniform thickness and minimal entrapped air bubbles. The specimens (weights ca. 0.4−0.5 g, thickness ca. 0.9−1.05 mm) were then immersed in phosphate buffered saline (pH 7.4) at 50 °C. This temperature was chosen rather than the more usual 37 °C in view of the long times required for significant degradation, so that comparative degradation behaviors could be studied on a realistic time scale. At specified time intervals, the samples were taken out and dried under vacuum at room temperature for 24 h and at 30 °C for a further 12 h. Aging/degradation of the various materials was monitored by measuring molar mass changes (SEC). The molecular weight at the maximum of the distribution curve (M_p) was selected as the key indicator for monitoring changes in overall molecular weight in order to reduce the variability caused by the polydispersity dependence of M_w.

Results and Discussion

Synthesis of Macromonomers. PLA macromonomers terminated with an oxanorbornyl group were synthesized by ROP of DL-lactide in the presence of mono- or dialcohol derivatives of oxanorbornene as an initiator (Scheme 1). Stannous octoate, also known as tin(II) 2-ethylhexanoate, $Sn(Oct)_2$, was chosen as catalyst for three reasons. First, $Sn(Oct)_2$ is one of the most widely used compounds for initiating the ROP of various lactones and lactides.[23,24] It is easy to handle and is soluble in common organic solvents. Second, this catalyst is highly efficient and allows almost complete conversions even at low concentration.[25] Finally, $Sn(Oct)_2$ has been accepted as a food additive by the U.S. FDA because its toxicity is extremely low compared to other heavy metal salts.

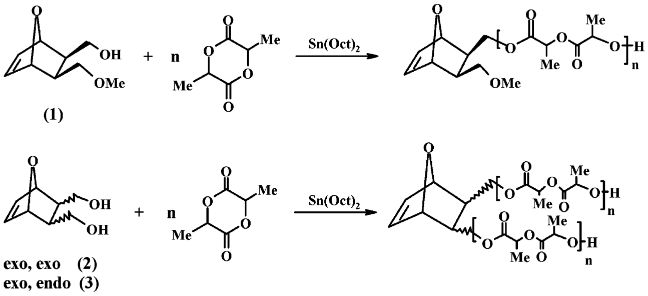
A series of macromonomers with different PLA chain length were prepared and characterized. Their characteristics are presented in Table 1. All PLA macromonomers were characterized by ^1H NMR spectroscopy and size exclusion chromatography (SEC). The oxanorbornyl end group of the PLA chain is readily observed by ^1H NMR spectroscopy (Figure 2). The main evidence for attachment of the oxanorbornyl group is the chemical shift of the methylene groups. For example, after ROP of LA initiated by alcohol **2** signals corresponding to methylene protons (7,8) shifted to lower frequency (down to 4.33 and 4.06 ppm). It is possible to calculate the PLA/oxanorbornene molar ratio by integration of the methylene protons of PLA (c) and the olefinic protons (2,3) of the oxanorbornyl group and, therefore, calculate the average number of LA units in PLA chain end-capped with oxanorbornene group (degree of LA polymerization, DP). For low-molecular-weight PLA macromonomers (up to 25 LA units per chain) these values agree within experimental error with the theoretical value. However,

Table 1. Characterization of PLA Macromonomers (M) Synthesized by ROP of LA Catalyzed by Sn(Oct)$_2$[a]

					SEC analysis			^{1}H NMR analysis	
ROH	[LA]/[OH]	M	time (h)	theor M_n	M_n	PDI	DP	M_n	DP
1	5	**1A**	24	890				1000	6
	10	**1B**	24	1610	1400	1.28	9	1600	10
	25	**1C**	24	3770	3500	1.24	23	3500	23
	50	**1D**	72	7370	7300	1.20	49	8800	60
2	5	**2A**	24	1600				1600	5
	10	**2B**	24	3040	3500	1.22	11	3000	10
	25	**2C**	72	7360	5700	1.27	19	5300	18
	50	**2D**	7 days	14560	6900	1.90	23	14800	51
3	5	**3A**	24	1600				1600	5
	10	**3B**	24	3040	3000	1.27	10	3300	11
	25	**3C**	72	7360	6900	1.32	23	6200	21
	50	**3D**	7 days	14560	8300	1.51	28	10200	35

[a] Reaction conditions: $[LA]_0 = 1$ M; $[LA]_0/[Sn(Oct)_2]_0 = 200$; solvent PhMe, $T = 70$ °C.

Scheme 1. Synthesis of PLA Macromonomers with One (1) and Two PLA Chains (2 and 3); Monomers 1 and 3 are Racemic



with higher molecular weight PLA macromonomers, similar calculations do not provide any useful information. This is explained by the large differences in intensity between signals due to PLA and oxanorbornene.

The lack of agreement between molecular weights of macromonomers measured by SEC against polystyrene standards and those calculated from ^{1}H NMR results arises from differences in the hydrodynamic volume of polystyrene relative to PLA macromonomer and also to the presence of uncapped polylactide. The molecular weight distribution indexes (PDI) of the macromonomers range between 1.20 and 1.67 and are broader for those prepared in the presence of dialcohol derivatives of oxanorbornene (Table 1). In addition, PDI became broader when the reaction time required for the complete consumption of LA was extended to 7 days, which is typical for polylactides prepared using tin compounds.[25] The degree of LA polymerization was in good agreement with the lactide-to-alcohol ratio only in the case of macromonomers with one PLA chain (**1A**−**1D**). For macromonomers containing two PLA chains, the average number of LA units in the PLA chains decreased as the lactide-to-alcohol molar ratio increased. These results can be explained by consideration of the mechanism of initiation involved in the reaction of alcohol with Sn(Oct)$_2$.[26−28] In the case of initiators **2** and **3**, two OH groups must be activated to give a macromonomer with two PLA chains. On the other hand, impurities such as water or 2-ethylhexanoic acid, which are always present in commercial Sn(Oct)$_2$, may act also as co-initiators and hence increase the molecular weight distribution of PLA macromonomer.[28] Moreover, inspection of the MALDI-TOF mass spectra of the macromonomers proves the presence of an intermolecular transesterification side reaction.[29] The spectra show the presence of two distinct series of signals with higher and lower intensity. The higher intensity series comes from PLA macromonomers with an even number of lactoyl (C(O)CH(CH$_3$)O) repeating units. However, the side reaction leads to macromonomers with an odd number of lactoyl units, which is observable as the lower intensity series.

ROMP of PLA Macromonomers. Well-characterized macromonomers with one (**1A**−**1D**) and two (**2A**−**2D** and **3A**−**3D**) PLA chains of varying lengths were subjected to ROMP using first generation Grubbs ruthenium initiator, **I** (Figure 1), and the living polymers were terminated using ethyl vinyl ether to give the final product (Scheme 2). The results are shown in Table 2.

The molecular weight of the graft copolymer was controlled by varying the macromonomer-to-initiator molar ratio [M]/[I]. All graft copolymers were characterized by SEC to estimate the amount of unreacted macromonomer. As discussed above, only relative molecular weights can be calculated against polystyrene standards due to the different hydrodynamic volumes of the copolymers.

The macromonomer **1A** was polymerized well with initiator **I**. Examination of the ^{1}H NMR spectra of the copolymer showed no signals due to the oxanorbornyl end group in the macromonomer. However, the SEC chromatogram of this product showed the presence of a major high molecular weight peak and a minor low molecular weight peak. The low molecular weight peak had the same retention time as that of macromonomer **1A**, and extended reaction times did not significantly diminish the intensity of this signal. Thus, we concluded that graft copolymers were contaminated with PLA homopolymer without an oxanorbornene end group (uncapped PLA) produced in a side reaction during ROP of LA. The ROMP of macromonomers with longer PLA chains (**1B**−**1D)** stopped before complete consumption of macromonomer even at longer reaction times and at higher concentration of initiator. Similar results were obtained from ROMP of macromonomers bearing two *exo*-PLA chains (**2A**−**2D**). However, attempts to prepare graft copolymer from **2A** with 50 oxanorbornene units in the backbone chain and 5 LA units in each side chain proceeded almost to completion after 2 days of reaction. Macromonomers with longer PLA side chains were not polymerized to completion with **I** even if the ratio of [M]/[I] was low or the reaction was continued for longer times. The polymerization of macromonomer **2D** went to less than 50% conversion even if the monomer-to-initiator molar ratio was as low as 10:1. Raising the reaction temperature to 40 °C also resulted in the observation of unreacted macromonomer.

Attempts to polymerize PLA macromonomers bearing one *exo* and one *endo* PLA chain (**3A**−**3D**) by initiator **I** did not proceed to full conversion. Even for the samples with chains only 5 LA units long (**3A**) only 16% of macromonomer had polymerized after 24 h of reaction. The ROMP of **3B** did not proceed to completion for [M]/[I] of 10 despite leaving the reaction for 13 days. Attempts to obtain polymers with the PLA side chains longer than 10 LA units failed even if the monomer-

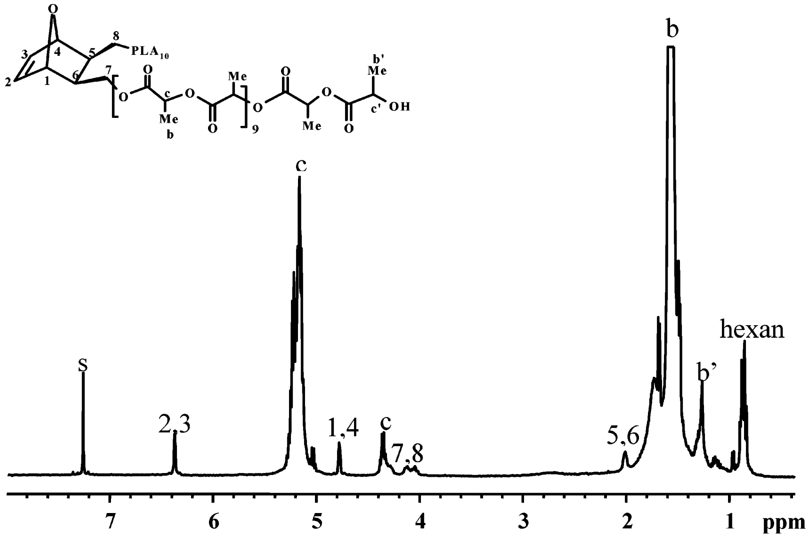
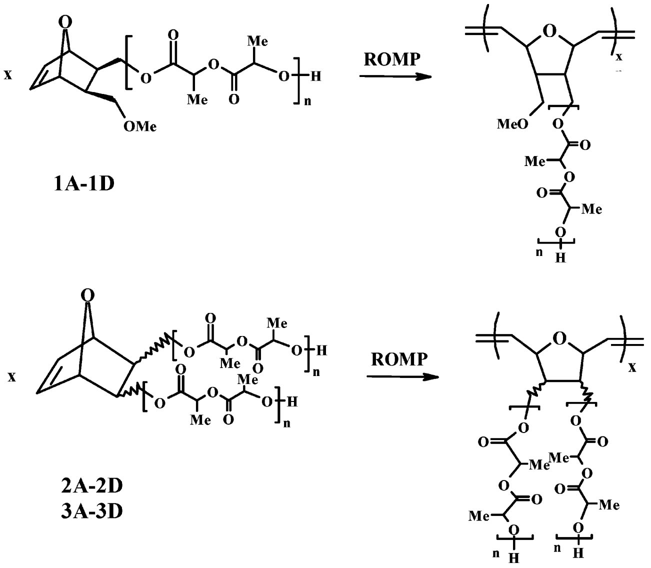


Figure 2. ^{1}H NMR spectrum of the oxanorbornenyl PLA macromonomer **2A**.

Scheme 2. ROMP of PLA Macromonomers Using Grubbs Ruthenium Initiators



to-initiator molar ratio was low or the reaction temperature was high (**3D**).

The behavior of these PLA macromonomers in ROMP is due to steric crowding, which develops between macromonomers as they are added to the growing graft copolymer.[14] In contrast to macromonomers having two PLA side chains on the same oxanorbornene unit, copolymers can be prepared from macromonomers with one PLA chain per unit with longer backbone and side chains as a consequence of reduced steric hindrance.[30] In the case of *endo,exo*-macromonomers, in addition to steric hindrance, another factor plays an important role in preventing effective ROMP. It is well-known that the ROMP of *endo,exo*-norbornene derivatives containing oxygen is slower than ROMP of the corresponding *exo,exo*-species.[31,32] This is due to the formation of relatively stable resting states of the propagating polymer chain, such as species in which a six-membered ring is created by chelation of the oxygen of the side group to the ruthenium.[32] A significant decrease in polymerization rate with increasing the length of side chain could be also attributed to the vanishingly small quantities of initiator used. For example, in ROMP of **1B** with a ratio [M]/[I] of 10, the concentration of initiator was 0.82 mg/mL, while in the corresponding ROMP of **1D** the concentration decreased to 0.41 mg/mL and further to 0.16 mg/mL for [M]/[I] of 25. It has been shown that the concentration of initiator plays an important role in determining the rate of ROMP reactions and that reactions are slower for dilute systems.[14,33]

Table 2. ROMP of PLA Macromonomers (M) Using First Generation Ruthenium Initiator (I)

				SEC analysis	
monomer (M)	DP of LA	[M]/[I]	reaction time (days)	no. of peaks	unreacted M (%)
1A	5	25/1	1	2	18 (uncapped)
	5	50/1	2	2	17 (uncapped)
1B	10	10/1	1	2	23 (uncapped)
	10	25/1	2	2	24 (uncapped)
1C	25	10/1	1	2	38
	25	25/1	2	2	37
	25	50/1	9	2	78
1D	50	10/1	1	2	40
	50	25/1	5	2	43
2A	5	10/1	1	2	18 (uncapped)
	5	25/1	2	2	20 (uncapped)
	5	50/1	2	2	22
2B	10	10/1	2	2	26
	10	25/1	10	2	36
2C	25	10/1	1	2	29
	25	25/1	4	3	40
	25	50/1	12	3	71
2D	50	10/1	2	3	60
	50	25/1	1[a]	3	56
3A	5	10/1	1	2	84
3B	10	10/1	13	2	36
3C	25	5/1	5	1	100
3D	50	10/1	5	1	100
	50	10/1	1[b]	1	100

[a] Solvent C_6H_6, 24 h at 40 °C. [b] Solvent C_6H_6, 24 h at 60 °C.

We expected that difficulties with the synthesis of higher molecular weight copolymers by complex **I** could be overcome by using a more active initiator, namely the second generation ruthenium initiator, **II** (Figure 1). Although replacement of one of the phosphine ligands with an N-heterocyclic carbene ligand gives a complex which displayed dramatically improved metathesis activity, thermal stability, and inertness toward oxygen and moisture compared with complex **I**, it is generally accepted that this catalyst is not an appropriate choice for the initiation of ROMP of most monomer systems.[34] However, sterically hindered substrates with bulky substituents have been successfully polymerized to yield polymers with a low PDI.[14,15]

Table 3. ROMP of PLA Macromonomers (M) Using Second Generation Ruthenium Initiator (II)

monomer (M)	DP of LA	[M]/[II]	reaction time (h)	SEC analysis no. of peaks	unreacted M (%)
2D	50	25/1	4	3	36
	50	50/1	24	2	32
3B	10	10/1	2	2	16 (uncapped)
	10	25/1	2	2	17 (uncapped)
3D	50	10/1	4	2	62
	50	25/1	4	2	78

Table 4. ROMP of PLA Macromonomers (M) Using Modified Second Generation Ruthenium Initiator (III)

macro-monomer (M)	DP of LA	[M]/[III]	reaction time (days)	SEC analysis no. of peaks	unreacted M (%)
1B	10	10/1	1	2	24 (uncapped)
	10	25/1	2	2	24 (uncapped)
1C	25	10/1	19 h	2	19 (uncapped)
	25	25/1	2	2	22 (uncapped)
	25	50/1	2	2	40
1D	50	10/1	2	2	32
	50	25/1	3	2	32
2A	5	50/1	1	2	16 (uncapped)
2B	10	10/1	1	2	17 (uncapped)
	10	25/1	2	2	25
2C	25	10/1	1	2	21 (uncapped)
	25	25/1	2	2	23 (uncapped)
	25	50/1	2	2	27
2D	50	10/1	1	2	22 (uncapped)
	50	25/1	3	2	29
3A	5	10/1	1	2	22 (uncapped)
3B	10	10/1	1	2	38
	10	10/1[a]	1	2	18 (uncapped)
	10	25/1	2	2	53
	10	50/1	3	2	64
3C	25	10/1	3	2	39
	25	10/1[a]	1	2	29 (uncapped)
3D	50	10/1	4	2	62
	50	10/1[a]	3	2	31 (uncapped)
	50	25/1	8	2	63

[a] Solvent THF.

In our studies macromonomers containing two PLA chains were subjected to ROMP by **II** (Table 3). We believed that the steric crowding present in these macromonomers would prevent the initiator from reacting with double bonds in the growing copolymer's backbone ("backbiting"). Although the conversion of **2D** was higher in the ROMP using [M]/[II] of 25 (in a shorter time and at room temperature) than in ROMP using initiator **I** (Table 3), three peaks were observed in the SEC of the product. One of these corresponds to unreacted macromonomer, but the other two correspond to graft copolymer. Using [M]/[II] of 50 for the ROMP of **2D,** incomplete reaction and broad molecular weight distribution of the copolymer produced was observed after 24 h. These results suggest that the reactions are not living and could be accompanied by backbiting and other secondary metathesis reactions.[14]

Although the initiator **II** polymerized the sterically hindered *endo,exo*-macromonomer with 10 LA units in each chain (**3B**) to completion after 2 h, a broad molecular weight distribution of copolymer product was observed. The polymerizations of more sterically crowded *endo,exo*-macromonomers with 50 LA units per chain (**3D**) using [M]/[II] of 10 and 25 gave only 38% and 22% of polymer, respectively, after 4 h but resulted in copolymers with relatively narrow peaks in SEC. These results indicate that only in the case of *endo,exo*-macromonomers with 50 LA units in each chain (**3D**) is the steric crowding of side chains sufficient to prevent the ruthenium center from reacting with double bonds of the oxanorbornene backbone. As a consequence, polymers with monomodal molecular weight distribution were obtained.

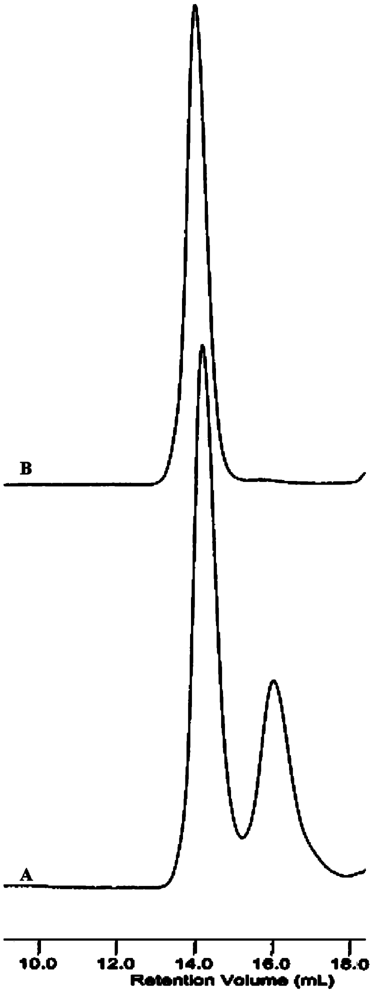


Figure 3. SEC chromatograms of *exo*-copolymer with 25 LA units in chain before (A) and after purification (B).

Since the ROMP of PLA macromonomers by **II** results in largely uncontrolled polymerization processes, we decided to use the second Grubbs ruthenium initiator modified with 3-bromopyridine, **III** (Figure 1). Previous investigations have shown high activity of **III** in the ROMP of *endo,exo* 2,3-disubstituted norbornene moieties.[32,35,36] In addition, in contrast to **II**, in the presence of this complex polymerizations exhibit much higher values of k_i relative to k_p and hence yield polymers with narrow molecular weight distributions.[17,32,35] When a green solution of **III** was added to a colorless solution of monomer, the color immediately changed to yellow, which implies the immediate initiation of **III**. The polymerizations of PLA macromonomers with one short chain per oxanorbornene (**1B**) went to completion for [M]/[III] of 10 and 25 (Table 4). However, in the case of PLA macromonomer **1C**, the ROMP at [M]/[III] of 50 stopped before complete consumption of **1C**. Surprisingly, attempts to polymerize PLA macromonomer **1D** resulted in a copolymer contaminated with small amounts in unreacted **1D**. The reason for this behavior is unknown and requires additional investigations.

Experiments to polymerize macromonomers containing two *exo*-PLA chains with **III** resulted in high conversions at short reaction times. Polymerization of **2C** using [M]/[III] of 10 and 25 went to completion in 24 and 48 h, respectively. Moreover,

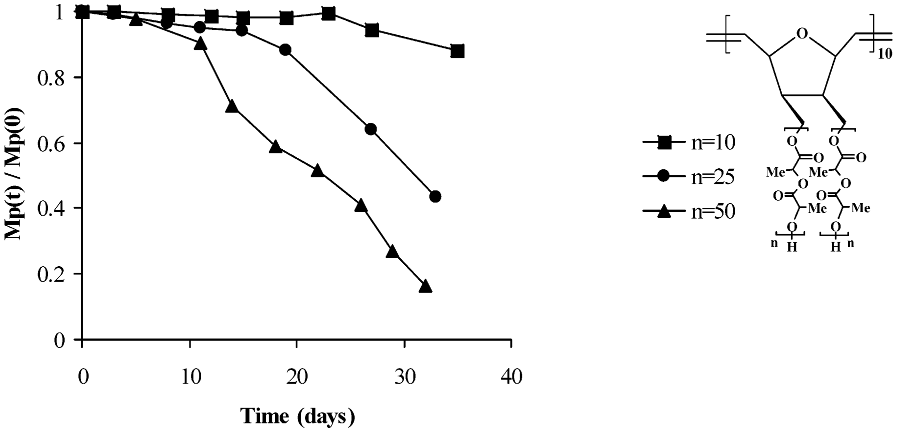


Figure 4. Degradation of *exo,exo*-copolymers with different length of PLA side chains in PBS at 50 °C.

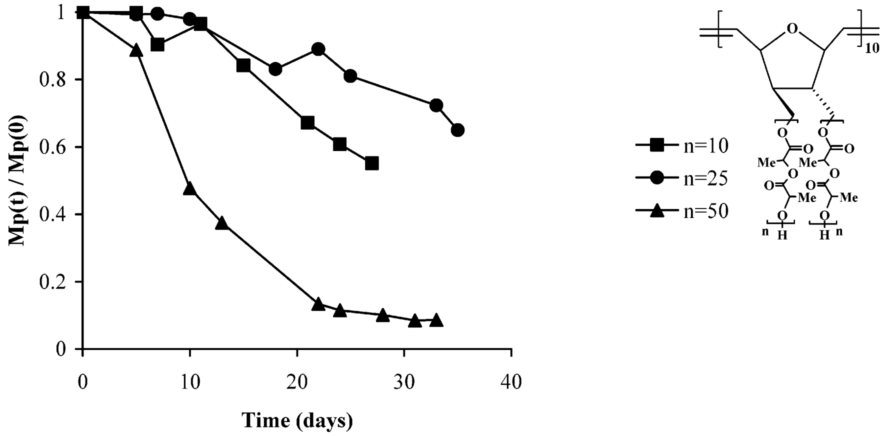


Figure 5. Degradation of *endo,exo*-copolymers with different length of PLA side chains in PBS at 50 °C.

the PLA macromonomer **2D** was successfully polymerized using [M]/[III] of 10 after 1 day. ROMP of **2D** using [M]/[III] of 25 resulted in a graft copolymer with both long PLA side chains and a relatively long backbone chain.

However, the use of initiator **III** in the ROMP of macromonomers with two *endo,exo*-PLA chains in CH_2Cl_2 did give copolymers, in contrast to initiator **I**, but the reaction went to completion only in the case of the macromonomer with 5 LA units in each chain (**3A**). ROMP of PLA macromonomers **3B** and **3C** did not go to completion even for [M]/[III] of 10. Polymerization of the macromonomer with the longest PLA side chains, **3D**, in dichloromethane stopped before complete consumption of PLA macromonomer even at long reaction times. Surprisingly, a change of solvent from dichloromethane to THF resulted in 100% conversion of *endo,exo*-macromonomers. For example, ROMP of the macromonomer with the longest PLA side chains, **3D**, using [M]/[III] of 10 went to completion in 3 days while the same reaction in dichloromethane resulted in unreacted PLA macromonomer after a reaction time of 4 days. One reason for this behavior could be slightly better solubility of PLA macromonomers in THF than in CH_2Cl_2.

All the graft copolymers produced were contaminated with PLA homopolymer, as discussed above. The amounts of uncapped PLA estimated from SEC chromatograms of the copolymers depended on the molar ratio of LA to alcohol-substituted oxanorbornene and slightly increased with increasing length of PLA chain in the macromonomer. Therefore, we used the difference in solubility in CH_2Cl_2 between the macromonomers and copolymers to develop a procedure for the purification of the graft copolymers. SEC chromatograms of the purified white material showed only one high molecular weight peak due to graft copolymers (Figure 3B). The signal due to uncapped PLA observed in SEC chromatograms of the crude material (Figure 3A) disappeared after passing the crude material through a silica column. Moreover, the purification method allowed the removal not only of uncapped PLA but also of unreacted macromonomer.

The PDI's for the column-purified graft copolymers produced by ROMP using initiator **III** were in the range of 1.05 and 1.14, indicating a well-behaved polymerization reaction.

Hydrolysis Degradation of Macromonomers and Graft Copolymers. Various graft copolymers with 10 oxanorbornene units in the backbone chain and varying lengths of PLA side chains were selected for hydrolysis studies. The degree of polymerization (DP = 10) was established from the macromonomer-to-initiator ratio by the observation from the ^1H NMR spectra that the rate of ROMP initiation is much greater than the rate of ROMP propagation and that all the macromonomer undergoes ROMP. All experiments were carried out in phosphate buffered saline (PBS) at 50 °C. The influence of various parameters on the kinetics of degradation has been examined including the polyoxanorbornene/PLA ratio, different configurations of PLA side chain on polyoxanorbornene backbone chain, and the purification of copolymer. Before immersion, the specimens are generally transparent and colorless (macromonomers) or slightly yellow (copolymers). They became progressively whitish or yellowish with aging time, and their brittleness also increased. Moreover, the degrading polymer samples became thinner and hollow as the hydrolysis time increased.

Figure 4 shows the changes of average molar weights as determined from SEC chromatograms of degraded graft co-

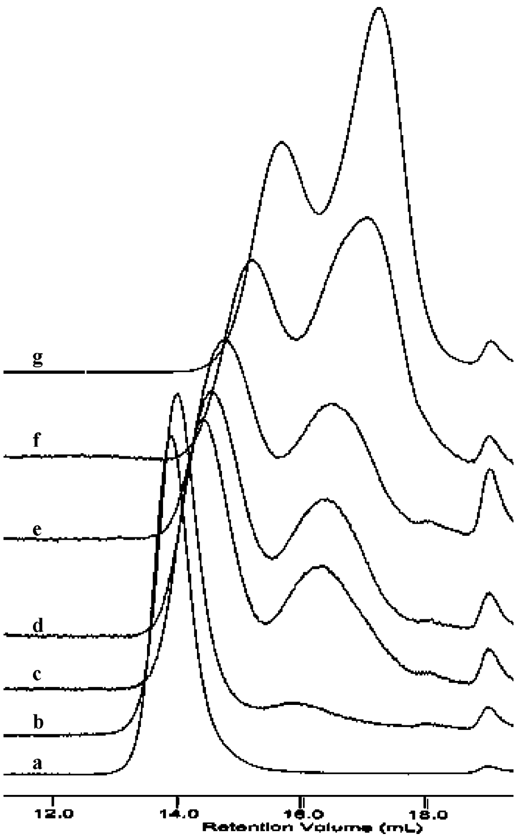


Figure 6. SEC chromatograms of partially degraded *exo,exo*-copolymers with 50 LA units in each chain for different aging durations: 0 (a), 11 (b), 18 (c), 22 (d), 26 (e), 29 (f), and 32 days (g).

polymers bearing two *exo*-PLA side chains with different length. The initial decrease of molecular weights was substantially smaller in the case of copolymers containing side chains with 10 LA units. Additionally, the rate of molecular weight loss after the induction period was clearly higher for graft copolymer bearing long PLA chains. These results indicate that the proportion of oxanorbornene/LA units ratio in the copolymer plays an important role in the degradation of material and that shorter PLA chains lead to a lower rate of copolymer degradation.

These findings are in good agreement with those observed in the degradation of *endo,exo*-copolymers (Figure 5). However, the differences in molecular weight loss for degradable *endo,-exo*-copolymers with 10 and 25 LA are rather small. This could be explained by the similar average weight mass of those materials, as estimated by SEC (28 600 for $n = 10$ and 30 400 for $n = 25$).

SEC at different hydrolysis times for *exo,exo*-copolymers with the longest length of PLA chains are shown in Figure 6. The molecular weights of the degraded species shifted to lower values, and the formation of low molecular weight peak was observed with increasing hydrolysis time. Bimodal SEC chromatograms were observed in the case of all degraded polymers, irrespective of the length of the PLA side chains, and is typical of heterogeneous degradation of amorphous noncrystallizable DL-PLA.[2,37] Interestingly, this type of degradation was shown to be size dependent and occurred predominantly in the case of plates.[5]

The influence of the different configurations of PLA side chain (*endo/exo*) on the rate of degradation of these three types of graft copolymers was investigated by comparison of the degradation behavior of copolymers with the same length of backbone and PLA side chains (Figure 7). Among the three copolymers, that with one PLA side chain exhibits the fastest rate of degradation. This result implies that the presence of two PLA side chains on each oxacyclopentane ring in the backbone chain results in steric hindrance and therefore reduces the rate of degradation.

It has been established previously that one of the parameters that influence hydrolysis is the presence of impurities in the degradable material.[2] Thus, we decided to perform comparative studies of purified and unpurified *exo,exo*-copolymer degradations at 50 °C. Unpurified *exo,exo*-copolymer with 25 LA units in each chain contained ~20% of uncapped PLA (Table 4). As shown in Figure 8, degradation of the unpurified material was substantially faster than its purified counterpart. Moreover, the overall rate of degradation of this copolymer is essentially the same as the rate of degradation of macromonomer at the same hydrolysis time. These results clearly show that impurities, such as low molecular weight PLA, increase the rate of hydrolytic degradation of the final copolymer. This behavior could be explained by the hydrolytic degradation mechanism previously proposed in the case of these graft copolymers. According to that theory, heterogeneous degradation causes an increase in the number of carboxylic chain ends, which are known to autocatalyze the ester hydrolysis of PLA side chains.[38] Studies

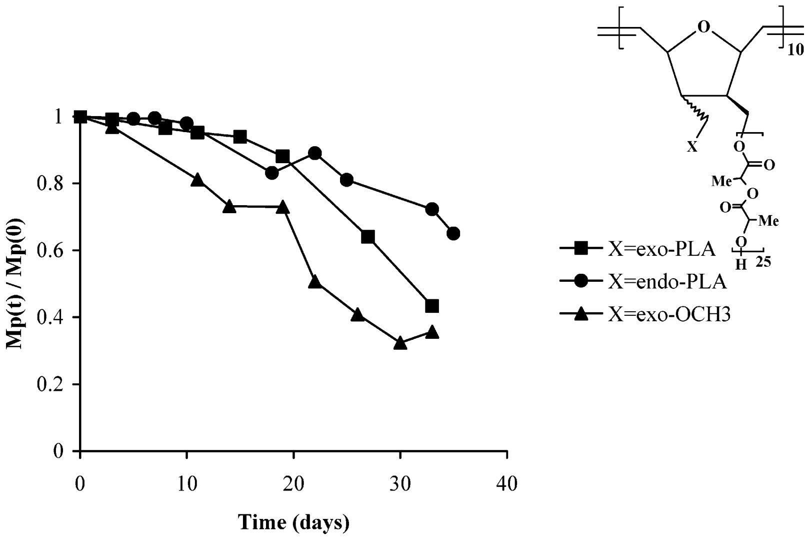


Figure 7. Degradation of various graft copolymers with 25 LA units per chain in PBS at 50 °C.

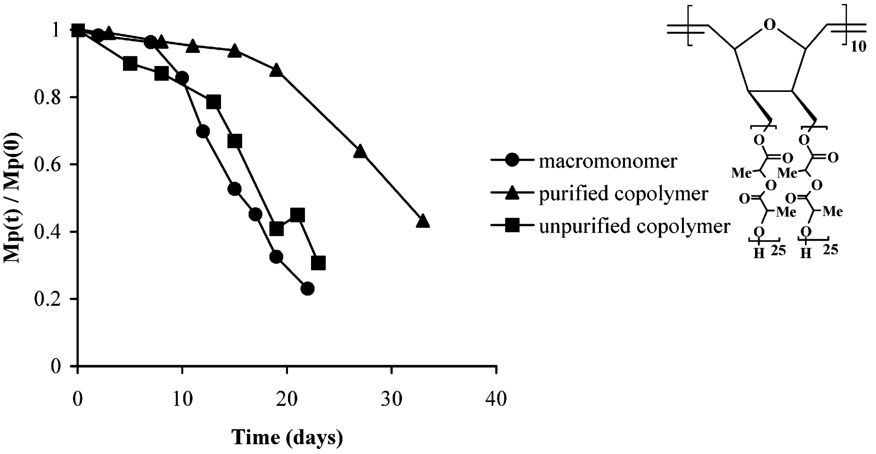


Figure 8. Effect of purification on degradation behavior of *exo,exo*-copolymers with 25 LA units in each side chains, in PBS at 50 °C.

of the factors governing the bioabsorption rate of L-PLA contaminated with unreacted monomer showed that impure PLA resorbed much more quickly than purified polymer.[39] The hydrolytic degradation was also dependent on the molecular weight of the polymer itself[6] as well as on the presence of catalysts.[7] Thus, uncapped PLA present in our unpurified material degraded faster than the copolymer and therefore led to an increase in the overall degradation rate.

Conclusions

The synthesis of well-characterized polyoxanorbornene graft copolymers containing PLA grafts using a combination of two polymerization mechanisms (ROP of lactide and ROMP of oxanorbornene derivatives) has been reported. A series of well-characterized macromonomers with one *exo*- and two *exo,exo* and *endo,exo*-PLA chains were subjected to ROMP by three well-defined Grubbs ruthenium initiators. The results using Grubbs first generation initiator showed that this initiator was ineffective for the polymerization of macromonomers with two PLA side chains. Although, Grubbs second generation initiator was much more active in the ROMP of macromonomers bearing two PLA chains, the polymerization reactions were not well controlled in terms of the molecular weight distributions. Given these results, Grubbs second generation initiator modified with 3-bromopyridine was successfully applied to the synthesis of graft copolymers with long polyoxanorbornene backbone chain and long PLA grafts length.

The hydrolytic degradation of graft copolymers depended to a significant degree on the polyoxanorbornene-to-polylactide molar ratio in copolymers, and the rate of degradation of the PLA is greatly reduced by attaching it to polyoxanorbornene backbone chain. In addition, the presence of PLA homopolymer as an impurity in the copolymers significantly increases the rate of degradation of the final material. Therefore, we developed procedure for the purification of copolymers which allowed us to eliminate that factor from the degradation behavior of the materials. Our results indicate that, by changing the length of the polyoxanorbornene backbone chain and the PLA grafts, we can tailor the properties of the polymers under degradation to enhance their potential utility in biomedical applications.

In summary, our results clearly show the following:

1. The alcohol-substituted oxanorbornenes were efficient initiators in the ROP of lactide (LA) catalyzed by stannous octoate, for the production of oxanorbornene end-capped PLA macromonomers.

2. The most effective Grubbs ruthenium initiator for the ROMP of the macromonomers was the modified second generation ruthenium initiator.

3. The length of polyoxanorbornene backbone chain and the length of PLA side chains in the target graft copolymer play an important role in determining the rate of degradation of material.

4. The rate of degradation for target graft copolymers with long polyoxanorbornene backbone and short PLA side chains is slower than that for the target graft copolymers with short polyoxanorbornene backbone and long PLA side chains.

5. The target graft copolymers with two PLA side chains on each oxacyclopentane ring exhibit the slowest rate of degradation. This is believed to be due to the steric interactions between the two PLA chains.

6. The presence of PLA homopolymer as impurities in the target graft copolymers significantly increases the rate of degradation of the final material. Therefore, we developed a convenient procedure for the purification of graft copolymers.

7. The degradation tests on materials based on pure PLA show 80% weight loss in about 80 days, whereas the weight loss for our target graft copolymers is 40% over the same period of time. This clearly demonstrates that the rate of degradation of the PLA is greatly reduced by attaching it to polyoxanorbornene backbone chain.

8. By changing the length of polyoxanorbornene backbone chain and PLA grafts, we can tailor the properties of the polymers under degradation to enhance their potential utility in biomedical applications.

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