Journal of Applied Polymer Science

Copolymerization and terpolymerization of glycolide with lactones by dimethyl(salicylaldiminato)aluminum compounds

Tiziana Fuoco,[1]* Angelo Meduri,[2]* Marina Lamberti,[3] Claudio Pellecchia,[1] Daniela Pappalardo[2]

[1]Dipartimento di Chimica e Biologia, Università di Salerno, Fisciano, Italy

[2]Dipartimento di Scienze e Tecnologie, Università del Sannio, Benevento, Italy

[3]Dipartimento di Fisica "E. Caianiello", Università di Salerno, Fisciano, Italy

*These authors equally contributed to this article.

Correspondence to: D. Pappalardo (E-mail: pappalardo@unisannio.it)

ABSTRACT: The aliphatic poly(esters) are the most common biodegradable and biocompatible synthetic materials used by far for diverse biomedical applications. Co-polymers and ter-polymers of glycolide with ε-caprolactone and lactide are produced in the presence of dimethyl aluminum compounds, bearing salicylaldiminato bidentate ligands differing for the steric hindrance on the ortho position of the phenolato ring. The formation of random poly[glycolide-*co*-(ε-caprolactone)] samples is favored with more encumbered catalyst. Transesterification reactions of the second mode also contribute to randomize the structure. Copolymers from semicrystalline to amorphous are produced by decreasing the glycolide/ε-caprolactone feed ratio. The terpolymerization of glycolide with ε-caprolactone and *rac*-lactide with the same catalysts affords amorphous and random poly[(glycolide-*co*-lactide-*co*-(ε-caprolactone)] samples. The incorporation of the monomers is in this case determined by the bulkiness of the catalysts and by the higher coordination ability of the cyclic diesters. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 42567.

KEYWORDS: polyesters; ring-opening polymerization; synthesis

Received 15 May 2015; accepted 27 May 2015

DOI: 10.1002/app.42567

INTRODUCTION

Aliphatic polyesters such as poly(glycolide) (PGA), poly(lactide) (PLA), poly(caprolactone) (PCL), and their copolymers are sustainable materials whose biocompatibility and bioresorption properties are highly desirable features for a wide range of medical applications from drug delivery systems to surgical implants and tissue engineering. The ring-opening polymerization (ROP) by designed metal complexes of cyclic esters, such as glycolide (GA), lactide (LA), and ε-caprolactone (Cap), represents the best method to obtain such materials.[1–4]

In particular, PGA is a very promising polymer, but it is hydrolytically unstable, hardly processable, and too brittle for many applications.[1–4] Modification of its physical and chemical properties can be obtained by the incorporation of an appropriate comonomer into the PGA chains. The use of LA as comonomer represented the common choice and produced the well-known poly(lactide-*co*-glycolide) (PLGA) copolymers, by far the most widely used biodegradable materials in packaging, textile and surgical fibers, drug delivery systems, and stem cell scaffoldings.[5–8]

On the other hand, Cap has been less used as comonomer, although it could impart different hydrophilicity, elasticity, solubility, crystallization, and degradation rates. Indeed, copolymers of GA and Cap could allow a broad variation of properties for the final obtained poly[glycolide-*co*-(ε-caprolactone)] (PGCA) materials.[9–16] In turn, the incorporation of Cap into PLGA chains, resulting in poly[(glycolide-*co*-lactide-*co*-(ε-caprolactone)] (PGLC) terpolymer,[17–20] has been also found to be beneficial for the application of these materials in drug delivery and tissue engineering.[21–24]

Currently, the most used initiator for the homopolymerization and copolymerization of GA is Sn octoate.[1–3] However, the search for novel catalysts active in the ROP of lactones and LAs is a field of increasing interest, involving both academic and industrial research. Indeed, other catalysts and initiators have been reported to be active for the target reactions. In the case of PGCAs, initiators based on Fe, Al, Zn,[9] Zr,[11,14,19] Ca,[12] Mg,[16] and Bi[25–27] were reported. Notably, $FeCl_3$ and zirconium acetylacetonate yielded random copolymers having length of glycolidyl blocks (L_{GG}) close to 2, although at long reaction times ($t \geq 44$ h).[9,14]

Additional Supporting Information may be found in the online version of this article.

On the other side, in the case of PGLCs, besides Sn octoate, only two other catalysts are reported, namely zirconium acetylacetonate[19,28] and bismuth subsalicylate,[20] with the former leading to random terpolymers. Moreover, sequence-defined PGCAs and PGLCs were also obtained by step-growth condensation of "ad hoc" synthesized building blocks.[29]

Recently, we have described dimethyl(salicylaldiminato)aluminum compounds as efficient and versatile initiators in the homopolymerization and copolymerization of Cap and LA,[30] and of GA and LA to random or block copolymers, depending on the reaction conditions.[8] The same initiators were also efficient catalysts in the polymerization of a large ring size lactone.[31] Notably, this class of catalyst was described in the ROP of various cyclic esters.[32–37]

As an extension of these studies, we evaluated the dimethyl(salicylaldiminato)aluminum compounds **1–3**, depicted in Chart 1, in the GA/Cap and in the GA/*rac*-lactide/Cap copolymerizations. The results of these studies are described and discussed herein.

EXPERIMENTAL

General Procedures

Moisture and air-sensitive materials were manipulated under nitrogen using Schlenk techniques or a MBraun Labmaster glovebox. Before use, glassware was dried overnight in an oven at 120°C and solvents were refluxed over a drying agent and distilled under nitrogen: toluene and methanol (Sigma-Aldrich) over Na; tetrahydrofuran (THF) (Delchimica) over Na/benzophenone. Monomers (Sigma-Aldrich) were purified prior to use: GA was recrystallized from THF; Cap was distilled under vacuum on CaH_2 and stored over 4 Å molecular sieves; *rac*-lactide was dried *in vacuo* with P_2O_5 for 72 h, and afterward stored at −20°C in glovebox. Deuterated dimethyl sulfoxide (DMSO-d_6) was stored and used in agreement with the recommendations by the producer (Eurisotop). Complexes **1–3** were synthesized according to the literature methodologies.[8,38] All other reagents and solvents were commercially available and used without further purification for synthetic and spectroscopic purposes.

Instruments and Measurements

Nuclear magnetic resonance (NMR) spectroscopic analysis of polymers were performed in DMSO-d_6 at 100°C on a Bruker Avance 300 spectrometer (^{1}H: 300.13 MHz; ^{13}C: 75.47 MHz). The resonances are reported in ppm (δ) and coupling constants in Hz (J), and they were referenced to the residual solvent peak vs. $Si(CH_3)_4$: at δ 2.50 (^{1}H) and δ 39.5 (^{13}C). All spectra recording was performed on Bruker TopSpin v2.1 software. Data processing was performed on TopSpin v2.1 or MestReNova v6.0.2 software.

Molecular weights (M_n and M_w) and molecular-weight dispersities (M_w/M_n) were measured by gel permeation chromatography (GPC). The measurements were performed at 30°C on a Waters 1525 binary system equipped with a Waters 2414 Refractive Index (RI) detector and a Waters 2487 Dual λ Absorbtion (UV, λ_{abs} = 220 nm) detector, using THF as eluent (1.0 mL min^{-1}) and employing a system of four Styragel HR columns (7.8 x 300 mm; range 10^3−10^6 Å). Narrow polystyrene standards were used as reference and Waters Breeze v3.30 software for data processing.

Glass transition temperatures (T_g), melting points (T_m), and enthalpy of fusion (ΔH_m) of the (co)polymers were measured by differential scanning calorimetry (DSC) using aluminum pans and either a DSC 2920 or a DSC Q20 TA Instruments, calibrated with indium. Measurements were performed in nitrogen flow with a heating and cooling rate of 10°C min^{-1} in the range of −60 to +260°C. The data were processed with TA Universal Analysis v2.3C or Universal Analysis 2000 v4.7A softwares and are reported for the second heating cycle.

Copolymerization of Glycolide and ε−Caprolactone

In a typical copolymerization run, a screw vial (20 mL) was charged sequentially with monomers (total amount = 2.50 mmol), precatalyst (12 μmol), and MeOH (0.12 mL of a 0.1 *M* toluene solution; 12 μmol). The vial was put into an oil bath, preheated and thermostated at 140°C, and was magnetically stirred. After 75 min, product isolation was attained by dissolving the reaction mixture in CH_2Cl_2 and by dropwise pouring this solution into rapidly stirring methanol. Precipitated polymer was recovered by filtration, washed with methanol, and dried at 60°C in vacuum oven overnight.

Poly[(glycolide)-*co*-(ε−caprolactone)] = ^{1}H NMR (300 MHz, DMSO-d_6, 100°C) δ 4.87 (s, 2H; —C(O)OCH_2—; GGGG), 4.85 (s, 2H; —C(O)OCH_2—; CapGGGG and GGGGCap), 4.83 (s, 2H; —C(O)OCH_2—; CapGGGCap), 4.75 (s, 2H; —C(O)OCH_2—; GGGGCap), 4.73 (s, 2H; —C(O)OCH_2—; CapGGGG and CapGGGCap), 4.71 (s, 2H; —C(O)OCH_2—; CapGGCap), 4.61 (s, 2H; —C(O)OCH_2; CapGCap), 4.13 (m, 2H; —C(O)OCH_2—; CapG), 4.02 (t, J = 6.6 Hz, 2H; —C(O)OCH_2—; CapCap), 3.71 (s, 3H; CH_3O-GG), 3.70 (s, 3H; CH_3O-GGCap), 3.605 (s, 3H; CH_3O-Cap), 3.42 (t, J = 6.4 Hz, 3H; Cap-OH), 2.39 (m, 2H; —CH_2CO—; CapG), 2.28 (m, 2H; —CH_2CO—; CapCap), 1.60 (m, 4H; —C$H_2$$CH_2$CO— and —C(O)OC$H_2CH_2$—), 1.37 (m, 2H; —C(O)O($CH_2$)$_2CH_2$($CH_2$)$_2$CO—).

^{13}C NMR (75 MHz, DMSO-d_6, 100°C) δ 172.0 (—C(O)O—; CapCap), 171.6 (—C(O)O—; CapGCap), 171.4 (—C(O)O—; CapGG), 167.0 (—C(O)O—; CapGCap), 166.7 (—C(O)O—; CapGGCap), 166.6 (—C(O)O—; CapGGGG), 166.4 (—C(O)O—; CapGGGCap), 166.3 (—C(O)O—; GGGGCap), 166.05 (—C(O)O—; CapGGGCap), 166.0 (—C(O)O—; CapGGGG), 165.95 (—C(O)O—; GGGGCap), 165.9 (—C(O)O—; GGGG), 64.2 (—C(O)OCH_2—; GGCap), 64.15 (—C(O)OCH_2—; GGCap), 64.0 (—C(O)OCH_2—; CapGCap), 62.9 (—C(O)OCH_2—; CapCap), 60.7 (—C(O)OCH_2—; CapGGGCap), 60.6 (—C(O)OCH_2—; CapGGGG), 60.3(—C(O)OCH_2—; GGGGG), 60.1 (—C(O)OCH_2—; GGGGCap), 60.0 (—C(O)OCH_2—; CapGCap), 59.55 (—C(O)OCH_2—; GGCap); 33.0 (—CH_2CO—; CapCap), 32.95 (—CH_2CO—; CapGG), 32.5 (—CH_2CO—; CapGCap), 32.5 (—CH_2CO—; CapGG), 32.45 (—CH_2CO—; CapGG); 27.3 (—C(O)OC$H_2$$CH_2$—; CapCap), 27.3 (—C(O)OC$H_2$$CH_2$—; CapGG), 27.15 (—C(O)OC$H_2$$CH_2$—; CapGCap), 27.1 (—C(O)OC$H_2$$CH_2$—; CapGG), 27.05 (—C(O)OC$H_2$$CH_2$—; CapGG); 24.4 (—$CH_2$$CH_2$CO—; CapCap), 24.3 (—$CH_2$$CH_2$CO—; CapGCap), 24.25 (—$CH_2$$CH_2$CO—; CapGG), 24.1 (—$CH_2$$CH_2$CO—; CapGG); 23.5 (—C(O)O(CH_2)$_2$$CH_2$($CH_2$)$_2$CO—; CapCap), 23.45 (—C(O)O (CH_2)$_2$$CH_2$($CH_2$)$_2$CO—;

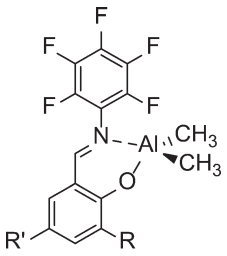
CapGCap), 23.4 (—C(O)O(CH_2)$_2$ CH_2(CH_2)$_2$CO—; CapGCap), 23.35 (—C(O)O(CH_2)$_2$$CH_2$($CH_2$)$_2$ CO—; CapGG), 23.3 (—C(O)O (CH_2)$_2$$CH_2$($CH_2$)$_2$CO—; CapGG).

Terpolymerization of Glycolide, Rac−Lactide, and ε−Caprolactone

In a typical terpolymerization run, a screw vial (20 mL) was charged sequentially with monomers (total amount = 2.50 mmol), precatalyst (25 μmol), and MeOH (0.25 mL of a 0.1 *M* toluene solution; 25 μmol). The vial was put into an oil bath, preheated and thermostated at 140°C, and was magnetically stirred. After 75 min, workup was performed as described above.

Poly[(glycolide)-*co*-(*rac*-lactide)-*co*-(ε-caprolactone)] = ^{1}H NMR (300 MHz, DMSO-d_6, 100°C) δ 5.32—5.17 (m, 1H; —C(O)OC*H*(CH_3)—; LLLL) 5.17—5.05 (m, 1H; —C(O) OC*H*(CH_3)—; LLGG+LLCap+CapLL+GGLL); 4.88 (s, 2H; —C(O)OCH_2—; GGGG), 4.86 (s, 2H; —C(O)OCH_2—; CapGGGG and GGGGCap), 4.85 (s, 2H; —C(O)OCH_2—; GGL and LGG); 4.84 (s, 2H; —C(O)OCH_2—; CapGGGCap), 4.83 (s, 2H; —C(O)OCH_2—; LGL); 4.75 (s, 2H; —C(O)OCH_2—; GGGGCap), 4.73 (s, 2H; —C(O)OCH_2—; CapGGGG and CapGGGCap), 4.71 (s, 2H; —C(O)OCH_2—; CapGGCap), 4.61 (s, 2H; —C(O)OCH_2; CapGCap), 4.20—4.07 (m, 2H; —C(O)OCH_2—; CapG and CapL), 4.03 (t, *J* = 6.6 Hz, 2H; —C(O)OCH_2—; CapCap), 3.71 (s, 3H; CH_3O-GG), 3.69 (s, 3H; CH_3O-LL), 3.61 (s, 3H; CH_3O-Cap), 3.42 (t, *J* = 6.4 Hz, 3H; Cap-OH), 2.43—2.32 (m, 2H; —CH_2CO—; CapG), 2.28 (t, *J* = 7.3 Hz; 2H; —CH_2CO—; CapCap), 1.75—1.55 (m, 4H; —C*H*$_2$$CH_2$CO—, —C(O)O$CH_2$C*H*$_2$— and —CH(C*H*$_3$)—), 1.45—1.20 (m, 2H; —C(O)O(CH_2)$_2$C*H*$_2$(CH_2)$_2$CO—).

^{13}C NMR (75 MHz, DMSO-d_6, 100°C) δ 172.0 (—C(O)O—; CapCap), 171.6 (—C(O)O—; CapGCap), 171.4 (—C(O)O—; CapGG+CapLL), 169.0 and 168.95 (—C(O)O—; CapLL+LLCap), 168.4 (—C(O)O—; LLGG), 168.3 (—C(O)O—; LLLL), 168.25 (—C(O)O—; GLG), 168.20 and 168.1 (—C(O)O—; LLLL), 167.0 (—C(O)O—; CapGCap), 166.6 (—C(O)O—; CapGGGG), 166.5 (—C(O)O—; CapGGGCap), 166.4, 166.3 and 166.0 (—C(O)O—; GGGGCap), 165.85 (—C(O)O—; GGGG), 165.8 and 165.7 (—C(O)O—; GGLL), 68.7, 68.5, 68.45, 68.4, 68.35, 68.3, 68.2, 68.0, 67.4, 67.3, and 67.25 (—C*H*(CH_3)—), 64.7, 64.3, 64.2, 63.95, 63.9 and 62.9 (—C*H*$_2$OC(O)—; Cap), 60.7, 60.6, 60.55, 60.3, 60.25, 60.2, 60.1, 60.0, 59.6, 59.5, 59.4, 59.2, 59.15, 59.1 (—C*H*$_2$OC(O)—; G), 32.95, 32.6, 32.5, 32.4, 27.3, 27.25, 27.2, 27.1, 27.05, 24.4, 24.3, 24.25, 24.2, 24.1, 23.5, 23.45, 23.4, 23.35, and 23.3 (—C*H*$_2$—; Cap), 15.85, 15.8, 15.7 (—CH_3).



1: R = R' = H
2: R = ^{t}Bu ; R' = H
3: R = R' = cumyl

Chart 1. Dimethyl(salicylaldiminato)aluminum compounds **1–3**.

Table I. Copolymerization of Glycolide and ε-Caprolactone in Bulk at 140°C[a]

Run	Catalyst	f_{GA}[b]	Yield (%)	F_{GA}[c]	L_{GG}[d]	L_{Cap}[d]	T_{II}[e]
1	**1**	70	85	57 (77[f])	2.01	1.52	0.66
2	**1**	50	83	40	1.15	1.73	0.86
3	**1**	30	87	32	0.76	1.62	0.97
4	**2**	70	94	62 (73[f])	2.66	1.63	0.20
5	**2**	50	76	50	1.90	1.90	0.31
5bis[g]	**2**	50	96	50	1.55	1.56	0.75
6	**2**	30	90	28	0.81	2.07	2.11
7	**3**	70	82	70 (80[f])	3.36	1.44	0.14
8	**3**	50	93	52	1.65	1.52	0.36
9	**3**	30	82	24	0.63	2.01	0.90
10[h]	**2**	33	96	33	1.02	2.08	1.43

[a] Polymerization conditions: precatalyst = 12 μmol; MeOH = 12 μmol (0.12 mL of a 0.1 *M* toluene solution); *T* = 140°C; *t* = 75 min; mol ratio of monomers to precatalyst in the feed = 200.
[b] f_{GA}, molar percentage of glycolide in the feed.
[c] F_{GA}, content of glycolide (% mol) in the copolymer, as determined by ^{1}H NMR (DMSO-d_6, 100°C).
[d] Average length of glycolidyl (GG) and caproyl (Cap) blocks in the copolymer; calculated from ^{1}H NMR (DMSO-d_6. 100°C).
[e] Yield of the second mode of transesterification (% CapGCap) of the glycolidyl sequences; calculated from ^{1}H NMR (DMSO-d_6, 100°C).
[f] Calculated from ^{1}H NMR ($CDCl_3$/TFA 1/1, RT) data of monomers conversion. TFA = 2,2,2-trifluoroacetic acid.
[g] Same conditions as run 5, but *t* = 150 min.
[h] Polymerization conditions: precatalyst = 25 μmol; MeOH = 25 μmol; *T* = 140°C; *t* = 7 h; mol ratio of monomers to precatalyst in the feed = 900.

RESULTS AND DISCUSSION

Copolymerization of Glycolide and ε-Caprolactone

The aluminum complexes **1–3**, bearing bidentate ligands differing for the steric hindrance on the ortho position of the phenolato ring (Chart 1), were synthesized according to the literature methodologies,[8,38] and were tested as precatalysts in the ring-opening copolymerization of GA and Cap under different reaction conditions in the presence of one equivalent of methanol.

A first catalytic screening was performed in bulk at 90°C (see Table S1, in Supporting Information). The ^{1}H NMR analysis showed that, under these reaction conditions, complete conversion of monomers was not attained and GA was preferentially incorporated into the final product. This result is in line with the literature data regarding the ROP of glycolide and Cap at temperature values below 100°C.[9,11] When the polymerization runs were performed at higher temperature (140°C), almost complete conversion of both monomers was obtained within 75 min with all

Table II. Molecular Weight and Molecular-Weight Dispersities of the Copolymer Samples of Glycolide and ε-Caprolactone Obtained in Bulk at 140°C[a]

Run	Catalyst	F_{GA}[b]	$M_{n,th}$ (kDa)[c]	$M_{n,NMR}$ (kDa)[d]	M_n/M_w[e]
1	**1**	57	19.6	23.2	-
2	**1**	40	19.1	20.3	-
3	**1**	32	20.8	22.1	1.6
4	**2**	62	21.7	n.d.	-
5	**2**	50	17.4	19.6	-
6	**2**	28	20.8	25.5	1.6
7	**3**	70	19.0	22.3	-
8	**3**	52	21.4	20.4	-
9	**3**	24	19.6	18.5	1.3
10[f]	**2**	33	98.5	n.d.	1.4
11[g]	**1**	49	9.3	10.2	-
12[g]	**3**	45	10.5	12.6	-

[a] Polymerization conditions: precatalyst = 12 μmol; MeOH = 12 μmol (0.12 mL of a 0.1 *M* toluene solution); T = 140°C; t = 75 min; mol ratio of monomers to precatalyst in the feed = 200.
[b] F_{GA}, content of glycolide in the copolymer (mol %), as determined by ^{1}H NMR (DMSO-d_6, 100°C).
[c] Theoretical molecular weight.
[d] Molecular weight determined by ^{1}H NMR (DMSO-d_6, 100°C).
[e] Molecular-weight masses dispersities determined by GPC (THF, 35°C) vs. polystyrene standards.
[f] Polymerization conditions: precatalyst = 25 μmol; MeOH = 25 μmol; T = 140°C; t = 7 h; mol ratio of monomers to precatalyst in the feed = 900; $M_{n,GPC}$ = 89.3 kDa.
[g] Precatalyst = 25 μmol; MeOH = 25 μmol (0.25 mL of a 0.1 *M* toluene solution); mol ratio of monomers to precatalyst in the feed = 100.

the catalysts (Tables I and S2). The polymeric materials were characterized by ^{1}H (Supporting Information Figure S1) and ^{13}C NMR (Supporting Information Figure S2), GPC, and DSC analysis. The main results are reported in Tables (I–III).

Characterization of the polymers microstructure was attained by ^{1}H NMR analysis according to the literature.[11] The increase in reaction temperature resulted in a significant alteration of the PGCA microstructure, in line with the previous findings.[14]

In Figure 1, the methylene regions of the ^{1}H NMR spectra of the PGCAs obtained with initiator **3** at different composition are reported. The signals (1–7) in the GA methylene region were attributed to one homosequence and eight different heterosequences (*vide infra*); the two triplets in the caprolactone ε-methylene region were attributed to two diads (one homosequence and one heterosequence).

The copolymers compositions were evaluated by these data. The solubility of PGCAs having high amount of glycolide is very poor, even in highly polar solvents such as trifluoroacetic acid. Therefore, when the monomer feed is 70% in glycolide, the NMR analysis highlights a glycolide content lower than expected, whereas the glycolide content calculated from conversions data is more in line with the feed, thus evidencing the presence of an insoluble fraction. The average lengths of glycolidyl (GG) and caproyl (Cap) blocks (namely L_{GG} and L_{Cap}, respectively) of the copolymers obtained with catalysts **1–3** were also calculated from ^{1}H NMR data, according to the literature formulas.[39] Confirmation of the GA lengths was achieved by using as control the monomers composition ratio (F_{GA}/F_{Cap}).[11] Nicely, glycolidyl block lengths linearly increase by increasing the incorporation of GA into the copolymer (Figure 2).

While for any given feed composition the L_{Cap} values do not differ significantly, being in the range of 1.44–2.07, the L_{GG} glycolidyl blocks lengths vary depending both on the feed and on the catalyst. When the feed is enriched in Cap (f_{GA} = 30), the GA content in the copolymer slightly decreases by increasing the steric bulk on the catalyst. The L_{GG} values are lower than 1 for all the catalysts, indicating the cleavage of the glycolidyl blocks into glycolyl units, as also observed with other catalysts.[11,19] This behavior is clearly shown in the ^{1}H NMR spectra

Table III. Copolymerization of Glycolide and ε-Caprolactone: Thermal Properties[a]

Run	Catalyst	F_{GA}[b]	$T_{g,th}$ (°C)[c]	T_g (°C)[d]	T_m (°C)[d]	ΔH (J g^{-1})[d]
1	**1**	77[e]	−1.7	-	209.1	42.0
2	**1**	40	−33.1	−41.1	202.4	23.8
3	**1**	32	−38.9	−40.8	-	-
4	**2**	73[e]	−5.5	-	201.4	35.2
5	**2**	50	−25.3	−34.8	173.7	15.7
6	**2**	28	−41.8	−44.4	-	-
7	**3**	80[e]	1.2	-	204.2	48.0
8	**3**	52	−23.7	−24.4	185.9	8.2
9	**3**	24	−44.6	−46.2	-	-

[a] Polymerization conditions: precatalyst = 12 μmol; MeOH = 12 μmol (0.12 mL of a 0.1 *M* toluene solution); T = 140°C; t = 75 min; mol ratio of monomers to precatalyst in the feed = 200.
[b] F_{GA} content of glycolide in the copolymer (mol %), as determined by ^{1}H NMR (DMSO-d_6, 100°C).
[c] Theoretical values, as calculated with the Fox equation, using the following T_g values for the homopolymers: poly(CL) = -60°C;[41] poly(GA) = 22.0°C.[42]
[d] Values reported for the second heating cycle.
[e] Calculated from ^{1}H NMR ($CDCl_3$/TFA 1/1, RT) data of monomers conversion.

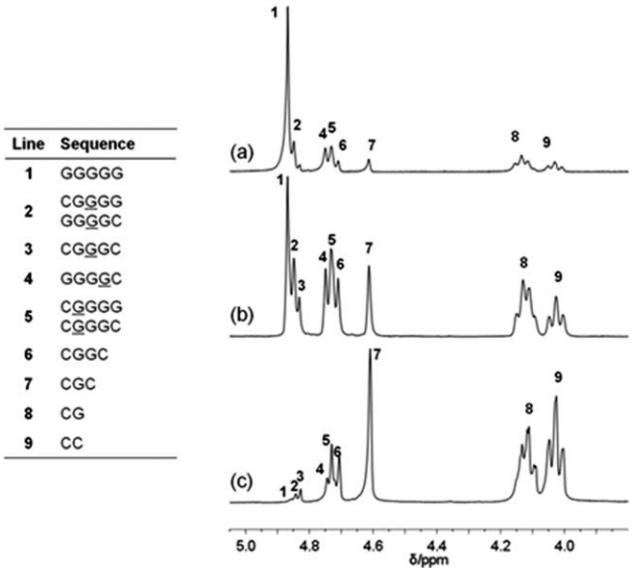


Figure 1. ^{1}H NMR (300 MHz, DMSO-d_6, 100°C) spectra in the methylene region of PGCA copolymers obtained with complex **3**: (a) $F_{GA} = 70$ (Table I, run 7), (b) $F_{GA} = 52$ (Table I, run 8), (c) $F_{GA} = 24$ (Table I, run 9).

of Figure 1. While for the $f_{GA}70$ copolymers (Figure 1a) there is the predominance of the GGGGG pentad (line 1), for the $f_{GA}30$ copolymers (Figure 1c) this pentad is almost completely absent in favor of the CapGCap line (line 7). The latter cannot be formed by the ROP of GA, but can derive from a transesterification reaction of the second mode, involving the attack of an active ε-caproyl chain end on the preformed -CapGG- sequence.[9] The yield of this transesterification process, T_{II}, was calculated by using literature formula.[14]

At $f_{GA} = 50$, catalyst **1** incorporates only 40% of the GA into the polymeric chains, while catalysts **2** and **3** have similar values of F_{GA} (50 and 52) and T_{II} (0.31 and 0.36). The L_{GG} values are below 2 (1.15–1.90), indicating random materials and the presence of CapGCap sequences. A polymerization test was performed in identical conditions of run 5, but increasing the polymerization time, to allow the system to reach almost full conversion (run 5bis). An increase of the transesterification yield was noticed, while the L_{GG} and L_{Cap} decrease and become close to 1.5.

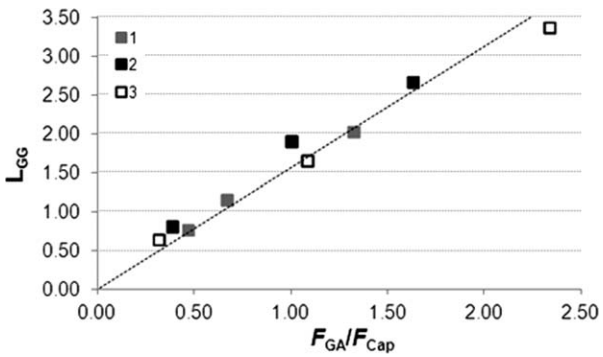


Figure 2. Plot of average length of glycolidyl (L_{GG}) blocks vs. copolymer composition (F_{GA}/F_{Cap}) for the copolymers obtained with catalysts **1–3** at 140°C (Table I, runs 1–9).

When the feed is enriched in GA ($f_{GA} = 70$), the polymeric samples are not completely soluble. Thus, the NMR analysis takes into account only the soluble fraction.

A copolymerization test was performed by increasing the monomers/Al molar ratio to 900/1 (run 10). Higher *M*n was obtained (*vide ultra*), while no significant effect on the polymer microstructure was noticed, thus proving the ability of the catalytic systems to produce high molecular weight polymers.

To get more insight on the origin of the copolymer microstructure, the analysis of end groups of the obtained materials was carried out by ^{1}H NMR in DMSO-d_6 at 100°C (Figure 3). The resonances were assigned by comparison with the spectra of the homopolymer samples. The three singlets at 3.71, 3.70, and 3.60 ppm were attributed to the GGGG-OCH_3 (**a**), CapGG-OCH_3 (**d**), and Cap-OCH_3 (**b**) end groups, respectively, generated by the insertion of the monomer into the Al-OCH_3 bond, formed by the reaction of the aluminum dimethyl complex with methanol. The relative abundance of the signals suggests a predominance of the GA insertion with respect to the Cap insertion. The triplet at 3.42 ppm is attributed to the hydroxyl end group bound to a caproyl unit HOCap- (c), and it is

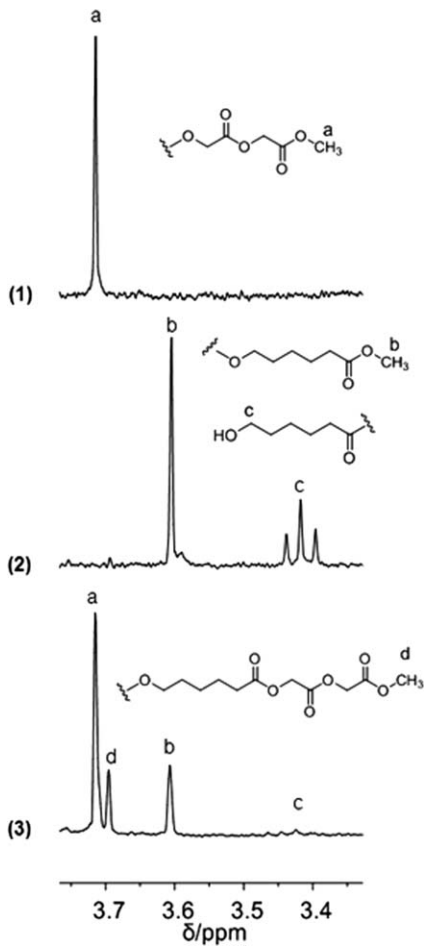


Figure 3. End-group analysis: ^{1}H NMR (300 MHz, DMSO-d_6, 100°C) spectra of: (1) poly(glycolide); (2) poly(ε-caprolactone) (Supporting Information Table S1, run 1); (3) poly(glycolide-*co*-ε-caprolactone) (Table I, run 5).

generated by the hydrolysis of the polymeric chain. The hydroxyl end group of the GA-capped polymeric chains (HOGG-), which is expected at 4.13 ppm,[8] could not be identified, since it may be overlapped with the signal of Cap heterosequences.

The above data, together with the analysis of the copolymer microstructure, provides a clear picture of the polymerization reaction: the first reaction steps privilege the insertion of the GA into the Al-OCH_3 bond, ensued by the formation of a predominantly GA block which allow ε-caprolactone insertion by transesterification processes, i.e., insertion of a caproyl chain end on preformed glycolidyl sequences. This picture is corroborated by the end-group analysis, that confirms the more readily pathway of the GA insertion into the Al-OCH_3; the ε-caproyl block lengths, that remain overall unaltered at any given feed ratio; the CapGCap transesterification yield, that increases by increasing the ε-caprolactone content and/or the reaction time.

Interestingly, the behavior of the catalysts **1–3** shows some differences. Information on this issue can be retrieved from the end-group analysis of the copolymers obtained at different feed ratio of the two monomers (see Figures S3 and S4 in Supporting Information). Notably, the comparison of the intensity of peaks **a** (relative to the GGGG-OCH_3 end group) and **d** (relative to the CapGG-OCH_3 end group) for the polymerization runs carried out with the different catalysts at the same feed ratio is indicative of the second insertion after the GA first insertion, and could be a representation of the relative rate of the two monomers during the polymer propagation steps. In particular, the ratio **d/a** increases from catalyst **1** to catalyst **3,** indicating that increasing the steric hindrance of the catalyst, the insertion rate of the GA monomer decreases. As a result, for the most encumbered catalyst **3**, the insertion rates of the two monomers are closer than for the other catalysts. As a fact, signals **d** and **a** result of comparable intensities in the NMR spectrum of the copolymer obtained with complex **3** starting from an equimolar mixture of the feed (f_{GA} 50) (see Supporting Information). Remarkably, this observation indicates that with catalyst **3** the two monomers have very similar propagation rates, which is a required condition to get random copolymers.

The molecular weights for the polymers were evaluated by gel permeation chromatography (GPC) and by NMR in solution, being known the polymer end groups determined by NMR. Representative results are reported in Table II.

As a consequence of the low solubility of PGCAs having high amount of GA. GPC analysis was allowed only for the copolymers with a high content of Cap (Table II, runs 3, 6, 9, and 10) soluble in THF. In these cases, the GPC evidenced monomodal distribution with dispersities in the range 1.3–1.6. The catalytic system is also able to produce high molecular weight polymers (Table II, run 10).

As highlighted by Meyer *et al.*, since the radius of gyration R_g of the GA-based copolymers is extremely sequence and solvent dependent, the GPC analysis is not reliable for the determination of their M_n,[40] while the NMR analysis is more reliable. Indeed, a good agreement between the molecular weights evaluated by NMR, $M_{n,NMR}$, and the theoretical molecular weights, $M_{n,th}$, calculated by the monomer/catalyst feed ratio was observed.

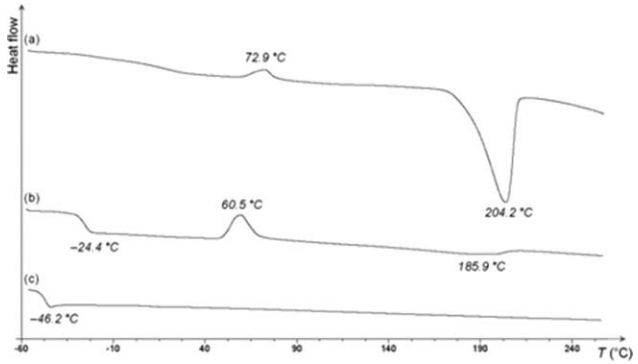


Figure 4. DSC thermograms (run II) of poly[glycolide-*co*-(ε-caprolactone)] obtained with complex **3**: (a) $F_{GA} = 70$ (Table I, run 7), (b) $F_{GA} = 52$ (Table I, run 8), and (c) $F_{GA} = 24$ (Table I, run 9).

Thermal Analysis

Thermal analysis of the copolymers was carried out by means of differential scanning calorimetry (DSC) from −60 to +260°C. The glass transition temperature, T_g, and the melting temperature, T_m, are given in Table III. Thermograms of polymeric samples are reported in Figure 4 and Supporting Information (Figures S5 and S6).

For the PCGAs with a GA content F_{GA} >50, a neat melting peak due to the GA homosequences is observable, evidencing semi-crystalline copolymers.

When the Cap content is increased (F_{GA} ~50), a glass transition peak is present in each thermogram. In particular, for the copolymer obtained with catalyst **3** the observed T_g is in perfect agreement with that calculated by Fox's equation for random copolymers, while the T_g values observed for the other two copolymers are lower than those calculated. A melting peak is observed in each case, although the results were affected by the more frequent GG-Cap junction points. Moreover, the heat of fusion decreases from catalyst **1** to catalyst **3** indicating the formation of a less crystalline copolymer in the last case.

Thus, the DSC results are in line with the previous speculations, confirming the higher propensity of complex **3**, with respect to catalyst **1** and **2**, to give random copolymers.

For copolymers with higher Cap content, no melting endotherm is observed for the GA blocks, as expected from the values of the average block lengths (L_{GG} <1) and from the high transesterification values (Table I). These observations confirm the picture of polymeric material where most of the GA units undergo G–G cleavage and glycolyl units are randomly distributed along with caproyl units, sometimes comprising –CapGG- blocks, as evidenced by ^{1}H NMR (Figure 1c). The experimental T_g of these copolymers reveal a nice match with the values predicted by the Fox equation: this is the first time that such a correlation is found for a poly(glycolide-*co*-caprolactone) synthesized by ROP.

Table IV. Terpolymerization of Glycolide, *Rac*−Lactide, and ε−Caprolactone[a]

Run	Catalyst	f_{GA}[b]	f_{LA}[b]	f_{CL}[b]	Yield (%)	F_{GA}[c]	F_{LA}[c]	F_{Cap}[c]	L_{GG}[d]	L_{LL}[d]	L_{Cap}[d]	T_{LGL}[e]	$T_{CapGCap}$[e]	T_{XLX}[e]
13	**1**	33	33	33	83	37	37	26	1.69	2.26	1.26	0.3	0.8	n.o.
14	**1**	20	40	40	74	24	46	30	1.36	1.92	1.33	0.3	0.7	n.o.
15[f]	**1**	20	20	60	90	18	16	66	0.85	0.95	1.91	0.2	0.9	0.1
16	**2**	33	33	33	85	41	24	35	1.40	1.66	1.28	0.4	0.7	n.o.
17	**3**	33	33	33	69	41	29	30	2.11	1.81	1.36	0.2	0.8	n.o.

[a] Polymerization reactions: precatalyst = 25 μmol; MeOH = 25 μmol (0.1 *M* in toluene); T = 140°C; t = 75 min; mol ratio of monomers to precatalyst in the feed = 100.
[b] Molar percentage of glycolide (f_{GA}), *rac*-lactide (f_{LA}), ε-caprolactone (f_{Cap}) in the feed.
[c] Molar percentage of glycolide (F_{GA}), *rac*-lactide (F_{LA}), ε-caprolactone (F_{Cap}) in the terpolymer, determined by ^{1}H NMR (DMSO-d_6, 100°C).
[d] Average block lenghts of glycolidyl (GG), lactidyl (LL) and caproyl (Cap) blocks in the terpolymer, determined by ^{1}H NMR (DMSO-d_6, 100°C).
[e] Second mode of transesterification (%) of glycolidyl (CapGCap, LGL) and lactidyl (XLX) sequences, determined by ^{1}H NMR (DMSO-d_6, 100°C).
[f] t = 150 min.

Terpolymerization of Glycolide, Rac−Lactide, and ε−Caprolactone

The complexes (**1–3**) were also tested as initiators in the terpolymerization of *rac*−lactide, GA, and ε−caprolactone. The obtained polymer samples were characterized by NMR spectroscopy (Figures S7 and S8), GPC, and DSC analysis. The results about composition and chain microstructural analysis are summarized in Table IV.

Polymerizations were carried out in bulk at 140°C in the presence of the selected catalyst and one equivalent of MeOH. The molar ratio of the comonomers to initiator was fixed at 100:1, and after 75 min of reaction, the polymeric samples were recovered in good yield (up to 85%) with all the used catalysts.

The chain microstructure of the terpolymers was studied by ^{1}H NMR analysis in the methylene and methine regions. The resonances were assigned according to the literature (Figure 5).[28] Selected regions of ^{1}H NMR spectra of the terpolymers samples for different compositions are shown in Figure 5. The calculation of average glycolidyl, L_{GG}, lactidyl, L_{LL}, and caproyl blocks, L_{Cap}, as well as the determination of contribution of sequences formed by transesterification of the second mode, was also obtained from the ^{1}H NMR analysis by using literature formulas.[19]

The chemical composition of the terpolymers was determined through the ratio of the integrated values of the methylene signal of the caproyl segment -O-CH_2-$(CH_2)_4$-C(O)- (Cap, centered at 4.00 ppm ca.), the methylene signal of the glycolyl segment -O-CH_2-C(O)- (G, centered at 4.80 ppm ca.), and the methine signal of the lactyl segment -O-CH(CH_3)-C(O)- (L, centered at 5.20 ppm ca.).

The effect of the catalyst was studied for equimolar amount of the three monomers (Table IV, runs 13, 16, 17). The effect of the monomers feed ratio was studied in the presence of complex **1** (Table IV, runs 13–15). The composition of the obtained polymeric samples was quite close to the feed in all the runs. Glycolide was generally more easily incorporated than the other monomers with all the catalysts. Notably, for equimolar amount

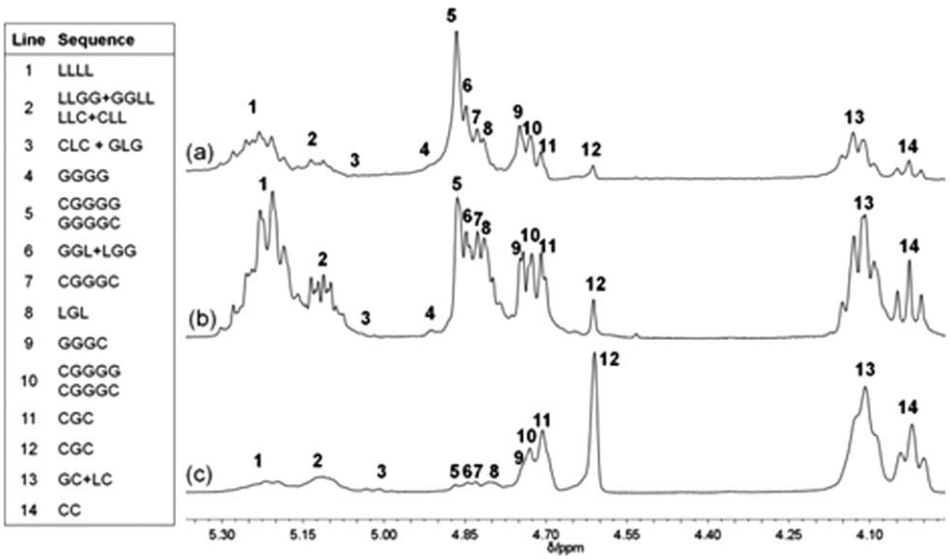


Figure 5. ^{1}H NMR (300 MHz, DMSO-d_6, 100°C) of poly[glycolide-*co*-(*rac*-lactide)-*co*-(ε-caprolactone)] obtained with complex **1**: (a) F_{GA} = 37; F_{LA} = 37; F_{Cap} = 26 (Table IV, run 13); (b) F_{GA} = 24; F_{LA} = 46; F_{Cap} = 30 (Table IV, run 14); (c) F_{GA} = 23; F_{LA} = 16; F_{Cap} = 61 (Table IV, run 15).

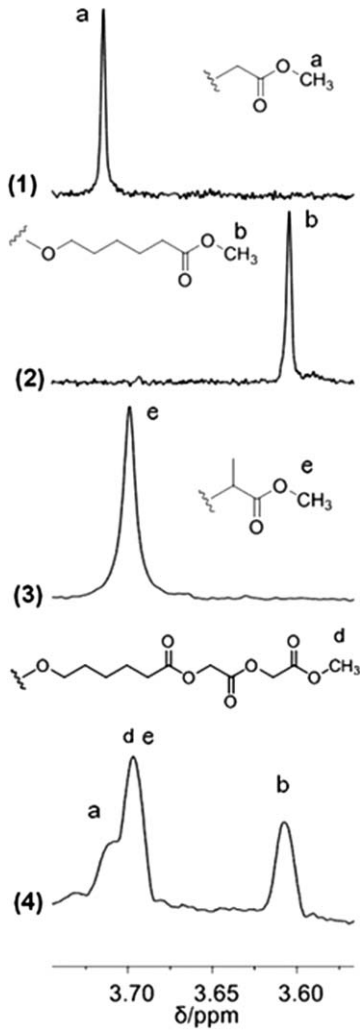


Figure 6. End-group analysis: ^{1}H NMR (300 MHz, DMSO-d_6, 100°C) spectra of: (1) polyglycolide; (2) poly(ε-caprolactone); (3) poly(*rac*-lactide); AND (4) poly[glycolide-*co*-(*rac*-lactide)-*co*-(ε-caprolactone)].

of the three monomers, the cyclic diesters (both GA and LA) were preferred incorporated with respect to ε-caprolactone with complex **1**. On the contrary, when complexes **2** and **3** were used, the composition of the terpolymers follows the order: $F_{GA} > F_{Cap} > F_{LA}$. Thus, with the bulkier catalysts **2** and **3**, while the GA is still the most incorporated monomer, the ε-caprolactone is preferentially incorporated than *rac*-lactide (Table IV, runs 13, 16, 17). This behavior should be explained on the basis of the bulkiness of the catalysts and of the higher coordination ability of the cyclic diesters with respect to that of the caprolactone. Thus, the less encumbered catalyst **1** preferentially incorporates the cyclic diesters with respect to ε-caprolactone. However, with the more hindered complexes **2** and **3**, the bulkier *rac*-lactide is disfavored, to the benefit of the less bulky and more flexible ε-caprolactone. A similar effect was reported by Nomura for the ε-caprolactone/LA copolymerization.[43]

The yield of transesterifications of the second mode, due to the attack of active chain end on the preformed segments, have been evaluated by using the coefficient T_{LGL}, $T_{CapGCap}$, T_{XLX} as previously reported (Table IV).[19] During the terpolymerization, the transesterification side reactions generated by the attack of active glycolidyl or caproyl chain ends on preformed lactidyl segments were absent or negligible (T_{XLX} higher value was 0.1 for run 15, Table IV). It is confirmed, therefore, the low tendency of this class of catalysts in breaking the lactidyl unit in two lactyl fragment.[8,30] The $T_{CapGCap}$ values, instead, are significantly higher, thus suggesting that the glycolidyl segment, GG, is quite completely broken by the attack of caproyl active chain end, as a result the GA is incorporated in CapGCap sequences along the polymeric chains. Coherently with this picture, Figure 5 shows that by increasing the amount of the ε-caprolactone, the CapGCap sequences increase and the GGGGG sequences decrease.

The ^{1}H NMR spectra showed also resonances attributable to the alkoxide -OCH_3 end groups. By comparison with the literature data, the signals due to the following end groups were recognized: -CH_2C(O)OCH_3 (G-OCH_3), -CH(CH_3)C(O)OCH_3 (L-OCH_3), and -$(CH_2)_4CH_2$C(O)OCH_3 (Cap-OCH_3, see Figure 6).

The presence of all the three signals indicates that the first step of these copolymerization reactions could be the insertion of all the three monomers into the Al-OCH_3 bond. However, the signals relative to the first insertion of LA on the Al-OCH_3 bond

Table V. Terpolymerization of Glycolide, *Rac*-Lactide and ε-Caprolactone: Analysis of Molecular Weights[a]

Run	Catalyst	C	F_{LA}[b]	F_{Cap}[b]	$M_{n,th}$ (kDa)[c]	$M_{n,NMR}$ (kDa)[d]	$M_{n,GPC}$ (kDa)[e]	M_w/M_n[e]
13	**1**	37	37	26	10.4	9.7	8.0	1.4
14	**1**	24	46	30	9.5	11.7	20.9	1.5
15[f]	**1**	18	16	66	10.9	20.2	27.0	1.4
16	**2**	41	24	35	10.5	11.0	21.9	1.7
17	**3**	41	29	30	8.5	7.4	16.4	1.5

[a] Polymerization conditions: precatalyst = 25 μmol; MeOH = 25 μmol (0.25 mL of a 0.1 *M* toluene solution); T = 140°C; t = 75 min; mol ratio of monomers to precatalyst in the feed =100.
[b] Content of glycolide (F_{GA}), *rac*-lactide (F_{LA}) and ε-caprolactone (F_{Cap}) in the terpolymer (mol %), as determined by ^{1}H NMR (DMSO-d_6, 100°C).
[c] Theoretical molecular weight.
[d] Molecular weight determined by ^{1}H NMR (DMSO-d_6, 100°C).
[e] Molecular weights and molecular-weight dispersivities determined by gel permeation chromatography (GPC) vs. polystyrene standards, elution solvent: tetrahydrofuran (THF).
[f] t = 150 min.

Table VI. Thermal Properties of Terpolymers[a]

Run	Catalyst	F_{GA}[b]	F_{LA}[b]	F_{Cap}[b]	$T_{g,th}$ (°C)[c]	T_g (°C)[d]
13	**1**	37	37	26	2.6	6.3
14	**1**	24	46	30	0.5	13.5
16	**2**	41	24	35	−8.6	−3.1
17	**3**	41	29	30	−2.9	6.6; 29.6

[a] Polymerization conditions: precatalyst = 25 μmol; MeOH = 25 μmol (0.25 mL of a 0.1 *M* toluene solution); T = 140°C; t = 75 min; mol ratio of monomers to precatalyst in the feed = 100.
[b] Content of glycolide (F_{GA}), *rac*-lactide (F_{LA}), and ε-caprolactone (F_{Cap}) in the terpolymer (mol %), as determined by ^{1}H NMR (DMSO-d_6, 100°C).
[c] Theoretical values, as calculated with Fox equation, using the following T_g values for the homopolymers: poly(CL) = -60°C;[41] poly(GA) = 22.0°C.[42] poly(D,LLA) = 48.3°C.[8]
[d] Values reported for the second heating cycle.

is overlapped with the signals of the -CapGGOCH$_3$ end group, therefore the relative intensities of the end groups signals could not be evaluated.

The molecular weights of the obtained polymers were evaluated by gel permeation chromatography (GPC) and by ^{1}H NMR, being known the end group signals (Figure 6). The results are reported in Table V.

Since the terpolymer samples were soluble in THF, their molecular weights were evaluated by GPC, vs. polystyrene standards, using THF as elution solvent at 35°C. However, as previously underlined in the literature, the radius of gyration R_g of the copolymers is extremely sequence and solvent dependent, thus the values obtained by GPC should be regarded with special care. However, the GPC analysis performed on all the samples disclosed monomodal molecular weight distributions with variable molecular-weight dispersities, in the range of 1.4–1.7. In detail, catalyst **1** produced the terpolymer having narrower dispersity than those obtained with the others catalysts for equimolar amount of the three monomers. The observed values of molecular-weight dispersities may be due to the transesterification side reactions (A terpolymer sample was prepared with catalyst **2**, using a 900/1 monomers/Al feed ratio. After 7 hours, the reaction yield was close to 70%. The polymer was insoluble in common laboratory solvent, thus preventing GPC and NMR analysis.).

Molecular weights were also calculated by ^{1}H NMR analysis, being known the end group signals, and a good agreement between the latter values ($M_{n,NMR}$), and the theoretical molecular weights, $M_{n,th}$, calculated by the monomer to precatalyst feed ratio was observed in most runs.

Thermal Analysis

Thermal properties of the terpolymers were studied by Differential Scanning Calorimetry (DSC) in the range from −60°C to 260°C at a heating rate of 10°C min^{-1}. The DSC thermograms were recorded for the second heating scan. Terpolymers transition temperatures were measured and the values are reported in Table VI.

All the polymeric samples were amorphous, and the measured T_g's were below 37°C. All polymers exhibited a unique glass transition, except in one case (run 17, Table VI), confirming that a single phase was retained for all samples, even if the composition changed. Indeed, experimental T_g's were in good agreement with the theoretical ones, $T_{g,th}$ determined by Fox equation (Table VI).

The DSC thermograms, recorded for the second heating scan, of the terpolymer samples obtained with different catalysts **1–3** for equimolar monomers feed are shown in Figure 7.

For terpolymers obtained with catalysts **1,2,** the average glycolidyl block lengths were lower than 2, DSC analysis showed a unique T_g. Whereas, for catalyst **3**, the thermogram showed two T_g values and glycolidyl block length was higher than 2, indicating a blocky structure of the terpolymer chain.

CONCLUSIONS

The most common degradable and biocompatible synthetic polymers are poly(lactide-co-glycolide) and their respective homopolymers, which have been used clinically for several decades as suture materials. There is a continuous search to modify and tune the properties of the materials in terms of composition, rate of degradation, mechanical, and thermal properties. In this regard, the search for efficient ROP initiators for the synthesis of copolymers having controlled composition and microstructure is a very stimulating field. Recently, we discovered salicylaldiminato aluminum compounds as efficient initiators in the homopolymerization and copolymerization of *rac*-lactide and GA, producing PLGAs with different microstructures, from random to blocky to multiblock, by changing the polymerization conditions. The same class of complexes has been now showed to be also efficient catalysts in the copolymerization of GA with ε-caprolactone, and in the terpolymerization of GA with ε-caprolactone and *rac*-lactide, thus producing biodegradable and biocompatible materials. The dimethyl salicylaldiminato aluminum catalysts are among the few still now

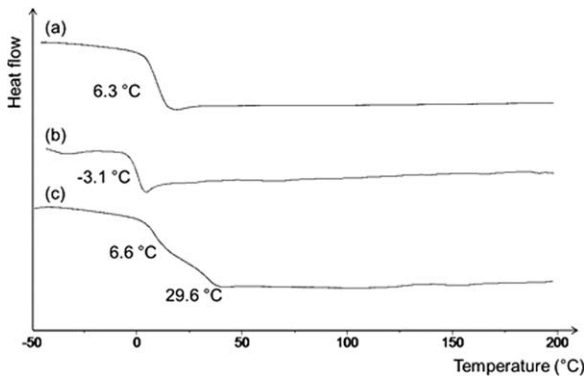


Figure 7. DSC thermograms (run II) of poly[glycolide-*co*-(*rac*-lactide)-*co*-(ε-caprolactone)] obtained with: (a) complex **1**, F_{GA} = 37; F_{LA} = 37; F_{Cap} = 26 (Table IV, run 13); (b) complex **2**, F_{GA} = 41; F_{LA} = 24; F_{Cap} = 35 (Table IV, run 16); (c) complex **3**, F_{GA} = 41; F_{LA} = 29; F_{Cap} = 30 (Table IV, run 17).

reported catalytic systems able to produce random copolymers,[9,20,28] resulting faster than the other literature systems producing random copolymers and terpolymers.[9,11,14,16–20]

In the copolymerization of GA with ε-caprolactone, copolymers from semi-crystalline to amorphous were produced by decreasing the GA/ε-caprolactone feed ratio. In detail, three aluminum complexes, bearing bidentate ligands differing for the steric hindrance on the ortho position of the phenolato ring, were selected. Interestingly, the net reactivities of the ε-CL and GA comonomers can be controlled by changing the bulkiness of the substituents in the ortho positions of the phenoxide groups. In particular, the most encumbered complex **3** showed the highest propensity to furnish random copolymers.

On the other hand, for the less encumbered catalyst **1** the transesterification reactions, involving the attack of ε-caproyl chain end on a GG block of another polymer chain, are more frequent with respect to the other two catalysts, thus allowing the randomization of the polymeric chain subsequently to the propagation events.

In the case of the terpolymerization, the polymeric samples were amorphous, and the composition could be modulated by the feed. The yield of transesterifications of the second mode, due to the attack of active chain end on the preformed segments contributed to the "randomized" structures. Notably, the transesterification side reactions generated by the attack of active glycolidyl or caproyl chain ends on preformed lactidyl segments were absent or negligible. It is thus confirmed the tendency of these complexes to break the lactidyl unit into two lactyl fragments is low.

ACKNOWLEDGMENTS

The research was supported by the Italian Ministry of University and Research (PRIN 2010–2011: Nanostructured polymeric materials with tailored molecular and crystalline structures, for advanced technologies and for the environment). The authors thank Dr. Patrizia Oliva for NMR technical assistance and Dr. Ilaria D'Auria for GPC technical assistance.

REFERENCES

1. Dubois, P.; Coulembier, O.; Raquez, J. M., Eds. Handbook of Ring-Opening Polymerization; Wiley-VCH Verlag GmbH & Co.: KGaA, Weinheim, **2009**.
2. Albertsson, A.-C.; Varma, K. I. *Biomacromolecules* **2003**, *4*, 1466.
3. Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissou, D. *Chem. Rev.* **2004**, *104*, 6147.
4. Thomas, C. M. *Chem. Soc. Rev.* **2010**, *39*, 165.
5. Gilding, D. K.; Reed, A. M. *Polymer* **1979**, *20*, 1459.
6. Grijpma, D. W.; Nijenhuis, A. J.; Pennings, A. *J. Polymer* **1990**, *31*, 2201.
7. Kasperczyk, J. *Polymer* **1996**, *37*, 201.
8. Meduri, A.; Fuoco, T.; Lamberti, M.; Pellecchia, C.; Pappalardo, D. *Macromolecules* **2014**, *47*, 534.
9. Kricheldorf, H. R.; Mang, T.; Jonté, J. M. *Macromolecules* **1984**, *17*, 2173.
10. Kricheldorf, H. R.; Jonté, J. M.; Berl, M. *Makromol. Chem.* **1985**, *12*, 25.
11. Bero, M.; Dobrzyński, P.; Kasperczyk, J. *Polym. Bull.* **1999**, *42*, 131.
12. Dobrzyński, P.; Kasperczyk, J.; Bero, M. *Macromolecules* **1999**, *32*, 4735.
13. Pack, J. W.; Kim, S. H.; Cho, I. W.; Park, S. Y.; Kim, Y. H. *J. Polym. Sci. Part A: Polym. Chem.* **2002**, *40*, 544.
14. Dobrzynski, P.; Li, S.; Kasperczyk, J.; Bero, M.; Gasc, F.; Vert, M. *Biomacromolecules* **2005**, *6*, 483.
15. Li, S.; Dobrzynski, P.; Kasperczyk, J.; Bero, M.; Braud, C.; Vert, M. *Biomacromolecules* **2005**, *6*, 489.
16. Dobrzyński, P.; Kasperczyk, J.; Jelonek, K.; Ryba, M.; Walski, M.; Bero, M. *J. Biomed. Mater. Res. Part A* **2006**, *79*, 865.
17. Cai, Q.; Bei, J.; Wang, S. *J. Biomater. Sci. Polym. Ed.* **2000**, *11*, 273.
18. Srisa-ard, M.; Molloy, R.; Molloy, N.; Siripitayananon, J.; Sriyai, M. *Polym. Int.* **2001**, *50*, 891.
19. Dobrzynski, P. *J. Polym. Sci. Part A: Polym. Chem.* **2002**, *40*, 3129.
20. Kricheldorf, H. R.; Rost, S. *Polymer* **2005**, *46*, 3248.
21. Zhang, H.; Bei, J.; Wang, S. *J. Appl. Polym. Sci.* **2007**, *106*, 3757.
22. Chan-Seng, D.; Ranganathan, T.; Zhang, X.; Tang, Y.; Lin, Q.; Kleiner, L.; Emrick, T. *Drug Deliv.* **2009**, *16*, 304.
23. Sanna, V.; Roggio, A. M.; Posadino, A. M.; Cossu, A.; Marceddu, S.; Mariani, A.; Alzari, V.; Uzzau, S.; Pintus, G.; Sechi, M. *Nanoscale Res. Lett.* **2011**, *6*, 260.
24. Oh, T.; Rahman, Md.; Lim, M. J.-H.; Park, M.-S.; Kim, D.-Y.; Yoon, J.-h.; Kim, W. H.; Kikuchi, M.; Tanaka, J.; Koyama, Y.; Kweon, O.-K. *J. Vet. Sci.* **2006**, *7*, 73.
25. Kricheldorf, H. R.; Rost, S. *Biomacromolecules* **2005**, *6*, 1345.
26. Kricheldorf, H. R.; Hachmann-Thiessen, H. *J. Polym. Sci. Part A: Polym. Chem.* **2005**, *43*, 3268.
27. Kricheldorf, H. R.; Behnken, G. *J. Macromol. Sci, Part A: Pure Appl. Chem.* **2008**, *45*, 693.
28. Kasperczyk, J.; Hu, Y.; Jaworskam, J.; Dobrzynski, P.; Wei, J.; Li, S. *J. Appl. Polym. Sci.* **2008**, *107*, 3258.
29. Weiss, R. M.; Jones, E. M.; Shafer, D. E.; Stayshich, R. M.; Meyer, T. Y. *J. Polym. Sci. Part A: Polym. Chem.* **2011**, *49*, 1847.
30. Pappalardo, D.; Annunziata, L.; Pellecchia, C. *Macromolecules* **2009**, *42*, 6056.
31. Fuoco, T.; Meduri, A.; Lamberti, M.; Venditto, V.; Pellecchia, C.; Pappalardo, D. *Polym. Chem.* **2015**, *6*, 1727.
32. Nomura, N.; Aoyama, T.; Ishii, R.; Kondo, T. *Macromolecules* **2005**, *38*, 5363.
33. Liu, J.; Iwasa, N.; Nomura, K. *Dalton Trans.* **2008**, 3978.
34. Iwasa, N.; Liu, J.; Nomura, K. *Catal. Commun.* **2008**, *9*, 1148.
35. Iwasa, N.; Fujiki, M.; Nomura, K. *J. Mol. Catal. A: Chem.* **2008**, *292*, 67.

36. Iwasa, N.; Katao, S.; Liu, J. Y.; Fujiki, M.; Furukawa, Y.; Nomura, K. *Organometallics* **2009**, *28*, 2179.
37. Normand, M.; Dorcet, B.; Kirillov, E.; Carpentier, J.-F. *Organometallics* **2013**, *32*, 1694.
38. Pappalardo, D.; Tedesco, C.; Pellecchia, C. *Eur. J. Inorg. Chem.* **2002**, 621.
39. Kasperczyk, J. *Macromol. Chem. Phys.* **1999**, *200*, 903.
40. Stayshich, R. M.; Meyer, T. Y. *J. Am. Chem. Soc.* **2010**, *132*, 10920.
41. Vanhoorne, P.; Dubois, P.; Jerome, R.; Teyssie, P. *Macromolecules* **1992**, *25*, 37.
42. Barakat, I.; Dubois, P.; Grandfils, C.; Jérôme, R. *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 294.
43. Nomura, N.; Akita, A.; Ishii, R.; Mizuno, M. *J. Am. Chem. Soc.* **2010**, *132*, 1750.