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Random Copolymerization of ε-Caprolactone with Lactide Using a Homosalen−Al Complex

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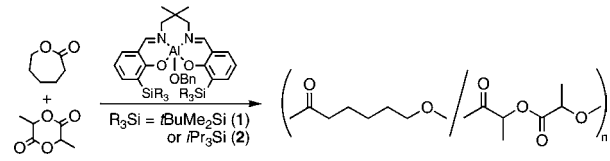
Some important properties of poly(ε-caprolactone) (PCL) and poly(D,L-lactic acid)/poly(racemic lactide) (PLA), both of which have received significant attention in medical and pharmaceutical applications,[1] are complementary. For example, PLA has a much shorter half-time in vivo (a few weeks) than PCL (1 year),[2] and PCL is permeable to many drugs with low molecular weights, while PLA is not because of its hydrophilicity.[2b] The copolymer synthesized from ε-caprolactone (CL) and D,L-lactide (racemic lactide, LA) is more permeable to drugs than PLA[2] and is of value for biodegradable devices because of its shorter lifetime relative to PCL. Therefore, it has been investigated for use in drug release media and nerve guides.[3] During the early stage of the copolymerization of CL with LA, however, LA is preferentially polymerized, after which CL is polymerized.[4] Consequently, a gradient or blocky distribution from LA to CL in each polymer molecule is observed, and the controlled copolymer that has an even distribution of two monomers throughout the copolymerization is desired and has been a target for decades. Metal complexes with salen-type ligands and their derivatives have played invaluable roles as catalysts in synthetic chemistry,[5,6] and we recently reported that homosalen−Al complexes are excellent catalysts for stereoselective ring-opening polymerization (ROP) of LA.[5e,7] We now report the controlled ring-opening copolymerization of CL and LA with practically random (Bernoullian) distributions using a homosalen−Al complex.

In most of the reported copolymerizations,[2b,4] the reactivity ratios of CL (r_{CL}) and LA (r_{LA}) were quite different ($r_{CL} < 1 \ll r_{LA}$).[8,9] For the synthesis of the random copolymer, $r_{CL} = r_{LA} = 1$ should be achieved, and as a result, the average sequence lengths of both the caproyl unit (L_{CL}) and the lactidyl unit (L_{LA}) of the random copolymer become 2.[10] In our previous studies, we observed that the bulky substituents of the homosalen ligands slowed the polymerization of LA.[7] We applied these homosalen−Al complexes in the copolymerization[11] of CL with LA. We first conducted the copolymerization of CL with LA using complex **1** (Table 1). The LA conversion was much higher than the corresponding CL conversion up to 5 h. The monomer conversions during the copolymerization suggested the formation of a tapered PLA−PCL, and both L_{CL} and L_{LA} reached ∼2 at high monomer conversions.[12,13] Complex **2** with the bulkier *i*Pr$_3$Si groups was then examined and found to be an excellent catalyst for the synthesis of a copolymer of CL with LA containing practically random sequences.[14] The copolymerization proceeded in a living manner with a narrow polydispersity. The two monomers were equally consumed during the copolymerization. The values of L_{CL} and L_{LA} were maintained at 1.7−2.0. The reactivity ratios were obtained using the nonlinear least-squares (NLLS) method ($r_{CL} = 1.0_9$, $r_{LA} = 0.73$).[11,13] The value $r_{CL}r_{LA} = 0.80$, being less than 1, indicates that the copolymer synthesized using complex **2** has a somewhat alternative tendency from the random copolymerization indicated by L_{CL} and L_{LA}.

Table 1. Copolymerization of CL with LA for Poly(CL-*ran*-LA)[a]



complex	time (h)	C_{CL}[b], C_{LA}[c] (%)	CL/LA in copolymer[d]	M_n[e] (M_w/M_n)[e]	L_{CL}[f]	L_{LA}[g]
1	1	14, 33	30:70	2500 (1.0_8)	1.4	2.8
	3	30, 50	37:63	5000 (1.1_1)	1.5	2.9
	5	43, 74	37:63	7100 (1.0_9)	1.5	2.8
	11	86, 95	47:53	11400 (1.1_0)	1.9	2.0
2	1	19, 17	52:48	4300 (1.1_0)	1.8	1.8
	2	36, 37	49:51	8800 (1.0_9)	1.8	2.0
	3	52, 52	50:50	13200 (1.0_7)	1.7	1.9
	10	97, 95	51:49	21600 (1.0_8)	1.8	1.9

[a] Polymerization conditions: CL, 0.99 mmol; LA, 1.00 mmol; catalyst, 0.030 mmol for **1** and 0.020 mmol for **2**; toluene, 3.0 mL; temp., 70 °C for **1** or 90 °C for **2**. [b] C_{CL}: conversion of CL as determined by ^{1}H NMR analysis. [c] C_{LA}: conversion of LA as determined by ^{1}H NMR analysis. [d] CL/LA mole ratio in the copolymer. [e] As determined by size-exclusion chromatography (polystyrene standards, $CHCl_3$). [f] Average sequence length of the caproyl unit as determined by ^{13}C NMR analysis. [g] Average sequence length of the lactidyl unit as determined by ^{13}C NMR analysis.

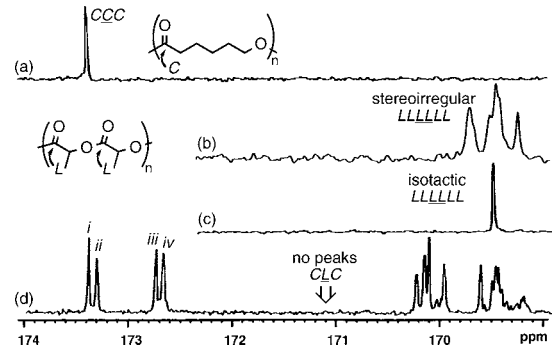


Figure 1. ^{13}C NMR spectra of (a) PCL (100 MHz), (b) stereoirregular PLA (M_n, 19 000; $M_w/M_n = 1.1_5$) obtained using Al(O*i*Pr)$_3$ (75 MHz), (c) isotactic PLA obtained using complex **1** (100 MHz), and (d) poly(CL-*ran*-LA) obtained using complex **2** (150 MHz). *i*, *CCC*; *ii*, *LLCC*; *iii*, *CCLL*; *iv*, *LLCLL*.

Figure 1 shows the ^{13}C NMR spectra of (a) PCL, (b) stereoirregular PLA, (c) isotactic PLA, and (d) poly(CL-*ran*-LA) obtained using complex **2**. Because of the stereoirregularity of PLA, some carbonyl carbon peaks appeared in Figure 1b.[15] On the other hand, the highly isotactic PLA obtained using complex **1** ($P_{meso} = 98\%$) nearly gave a single peak (Figure 1c). In Figure 1d, the integration ratios of the four peaks derived from the caproyl unit (*C*) between 172.6 and 173.4 ppm were *i*/*ii*/*iii*/*iv* ≈ 23:23:27:27 (the abundance ratios of the random copolymer would be *i*/*ii*/*iii*/*iv* = 25:25:25:

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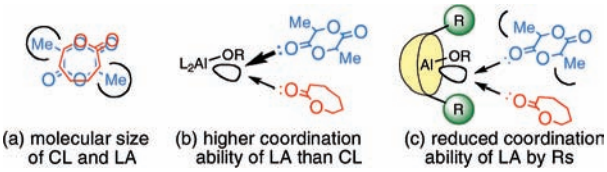
25). The peaks derived from the lactidyl unit (*LL*) were more complicated because of the two lactyl functions in the unit, and it is known that six peaks appeared (169.1−170.4 ppm, Figure 1d).[16] The minor peaks at 169.1−169.3 ppm were also observed and were attributed to the stereoirregularity of isotactic PLA (P_{meso} = 95% using complex **2**, stereoirregular *LLLLLL*); they are clearly observed in Figure 1b but inconsiderably in Figure 1c. There were no observed peaks corresponding to the *C*−*L*−*C* triads at 171.1 ppm as a result of transesterification of the cleavage of the lactyl−lactyl bond in the lactidyl unit.

ROP of lactones proceeds in multiple complex steps via a coordination−insertion mechanism,[11,17] and thus, it is difficult to discuss the detailed mechanism. The ring sizes of the six- and seven-membered unsubstituted lactones are comparable (Scheme 1a), and the two methyl groups of LA may have a significant steric effect on the formation of the coordination bond between the Al center and the oxygen atom of the O═C group. Although we do not yet have direct evidence, we assume that the reason for the generally higher reactivity of LA than CL over the steric effect in the copolymerization might be attributed to the higher coordination ability of LA than CL (Scheme 1b).[18−20] Whatever the reason, however, it is a fact that LA is preferentially incorporated into the copolymer when conventional catalysts are used, and reducing the reactivity of LA is a straightforward strategy for reducing the reactivity of LA in the random copolymerization. In the present system, the bulky substituents (R) strongly disturb the coordination of LA to the Al center, resulting in a decrease in the rate of incorporation of LA into the copolymer (Scheme 1c), but the bulky R groups showed less effect on the smaller CL.

Scheme 1. Plausible Mechanistic Illustrations



In conclusion, the designed homosalen−Al catalyst bearing *i*Pr$_3$Si groups allowed the controlled random copolymerization of CL with LA from a feedstock having CL/LA = 1. To the best of our knowledge, this is the first successful controlled random copolymerization of CL with LA using a designed catalyst. Because of the success of the practically random copolymerization using complex **2**, this system might be expanded to the synthesis of various monomer ratios of poly(CL-*stat*-LA) with no or little gradient in the monomer distribution of each copolymer molecule. Such studies aiming at an ideal copolymerization are now in progress in our laboratory.

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Supporting Information Available: Experimental details, homopolymerization of CL or LA using complex **2**, determination of r_{CL} and r_{LA}, the multistep mechanism of CL polymerization, and a DSC trace for poly(CL-*ran*-LA). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) $r_{LA} = k_{LA-LA}/k_{LA-CL}$ and $r_{CL} = k_{CL-CL}/k_{CL-LA}$, where k_{X-Y} is the rate constant for the addition of monomer Y to the chain end of the monomer X moiety.
(9) (a) Florcza and Duda recently reported another sophisticated approach using a chiral Al complex to adjust the reactivity of CL and L-lactide, but their chiral system is not applicable to the copolymerization using LA. See: Florcza, M.; Duda, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9088. Comprehensive references for the copolymerization of CL with LA are listed therein. Also see ref 4. (b) Duda, A.; Biela, T.; Libiszowski, J.; Penczek, S.; Dubois, P.; Mecerreyes, D.; Jérôme, R. *Polym. Degrad. Stab.* **1998**, *59*, 215.
(10) For $r_{CL} = r_{LA} = 1$, the rate constants for propagation and cross-addition are equal, and the insertion of the monomeric units in the copolymer occurs randomly (see: Gnanou, Y.; Fontanille, M. *Organic and Physical Chemistry of Polymers*; John Wiley & Sons: Hoboken, NJ, 2008; Chapter 8.5.11). As a result, $L_{CL} = L_{LA} = 2$. Caution should be exercised that $L_{CL} = L_{LA} = 2$ for the copolymer does not indicate the randomness, as shown in Table 1 for complex **1**.
(11) See the Supporting Information.
(12) $r_{CL} = 1.0_8$, $r_{LA} = 2.6$, and $r_{CL}r_{LA} = 2.8$ by the NLLS method.
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(14) The DSC measurement on the obtained random copolymer showed a distinct T_g at −16 °C, which was close to the T_g value of −13 °C for the random copolymer expected on the basis of the empirical relations of the Fox equation (see Chapter 11.2 of ref 10). No melting temperature was observed.
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(20) Even if the Lewis basicity of each carboxyl group of CL and LA is the same, LA has the double potential for coordination with the catalyst because each LA molecule has two carboxyl groups.

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