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Versatile Copolymerization of Glycolide and *rac*-Lactide by Dimethyl(salicylaldiminato)aluminum Compounds

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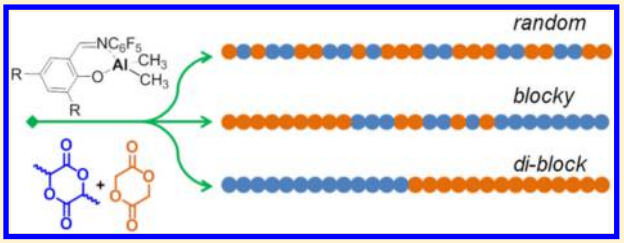
Supporting Information

ABSTRACT: The dimethylaluminum compounds $Al(CH_3)_2[(O\text{-}2\text{-}\{(C_6F_5)N{=}CH\}\text{-}4,6\text{-}R_2C_6H_2)]$, R = H (**1**) or cumyl (**2**), were synthesized and tested as initiators in the homo- and copolymerization of *rac*-lactide and glycolide. These complexes resulted active for the production of PLGA copolymers with variable microstructure. All the copolymers were fully characterized by NMR, GPC, and DSC analysis. The copolymerization reactions were performed in bulk and in solution, by varying comonomers ratio, monomer/catalyst feed ratio, temperature, reaction time, and solvent. Interestingly, by changing the reaction conditions, copolymers from random, to blocky, to diblock were obtained, demonstrating the effectiveness and versatility of such systems in modulating the copolymers microstructure and the related thermal properties.



INTRODUCTION

Over the past decades aliphatic poly(esters), such as poly(glycolide) (PGA), poly(lactide) (PLA), and their copolymers (PLGAs), have found rapidly increasing research interest. Because of their intrinsic biodegradability and bioassimilability, they are already used in a large range of applications from packaging and textile fibers to more sophisticated drug delivery systems, absorbable surgical fibers and stem cell scaffoldings.[1]

The final applications of PLGAs are obviously dictated by their properties, such as degradation rate and thermal and mechanical behaviors, which can be tuned by carefully modifying the polymer chain parameters such as molecular weight, molecular-weight dispersity, monomers ratio and sequence, and polymer chain-ends. In this regard, the ring-opening polymerization (ROP) of commercially available lactide (LA) and glycolide (GA) represents the most efficient method to produce these polymers.[2] The industrial and the most commonly used catalyst for the preparation of such polyesters is stannous octanoate. The first systematic studies on the preparation of PLGAs copolymers by this initiator revealed that the synthesized copolymers did not show a truly random monomer distribution.[3,4] Because of the higher reactivity of GA in comparison to LA, the copolymers initially formed were richer in GA than the monomer feed mixture. The blocky structure, however, was randomized to various extent by transesterification reactions. In other cases (i.e., for bulk polymerization at 150 °C), the detailed ^1H and ^{13}C NMR investigations of the polymer microstructure revealed the formation of shorter blocks, with average block lengths close to 2.[5] However, one drawback of the use of the stannous octanoate is the poor control of the polymerization and the scarce reproducibility of the polymerization results. As a consequence, the properties of the copolymers widely vary from batch to batch. This problem, obviously, involves all polymeric materials, but it is crucial for those used in biomedical field, where the *in vivo* applications require an absolute control on the polymer microstructure and monomers sequences.[6]

This aspect was elegantly addressed by Meyer et al. with the preparation of poly(lactic-*co*-glycolic acid) repeating sequence copolymers.[7,8] In their work, the strategy for producing these repeating sequence copolymers involved the assembly by condensation polymerization of preformed segmers comprising high degree of sequence and stereocontrol. The work of Meyer allowed a really extensive, systematic and thorough investigation of PLGA microstructure. Remarkably, it was demonstrated that an alternating PLGA exhibited a dramatic different hydrolysis behavior in comparison with a random one.

Truly alternated poly(glycolide-*alt*-lactide) copolymers were also obtained by polymerization of the 3-methyl-1,4-dioxan-2,5-dione, synthesized ad hoc, using stannous octanoate[9] or bimetallic alkoxide of Al and Zn as initiators.[10]

Although both the above-mentioned approaches allowed a precision synthesis of PLGAs, they are less efficient than ROP. Therefore, the search for ROP initiators that allow the preparation of PLGAs in a controlled and reproducible fashion still represents a challenge.

In fact, in addition to stannous octanoate, several catalysts and initiators have been tested in GA/LA copolymerization. Early studies include the testing of commercially available

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chlorides, alkoxides, oxides or sulfides of main groups and transition metals (Sn, Al, Zr, Ti, Pd, Cd, and Zn).[11] In this study only tin-based initiators were claimed to produce "random" copolymers, however the average blocks sequences were not reported. Cationic copolymerization in the presence of organic acids and salts (i.e., methyl triflate) clearly produced non random macromolecules, with average blocks sequences higher than 2.[12] Afterward, homoleptic metal-complexes of Li,[13] Mg,[13] Al,[5] Zn,[5,14] Ca,[15] Zr,[16] Fe,[17] and Bi[18] have been also tested and produced multiblock non random copolymers.

Subsequently, the preparation of poly(ethylene glycol)-*block*-PLGAs was obtained by an elaborate semibatch polymerization strategy requiring the stepwise addition of the more reactive glycolide to a solution containing the lactide monomer, the poly(ethylene glycol) macroinitiator and an organocatalyst.[19]

It is apparent, then, that in the literature there is still a paucity of ROP catalysts capable of producing truly random PLGAs. In the framework of our interest in the ROP of cyclic esters promoted by various well-defined organometallic catalysts,[20] we recently reported dimethyl(salicylaldiminato) aluminum compounds able to efficiently catalyze the *living* ROP of L- and D,L-lactide and ε-caprolactone.[20b] Interestingly, in the presence of these initiators random and block copolymers of ε-caprolactone and lactide were prepared, with a controlled chain growth, in the absence of transesterification reaction. Moreover, the simple formulation and the easy activation represent advantageous features with respect to most ROP aluminum catalysts based on more complex polydentate ligand systems. Although analogous aluminum phenoxy-imine complexes have been largely studied for the ROP of a variety of cyclic esters,[21] this class of catalysts has not been reported for the homopolymerization of glycolide and for PLGAs production. With these premises, in this work we have tested these compounds as precatalysts in the ROP of glycolide and *rac*-lactide, and studied the feasibility of random and block copolymerization in different experimental conditions.

EXPERIMENTAL SECTION

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 (indicated below) and distilled under nitrogen: toluene, xylenes, and methanol (Sigma-Aldrich) over Na; THF (Delchimica), *n*-pentane and *n*-hexane (Sigma-Aldrich) over Na/benzophenone. Monomers (Sigma-Aldrich) were purified prior to use: L-lactide and *rac*-lactide were dried in vacuo with P_2O_5 for 72 h, and afterward stored at −30 °C in glovebox; glycolide was recrystallized from tetrahydrofuran (THF).

Ligands **Lig1**[22] and **Lig2**[23] were synthesized according to literature methodologies.

Deuterated solvents were stored and used in agreement with the recommendations by the producer (Eurisotop: dimethyl sulfoxide d_6 (DMSO-d_6) and $CDCl_3$; Aldrich: C_6D_6); C_6D_6 was dried over molecular sieves before use.

All other reagents and solvents were commercially available and used without further purification for synthetic, spectroscopic and catalytic purposes.

Instruments and Measurements. Elemental analyses were recorded on a Thermo Finningan Flash EA 1112 series C, H, N, S analyzer in the microanalytical laboratory of the institute.

NMR spectra of complexes were performed in C_6D_6 at 25 °C on a Bruker Avance 400 spectrometer (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz; ^{19}F, 376.50 MHz), using NMR tubes equipped with J. Young valves. NMR spectra of polymers were performed in DMSO-d_6 at 100 °C and in $CDCl_3$ at 25 °C on a Bruker Avance 300 spectrometer (^{1}H, 300.13 MHz; ^{13}C, 75.47 MHz). 2D DOSY PGSE NMR spectrum of the block copolymer was performed on the Bruker Avance 400 spectrometer in DMSO-d_6 at 80 °C without spinning; parameters δ (1100 μs) and Δ (0.1 s) were kept constant during the experiments, whereas G was varied from 2 to 95% in 16 steps. The resonances are reported in ppm (δ) and coupling constants in Hz (J), and they are referenced to the residual solvent peak versus $Si(CH_3)_4$: C_6D_6 at δ 7.16 (^{1}H) and δ 128.1 (^{13}C), DMSO-d_6 at δ 2.50 (^{1}H) and δ 39.5 (^{13}C), $CDCl_3$ at δ 7.26 (^{1}H) and δ 77.0 (^{13}C); in the case of ^{19}F, resonances were automatically referenced versus $CF_3C_6H_5$ by the software. All spectra recording and data processing were performed on Bruker TopSpin v2.1 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. In the case of the analyses performed using THF as eluent (1.0 mL min^{-1}) a system of four Styragel HR columns (7.8 × 300 mm; range 10^3 − 10^6 Å) was employed. In the case of the analyses performed using $CHCl_3$/1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) 99/1 as eluent (1.0 mL min^{-1}) a system of two Styragel HR columns (7.8 × 300 mm; range 10^3−10^4 Å) was employed. 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 a DSC 2920 TA Instruments in nitrogen flow with a heating and cooling rate of 10 °C min^{-1} in the range of −20 to +260 °C. The data were processed with TA Universal Analysis v2.3 software and are reported for the second heating cycle.

*Synthesis of Al(CH$_3$)$_2$[O-2-{(C$_6$F$_5$)N=CH}C$_6$H$_4$] (**1**).* To a toluene solution (15 mL) of **Lig1** (1.5 g, 5.1 mmol) were added 10 mL of a *n*-hexane solution 0.56 M of $Al(CH_3)_3$ (5.5 mmol) dropwise via cannula at 0 °C. The reaction mixture was magnetically stirred for 1 h at 0 °C, then for 1.5 h at room temperature. After this time, the solvent was removed, the solid was washed with *n*-pentane and dried in vacuo. Yield: 1.610 g (92%). ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ 7.18 (s, 1H; N=C*H*), 7.04 (td, J = 8.6, 1.4 Hz, 1H; Ar*H*), 6.89 (dd, J = 8.6, 1.1 Hz, 1H; Ar*H*), 6.63 (dd, J = 7.8, 1.4 Hz, 1H; Ar*H*), 6.40 (td, J = 7.8, 1.1 Hz, 1H; Ar*H*), −0.28 (bs, 6H; Al−C*H*$_3$).

^{13}C NMR (101 MHz, C_6D_6, 25 °C): δ 176.5 (C(H)=N), 167.3 (^{Ar}C−O), 143.0 (^{Ar}C−F), 140.3 (^{Ar}C−H), 139.4 (^{Ar}C−F), 136.9 (^{Ar}C−F), 136.2 (^{Ar}C−H), 123.5 (^{Ar}C−H), 121.4 (^{Ar}C−N), 118.8 (^{Ar}C−C(H)=N), 118.2 (^{Ar}C−H), −9.2 (Al−CH_3).

^{19}F NMR (376 MHz, C_6D_6, 25 °C): δ −148.44 (d, J = 18.8 Hz, 2F; *o*-F), −154.07 (t, J = 22.5 Hz, 1F; *p*-F), −160.50 (td, J = 22.5, 5.4 Hz, 2F; *m*-F).

*Synthesis of Al(CH$_3$)$_2$[(O-2-{(C$_6$F$_5$)N=CH}-4,6-{C(CH$_3$)$_2$C$_6$H$_4$}$_2$C$_6$H$_2$)] (**2**).* To a toluene (25 mL) solution of **Lig2** (0.97 g, 1.86 mmol) were added 3 mL of a toluene solution 0.68 M of $Al(CH_3)_3$ (2.05 M) dropwise via cannula at 0 °C. The reaction mixture was magnetically stirred for 1 h at 0 °C, then for 2 h at room temperature. After this time, the solvent was removed and the solid dried in vacuo. Yield: 0.918 g (83%).

^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ 7.73 (d, J = 2.5 Hz, 1H; Ar*H*), 7.29−7.13 (m, 8H; Ar*H* cumyl), 7.12−7.06 (m, 2H; *p*-Ar*H* cumyl), 7.03 (s, 1H; N=C*H*), 6.77 (d, J = 2.5 Hz, 1H; Ar*H*), 1.63 (s, 6H; C*H*$_3$), 1.62 (s, 6H; C*H*$_3$), −0.57 (s, 6H; Al−C*H*$_3$).

^{13}C NMR (101 MHz, C_6D_6, 25 °C): δ 176.7 (C(H)=N), 164.2 (^{Ar}C−O), 150.3 (^{Ar}C−C), 150.0 (^{Ar}C−C), 143.0 (^{Ar}C−F), 142.5 (^{Ar}C−C), 140.5 (^{Ar}C−F),139.9 (^{Ar}C−C), 139.3 (^{Ar}C−F), 136.7 (^{Ar}C−H), 131.5 (^{Ar}C−H), 128.7 (^{Ar}C−H), 127.1 (^{Ar}C−H), 126.5 (^{Ar}C−H), 125.8 (^{Ar}C−H), 125.6 (^{Ar}C−H), 121.6 (^{Ar}C−N), 118.5 (^{Ar}C-C(H)=N), 42.7(C(CH$_3$)$_2$), 42.4 (*C*(CH$_3$)$_2$), 30.9 (C(*C*H$_3$)$_2$), 29.0 (C-(*C*H$_3$)$_2$), −10.3 (Al-*C*H$_3$).

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^{19}F NMR (376 MHz, C_6D_6, 25 °C): δ −148.28 (dd, J = 18.2, 5.6 Hz, 2F; *o*-F), −154.76 (t, J = 22.3 Hz, 1F; *p*-F), −160.87 (td, J = 22.3, 5.6 Hz, 2F; *m*-F).

Homopolymerization in Bulk. In a typical homopolymerization run, a vial (20 mL) was charged sequentially with monomer (2.50 mmol), precatalyst (25 μmol), and MeOH (25 μmol; 0.25 mL of a 0.1 M toluene solution). The vial was put into an oil bath, preheated and thermostated at 140 °C, and was magnetically stirred. After 75 min, the vial was allowed to cool at room temperature. Product purification was obtained by dissolving the reaction mixture in CH_2Cl_2, followed by a dropwise addition of this solution to rapidly stirring methanol. The precipitated polymer was recovered by filtration, washed with methanol, and dried at 60 °C in a vacuum oven overnight.

Poly(glycolide) = ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): 4.87 (s, 2H; $CH_2C(O)O$), 4.13 (s, 2H; CH_2OH), 3.72 (s, 3H; OCH_3).

Poly(*rac*-lactide) = ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): δ 5.25−5.16 (m, 1H; $CH(CH_3)C(O)O$), 4.23 (m, 1H; $CH(CH_3)OH$), 3.70 (s, 3H; CH_3O), 1.53−1.45 (m, 3H; $CH(CH_3)C(O)O$), 1.32 (d, J = 7.0 Hz, 3H; $CH(CH_3)OH$).

^{13}C NMR (75 MHz, DMSO-d_6): δ 168.3, 168.15, 168.1 ($CH(CH_3)C(O)O$), 68.5, 68.3 ($CH(CH_3)C(O)O$), 15.8, 15.7 ($CH(CH_3)C(O)O$).

Copolymerization in Bulk. In a typical copolymerization run, a vial (20 mL) was charged sequentially with monomers (total amount = 2.50 mmol, if not stated otherwise), precatalyst (25 μmol) and MeOH (25 μmol; 0.25 mL of a 0.1 M toluene solution). The vial was put into an oil bath, preheated, and thermostated at 140 °C, and was magnetically stirred. The polymerization work-up was performed as above.

Poly(glycolide-*co*-*rac*-lactide) = ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): δ 5.34−5.14 (m, 1H; $CH(CH_3)C(O)O$), 4.98−4.71 (m, 2H; $CH_2C(O)O$), 1.57−1.44 (m, 3H; $CH(CH_3)C(O)O$). ^{13}C NMR (75 MHz, DMSO): δ 168.4, 168.3, 168.2, 168.15, 168.1 ($CH(CH_3)C(O)O$), 165.8, 165.7 ($CH_2C(O)O$), 68.5, 68.3 ($CH(CH_3)C(O)O$), 60.3, 60.2 ($CH_2C(O)O$), 15.8, 15.7 ($CH(CH_3)C(O)O$).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 5.31−5.11 (m, 1H; $CH(CH_3)C(O)O$), 4.92−4.57 (m, 2H; $CH_2C(O)O$), 1.65−1.52 (m, 3H; $CH(CH_3)C(O)O$). ^{13}C NMR (75 MHz, DMSO): δ 169.6, 169.4 169.3, 169.2 ($CH(CH_3)C(O)O$), 166.4, 166.74 ($CH_2C(O)O$), 69.3, 69.2,69.0 ($CH(CH_3)C(O)O$), 60.9, 60.8, 60.7 ($CH_2C(O)O$), 16.7, 16.6 ($CH(CH_3)C(O)O$).

Synthesis of Low Molecular Weight Poly(glycolide-*co*-*rac*-lactide). The copolymers were prepared as above, but 0.50 mmol of glycolide and 0.50 mmol of *rac*-lactide were used.

^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): δ 5.34−5.14 (m, 1H; $CH(CH_3)C(O)O$), 4.98−4.71 (m, 2H; $CH_2C(O)O$), 4.23 (m, 1H; $CH(CH_3)OH$), 4.29−4.18 (m, 1H; $CH(CH_3)OH$), 4.13 (s, 2H; CH_2OH), 4.09 (m, 2H; CH_2OH), 3.72 (s, 3H; OCH_3), 3.70 (s, 3H; CH_3O), 1.57−1.44 (m, 3H; $CH(CH_3)C(O)O$), 1.32 (d, J = 7.0 Hz, 3H; $CH(CH_3)OH$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.4, 168.3, 168.2, 168.15, 168.1 ($CH(CH_3)C(O)O$), 165.8, 165.7 ($CH_2C(O)O$), 68.5, 68.3 ($CH(CH_3)C(O)O$), 60.3, 60.2 ($CH_2C(O)O$), 59.1 (CH_2OH), 15.8, 15.7 ($CH(CH_3)C(O)O$).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 5.34−5.10 (m, 1H; $CH(CH_3)C(O)O$), 4.95−4.55 (m, 2H; $CH_2C(O)O$), 4.46−4.34 (m, 1H; $CH(CH_3)OH$), 4.30 (s, 2H; CH_2OH), 4.28−4.23 (m, 2H; CH_2OH), 3.72 (s, 3H; OCH_3), 3.70 (s, 3H; OCH_3), 1.65−1.48 (m, 3H; $CH(CH_3)C(O)O$), 1.32 (d, J = 7.0 Hz, 3H; $CH(CH_3)OH$).

Copolymerization in Solution. In a typical polymerization run, a Schlenk tube (10 mL) was charged sequentially with monomer(s) (total = 5.00 mmol), precatalyst (25 μmol; 5 mM in the solvent), the solvent and MeOH (25 μmol; 0.25 mL of a 0.1 M toluene solution). The Schlenk tube was put into an oil bath, preheated and thermostated at the desired temperature, and was magnetically stirred. After the established time, the mixture was cooled to room temperature. Product purification was attained by dropwise addition of the reaction mixture, dissolved in CH_2Cl_2, to rapidly stirring methanol. The precipitated polymers were recovered by filtration, washed with methanol and dried at 60 °C overnight in a vacuum oven.

Poly(glycolide-*co*-*rac*-lactide). ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): δ 5.34−5.14 (m, 1H; $CH(CH_3)C(O)O$), 4.98−4.71 (m, 2H; $CH_2C(O)O$), 1.57−1.44 (m, 3H; $CH(CH_3)C(O)O$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.4, 168.3, 168.2, 168.15, 168.1 ($CH(CH_3)C(O)O$), 165.8, 165.7 ($CH_2C(O)O$),68.5, 68.3 ($CH(CH_3)C(O)O$), 60.3, 60.2 ($CH_2C(O)O$), 15.8, 15.7 ($CH(CH_3)C(O)O$).

Synthesis of Poly(glycolide-*block*-*rac*-lactide). The Schlenk tube (10 mL) was charged sequentially with *rac*-lactide (1.25 mmol), precatalyst (25 μmol; 5 mM in xylenes), xylenes, and MeOH (25 μmol; 0.25 mL of a 0.1 M toluene solution). The Schlenk tube was put into an oil bath, thermostated at 130 °C. After 4.5 h, glycolide (0.39 mmol) was added as a solid to the reaction mixture. The reaction was quenched after 10 min by addition of 2 mL of wet CH_2Cl_2. The mixture was then added to methanol (20 mL). The precipitated polymer was recovered by filtration, washed with methanol and dried at 60 °C overnight in a vacuum oven. The $M_{n,NMR}$ evaluated by ^{1}H NMR was 3.7 KDa.

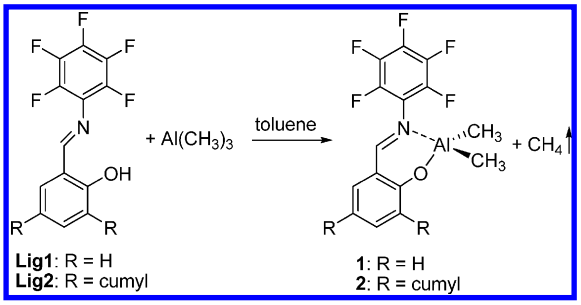
^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): δ 5.27−5.14 (m, 1H; $CH(CH_3)C(O)O$), 4.87 (s, 2H; $CH_2C(O)O$), 1.54−1.44 (m, 3H; $CH(CH_3)C(O)O$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.3, 168.15, 168.1 ($CH(CH_3)C(O)O$), 165.8 ($CH_2C(O)O$), 68.5, 68.3 ($CH(CH_3)C(O)O$), 60.3 ($CH_2C(O)O$), 15.8, 15.7 ($CH(CH_3)C(O)O$).

RESULTS AND DISCUSSION

Synthesis and Characterization of the Salicylaldiminato Aluminum Complexes. The complexes **1** and **2** were synthesized in toluene by the alkane elimination reaction between the corresponding proligand and $Al(CH_3)_3$, as previously described for analogous compounds.[24] The phenoxy-imine proligands have been synthesized following previously published procedures.[22,23]

The phenoxy-imine compounds coordinate to the aluminum atom as monoanionic ligands, yielding the dimethyl compounds **1** and **2** (Scheme 1) and one equivalent of methane. Complexes

Scheme 1. Synthetic Route for Complexes 1 and 2



1 and **2** were subsequently recovered, by evaporation of the solvent in vacuo, as yellow powders in good yields (**1**, 92%; **2**, 83%). They were fully characterized by multinuclear NMR spectroscopy.

The ^{1}H and ^{13}C NMR spectra of the obtained products indicated the formation of the desired complexes **1**-**2** bearing one salicylaldiminato ligand and two methyl groups. In the ^{1}H NMR spectra sharp singlets at −0.28 ppm and −0.57 ppm, respectively for complexes **1** and **2**, were observed for the methyl protons of the $Al(CH_3)_2$. The pattern of the protons of the salicylaldiminato ligands was unequivocally recognized in each spectrum and showed significant shifts with respect to the signals of the protons of free proligands (*see* Supporting Information). Accordingly, the ^{19}F NMR spectra showed three signals for the *ortho*, *meta*, and *para*-fluorine atoms on the aromatic ring bound to the nitrogen. ^{13}C NMR characterization was coherent with these data showing, in particular, signals at

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−9.2 and −10.3 ppm, respectively for complexes **1** and **2**, for the methyl carbons on the aluminum (*see* Supporting Information).

Homo- and Copolymerization of Glycolide and *rac*-Lactide in Bulk. Complexes **1** and **2** were tested in the ring-opening copolymerization of *rac*-lactide and glycolide carrying out the reaction under several experimental conditions. The homo- and copolymerizations of glycolide and *rac*-lactide were first performed in bulk at 140 °C in the presence of catalysts **1** or **2** and one equivalent of methanol. The obtained polymer samples were characterized by ^{1}H and ^{13}C NMR spectroscopy, GPC and DSC analysis. The main results are summarized in Tables 1 and 2.

Table 1. Homo- and Copolymerization of Glycolide and *rac*-Lactide in Bulk[a]

run	catalyst	f_{GA}[b]	yield (%)	F_{GA}[c]	L_{GG}[d]	L_{LL}[d]	T_{LGL}[e]	T_{GLG}[e]
1	**1**	100	>99	100	–	–	–	–
2	**1**	0	76	–	–	–	–	–
3	**2**	100	>99	100	–	–	–	–
4	**2**	0	92	–	–	–	–	–
5	**1**	70	78	70	3.55	1.52	1.59	0.01
6	**1**	50	75	51	1.67	1.61	1.19	0.07
7	**1**	30	64	30	1.17	2.72	0.71	0.11
8	**2**	80	89	81	6.13	1.44	4.39	0.10
9	**2**	70	83	72	3.44	1.34	1.85	0.08
10	**2**	60	92	59	2.29	1.59	1.34	0.10
11	**2**	50	77	53	2.05	1.82	1.07	0.15
12	**2**	40	81	41	1.40	2.01	0.90	0.12
13	**2**	30	89	34	1.14	2.21	0.94	0.15
14	**2**	20	74	22	1.18	3.05	0.74	0.32

[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 monomer(s) to precatalyst in the feed = 100. [b]Molar percentage of glycolide in the feed. [c]F_{GA}, molar percentage of glycolide in the copolymer, as determined by ^{1}H NMR (DMSO-d_6, 100 °C). [d]Average length of glycolidyl (GG) and lactydyl (LL) blocks in the copolymer; calculated from ^{13}C NMR (DMSO-d_6, 100 °C). [e]Yield of the second mode of transesterification (%) of glycolidyl (LGL) and lactydyl (GLG) sequences; calculated from ^{1}H NMR (DMSO-d_6, 100 °C).

For both the catalysts, after 75 min of reaction, full conversion in the homopolymerization of glycolide was assessed; almost complete conversion of *rac*-lactide was reached in the same time (Table 1, runs 1−4).

The copolymerizations were performed systematically varying the comonomers ratio and the monomer/catalyst feed ratio, and almost complete monomer conversion was reached in 75 min with both the catalysts. As shown in Table 1, the composition of the copolymers, evaluated by the ^{1}H NMR spectrum, parallels the feed ratio, as it would be expected for a copolymer at full conversion.

Because the chemical shifts of the carbonyl carbons are highly sensitive to their surroundings,[25] a detailed microstructure characterization of the copolymer chain of the samples was achieved through inspection of the ^{13}C NMR spectra.

The carbonyl regions of the ^{13}C NMR spectra (DMSO-d_6, 100 °C) of the copolymer samples prepared with catalyst **1** with different monomers feed (Table 1, runs 5−7) are shown in Figure 1. For comparison, the ^{13}C NMR spectrum (DMSO-d_6, 100 °C) of a poly(*rac*-lactide) prepared in the same conditions (Table 1, run 2) is also shown (Figure 1i). Providing that L and

Table 2. Molecular Weights and Dispersities of the Homo- and Copolymer Samples Obtained in Bulk[a]

run	catalyst	F_{GA}[b]	$M_{n,th}$ (kDa)[c]	$M_{n,NMR}$ (kDa)[d]	M_w/M_n[e]
2	**1**	0[f]	11.0	8.9	1.6[g]
4	**2**	0[f]	13.9	13.9	1.5[g]
5	**1**	70	12.2	9.2	2.4
6	**1**	51	12.7	9.4	2.2
7	**1**	30	8.9	15.4	1.9
8	**2**	81	11.7	10.7	1.3
9	**2**	72	10.3	9.5	1.1
10	**2**	59	12.0	8.3	1.4
11	**2**	53	12.2	8.5	1.4
12	**2**	41	10.7	7.6	1.5
13	**2**	34	12.2	7.3	1.3
14	**2**	22	12.2	8.1	1.8
15[h]	**1**	50	5.2	4.3	2.0[g]
16[h]	**2**	55	5.2	5.5	1.4[g]
17[i]	**1**	53	34.1	27.2	1.6
18[i]	**2**	53	32.7	19.0	2.0

[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 monomer(s) to precatalyst in the feed = 100. [b]F_{GA}, content of glycolide in the copolymer (mol %). [c]Theoretical molecular weight. [d]Molecular weight determined by ^{1}H NMR. [e]Molecular weights dispersities determined by gel permeation chromatography (GPC) vs polystyrene standards, elution solvent mixture: chloroform/HFIP 99/1. [f]Poly(*rac*-LA). [g]Elution solvent: tetrahydrofuran (THF). [h]The mol ratio of monomer(s) to precatalyst in the feed = 40. [i]The mol ratio of monomer(s) to precatalyst in the feed = 300.

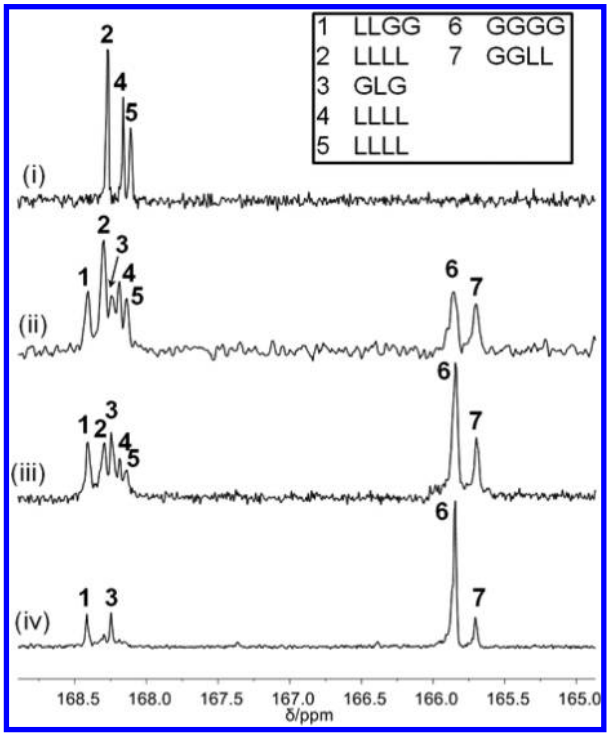

Figure 1. ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C) spectra in the carbonyl region of polymers obtained with complex **1**: (i) poly(*rac*-lactide) (Table 1, run 2); (ii) poly(glycolide-*co*-*rac*-lactide), F_{GA} = 30 (Table 1, run 7); (iii) poly(glycolide-*co*-*rac*-lactide), F_{GA} = 51 (Table 1, run 6); (iv) poly(glycolide-*co*-*rac*-lactide), F_{GA} = 70 (Table 1, run 5).

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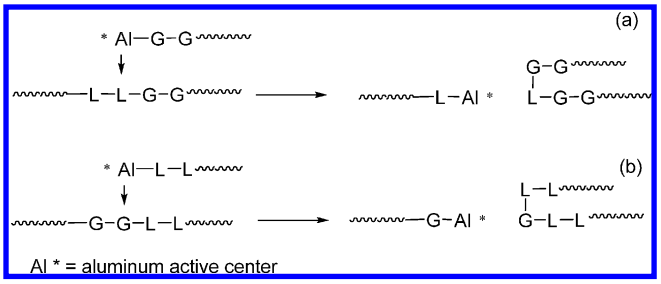
G represent respectively a lactyl $-CH(CH_3)C(O)O-$ and a glycolyl $-CH_2-C(O)O-$ unit, two resonances attributable to the hetero- and homosequences centered on the carbonyl of the glycolyl (GGLL at δ 165.7 ppm and GGGG at δ 165.8 ppm) were observed, accordingly with the literature.[26] At lower field, in the region centered on the carbonyl of the lactyl group, five resonances were observed. As previously reported, the resonance at δ 168.4 ppm was attributed to the heterosequence LLGG, while the resonance at δ 168.2 ppm was attributed to the GLG sequence.[26] The latter sequence cannot be formed by ring-opening of lactide and glycolide during the chain growth, but it derives from the transesterification of the second mode, during which the lactidyl and glycolidyl units undergo bond cleavage. Indeed, the GLG sequence could be generated by a transesterification reaction involving the attack of an active glycolidyl chain end −GGAl* on a preformed LLGG sequence (Scheme 2a).

Scheme 2. Transesterification Processes Occurring During the Copolymerization



The remaining three resonances (at δ 168.3, 168.15, 168.1 ppm) are attributable to the different stereochemical combination of the LLLL homosequence.[27] It is worth to note that in the homopolymerization of *rac*-lactide, in the absence of a stereoselective catalyst/initiator, 11 hexads or 5 tetrads of stereochemical sequences, resulting from the addition of D- and L-lactide molecules, are expected. However, due to either insufficient resolution or overlapping of the chemical shifts in DMSO-d_6 solvent, only 3 resonances are observed. The same resonances appeared in the ^{13}C NMR spectrum (DMSO-d_6) of the poly(*rac*-lactide) prepared with the same catalyst (Figure 1i). For this sample the methine region of the homonuclear decoupled ^1H NMR spectrum in $CDCl_3$[27] (see Figure S5) showed a slightly isotactically enriched microstructure (Pm = 0.64), as previously observed for the poly(*rac*-lactide) obtained in toluene solution with similar salicylaldiminato aluminum catalysts.[20b]

The average lengths of glycolidyl and lactidyl blocks (L_{GG} and L_{LL}) were also calculated from the ^{13}C NMR spectra, by using previously reported equations.[12] The so-calculated lengths were confirmed by using as control the monomers composition ratio (G/L) evaluated by ^1H NMR.[12]

The average block lengths linearly depend on the copolymer composition ratio (Figures 2 and Supporting Information) and the monomers feed. As a result, the copolymers microstructure could be easily tuned by adjusting the feed.

Interestingly, with catalyst **2**, in the case of a 50 to 50 monomer feed composition (Table 1, run 11), the L_{GG} and L_{LL} values were close to a value of 2, as expected for a random copolymer.

More information on the copolymers microstructures can be derived from the ^1H NMR spectra in the methylene region.

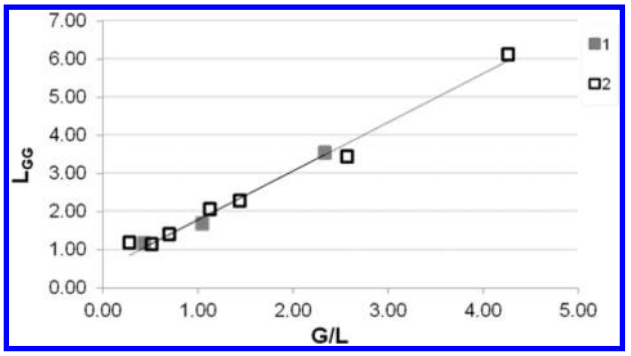


Figure 2. Plot of average length of glycolidyl (GG) blocks vs copolymer composition ratio (G/L) for the copolymers obtained with complexes **1** and **2** (Table 1, runs 5–7 and 8–14).

Signals at 4.83 ppm were attributed, according to the literature, to the presence of LGL sequences.[5,28] These sequences are formed by transesterification reaction of glycolidyl segments by active lactidyl chain end (Scheme 2b). The amount of transesterification sequences LGL and GLG (see above) have been evaluated by using the coefficients of the second mode of transesterification, T_{LGL} and T_{GLG}, as previously reported.[5,16] According to the definitions, the T_{LGL} and T_{GLG} values are close to 1 when the contribution of glycolyl and lactyl units in the chain are close to Bernoullian statistics, while they are higher than 1 when longer alternated sequences are present in the chains. The T_{LGL} values increase by increasing the amount of glycolide in the feed, and values higher than 1 are calculated for the copolymers obtained when the molar percentage of glycolide in the feed is higher than 50%.

For both the catalysts, the T_{LGL} values are higher than the T_{GLG} ones of 1 order of magnitude, thus indicating that the transesterification reaction involving the attack of active lactidyl chain end on preformed glycolidyl segments is preferred (Scheme 2b). Perusal of the literature showed only a similar precedent in the copolymers obtained in the presence of butyllitium, that also contained higher amount of T_{LGL} with respect to the T_{GLG} ones.[13] This behavior is definitely in contrast with previous results obtained with the classical $Sn(Oct)_2$ catalyst, and with $Zr(acac)_2$[16] or Fe based catalysts,[17] where the T_{GLG} values were higher than the T_{LGL} ones.

This feature can be tentatively explained taking into account that in the homopolymerization of *rac*-lactide by this class of aluminum catalysts, transesterification reactions were absent.[20b] It is therefore confirmed that the tendency of these complexes to break the lactidyl unit into two lactyl fragments is low.

Overall, the two initiators showed roughly analogous behavior in the polymerization performed in bulk. An accurate analysis of the copolymerization results, however, showed that transesterifications of the second mode were slightly higher for catalyst **2**, bearing a bulky cumyl groups as *ortho*-phenoxy substituents. Probably the steric hindrance of this group could have an influence on the relative rate of chain propagation and transesterification reaction.

The final microstructure of copolymer chain should reasonably result from the reactivity of comonomers as well as transesterification processes taking place together with the main copolymerization reaction. In particular, the main transesterification process operating in this system is involving the attack of active lactidyl chain end on preformed glycolidyl segments.

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End Groups Analysis by NMR. In order to get more information on the mechanism involved in these copolymerization reactions an accurate end group analysis was carried out by ^{1}H NMR spectroscopy in DMSO-d_6 at 100 °C. For this purpose, low molecular weight copolymer samples were prepared by conversion of 20 equiv of each monomer. The assignment of the different end groups was made by comparison with the spectra of the homopolymer samples (Figure 3, parts i and ii) and literature data.[9] Although PGA homopolymer is scarcely soluble in common solvent, olygomers of PGA were found to be soluble in DMSO-d_6 at 100 °C, thus allowing the analysis of end groups.

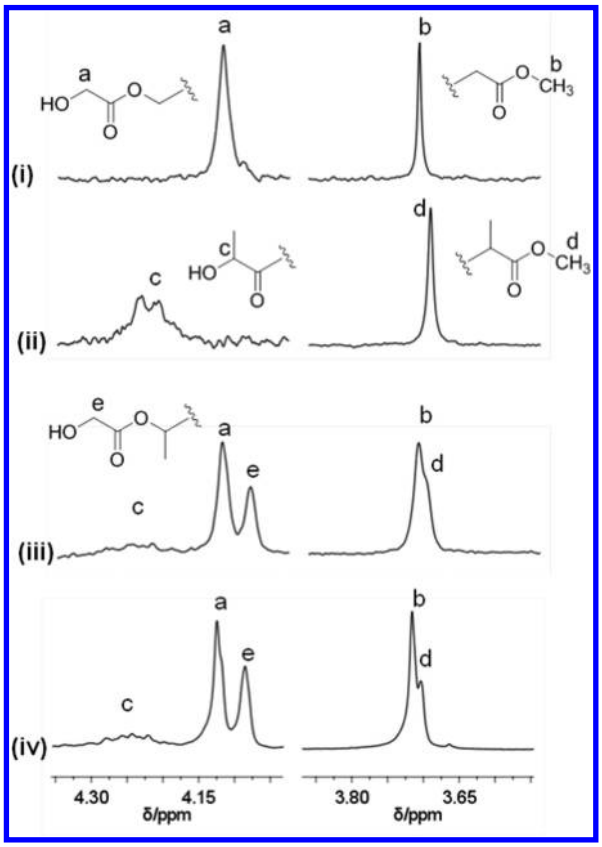

Figure 3. ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) spectra: (i) poly(glycolide) obtained with complex **1** (Table 1, run 1); (ii) poly(*rac*-lactide) obtained with complex **1** (Table 1, run 2); (iii) poly(glycolide-*co*-*rac*-lactide) obtained with complex **1** (Table 2, run 15); (iv) poly(glycolide-*co*-*rac*-lactide) obtained with complex **2** (Table 2, run 16).

Easily recognizable were the singlets due to the terminal alkoxide $-OCH_3$ group. Similar signals in the homopolymer spectra (Figure 3, parts i and ii) allowed us to distinguish the $-CH_2C(O)OCH_3$ (G$-OCH_3$) and the $-CH(CH_3)C(O)OCH_3$ (L$-OCH_3$) end groups in the copolymers. The presence of both signals indicated that the first step of these copolymerization reactions can be the insertion of either the glycolide unit or the lactide unit into the Al$-OCH_3$ bond. Although the partial overlapping of these signals did not permit an exact estimation of their relative abundance, it is possible to claim that, for both complexes, the preferred first step is the insertion of the glycolide monomer into the Al$-OCHH_3$ bond. This is in agreement with the higher reactivity of this monomer with respect to that of lactide. Moreover, the observed preference is more significant with catalyst **2** (Figure 3iv) suggesting a stronger discrimination in favor of the less hindered monomer by the most encumbered complex.

The most abundant hydroxyl end groups, generated by hydrolysis of the growing chain, were the $HOCH_2C(O)OCH_2-$ (HOGG−) (4.13 ppm) and the $HOCH_2C(O)OCH(CH_3)-$ (HOGL−) (4.09 ppm) groups (Figure 3, parts iii and iv). In particular, the latter may only derive from transesterification reactions generating the LGL sequence (Scheme 2b). As a matter of fact, this kind of transesterifications was the most abundant for the explored aluminum catalysts (see above). Accordingly, signals due to the hydroxyl end groups bound to a lactyl unit (HOLG−) (4.20 ppm), which can be only generated through the less abundant transesterification reactions depicted in Scheme 2a, always showed a negligible intensity.

Finally, the low intensity observed for the HOLL− (4.23 ppm) groups may be rationalized taking into account that the Al−lactidyl active centers, from which these end groups can be generated, are the most involved in the transesterification reactions.

The whole picture suggests that a coordination−insertion mechanism, proceeding through acyl−oxygen cleavage of both the monomers, should be operative in these systems. The occurrence of the different transesterification reactions with the relative frequencies detailed above well explains the relative ratio of the observed end groups.

Determination of the Molecular Weight of the Samples. The molecular weights of the obtained polymers were evaluated by gel permeation chromatography (GPC) and by NMR, being known the end group signals (*see* above). Representative results are reported in Table 2.

The molecular weight of the poly(*rac*-lactide)s, evaluated by GPC vs polystyrene standards, using THF as elution solvent, corrected by a factor of 0.58,[29] resulted $M_{n,GPC}$ = 11.4 kDa for run 2 and 12.2 kDa for run 4. Monomodal molecular weight distributions were observed. 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. On the contrary, the assessment of the molecular weights for the PGA homopolymers (see runs 1 and 3, Table 1) was not possible by either GPC or NMR analysis, since the polymers are insoluble in almost all solvents.[25]

The determination of the molecular weights of the poly(glycolide-*co*-*rac*-lactide) samples was performed by GPC in a chloroform/HFIP 99/1 solvents mixture. Low molecular weight samples, prepared by a lower monomer/inititator feed ratio, dissolved even in THF, therefore in these cases the GPC analysis was performed by using THF as eluent. As previously highlighted in the literature,[7] the radius of gyration *Rg* of the poly(glycolide-*co*-*rac*-lactide) samples 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 (1.1−2.4). In detail, catalyst **1** generally produced polymers having narrower dispersities than those obtained with catalyst **2**; this behavior should be related to the presence of the bulkier cumyl substituent on the phenolate ring, which should hamper the transesterification reactions.

Interestingly, the molecular weights evaluated by NMR are in reasonable agreement with the theoretical molecular weights,

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$M_{n,th}$, obviously indicating that the molecular weight could be easily tuned by adjusting the monomer/catalyst feed ratio. As a matter of fact, lower molecular weight samples ($M_n \approx 5$ kDa; Table 1, runs 15−16) and higher molecular weight samples ($M_n \approx 20-30$ kDa; Table 1, runs 17−18) have been obtained by adjusting the monomers feed.

Thermal Characterization of Poly(glycolide-*co*-*rac*-lactide). Thermal analysis of the copolymers was carried out by means of differential scanning calorimetry (DSC), from −20 to +260 °C. The glass transition temperature, T_g, and the melting temperature, T_m, are given in Table 3.

Table 3. Homo- and Copolymerization of Glycolide and *rac*-Lactide in Bulk: Thermal Properties[a]

run	catalyst	f_{GA}[b]	F_{GA}[c]	T_g (°C)[d]	T_m (°C)[d]	ΔH_m (J g^{-1})[d]
3	**2**	100	100	n.o.	222.6	83.8
4[e]	**2**	0	0	48.3	n.o.	n.o.
5	**1**	70	70	43.5	n.o.	n.o.
6	**1**	50	51	47.2	n.o.	n.o.
7	**1**	30	30	49.2	n.o.	n.o.
8	**2**	80	81	41.2	201.3	50.3
10	**2**	60	59	40.7	n.o.	n.o.
12	**2**	40	41	45.8	n.o.	n.o.
14	**2**	20	22	51.4	n.o.	n.o.

[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 monomer(s) to precatalyst in the feed = 100. [b]f_{GA}, molar percentage of glycolide in the feed. [c]F_{GA}, content of glycolide in the copolymer (mol %), as determined by ^{1}H NMR (DMSO-d_6, 100 °C). [d]Values reported for the second heating cycle. [e]F_{LA} = 100. n.o. = not observed.

In Figure 4 are shown the thermograms of the poly(glycolide) and of poly(glycolide-*co*-*rac*-lactide) samples

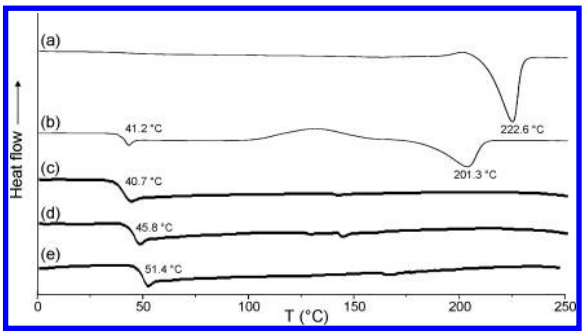

Figure 4. DSC thermograms (run II) of poly(glycolide-*co*-*rac*-lactide) obtained with complex **2**: (a) F_{GA} = 100 (Table 3, run 3); (b) F_{GA} = 81 (Table 3, run 8); (c) F_{GA} = 59 (Table 3, run 10); (d) F_{GA} = 41 (Table 3, run 12); (e) F_{GA} = 22 (Table 3, run 14).

obtained with catalyst **2**. The thermogram of the poly(glycolide) displays a melting peak at 226 °C, with endotherm of fusion of 83.8 J·g^{-1} (Figure 4a). The T_g of this poly(glycolide) sample was not observed with our analytical settings in agreement with the thermal behavior of a medium molecular weight poly(glycolide) (M_w = 10−20 kDa).[30]

All the copolymers were amorphous, apart from the sample prepared with 80 mol % of glycolide (Table 3, run 8); in this case a crystallization exotherm and a melting peak can be seen in the thermogram. This observation is in agreement with previously reported cases of poly(glycolide-*co*-*rac*-lactide) with a content of glycolide of 80 mol % or higher.[3,16,17]

The DSC thermograms recorded during the second scan for all the samples displayed a unique glass transition temperature with values intermediate between those of the pure homopolymers and changing as a function of the composition. The experimental T_g values linearly increase by decreasing the glycolide content in the copolymer (Figures 4 and Supporting Information), which in turn reflects the feed composition. It is noteworthy to highlight that it is possible to control the microstructure and the thermal properties, by choosing the appropriate monomers feed.

Copolymerization of Lactide and Glycolide in Solution. Copolymerization of glycolide and lactide were also performed in solution. In order to elucidate the influence of the reaction conditions on yields, molecular weights and composition of the copolyesters, the following experimental parameters were systematically varied: (i) nature of the catalyst, (ii) nature of the solvent, (iii) temperature, and (iv) reaction time. In all the cases equimolar amounts of the two monomers were used.

The obtained polymeric samples were characterized by ^{1}H and ^{13}C NMR, GPC, and DSC analysis. The main results are summarized in Tables 4 and 5.

Carrying out the polymerization experiments in toluene at 90 °C, only poly(glycolide) was obtained in agreement with the higher reactivity of glycolide. Polymerization tests performed at 90 °C with catalyst **1** in two solvents of different polarity, namely chlorobenzene and xylenes, afforded copolymers with higher incorporation of glycolide and very long glycolide sequences (Table 4, runs 20 and 22), thus confirming the higher reactivity of glycolide. The boiling points of these solvents allowed to carry out the polymerization runs at higher temperatures (see Table 4). In these cases, polymeric samples with a glycolide content ranging between 49 and 66% were obtained showing that, in these experimental conditions, comparable incorporation of both monomers is obtained. The randomness of these copolymers was assessed by the calculation of the block lengths of *rac*-lactide and glycolide within the copolymer chain, while the occurrence of the second mode of transesterification was quantified by analysis of the signals due to the GLG and LGL groups in the NMR spectra of the copolymers.[5,16]

For copolymers produced by complex **1** in the two different solvents, the average lactide and glycolide block lengths were higher than 2 (Table 4, runs 21, 23), indicating a nonrandom copolymer chain. DSC analysis of the copolymers obtained by complex **1** showed two T_g values (Table 5, runs 21, 23; Figures S11−S12). Melting endotherm of glycolide blocks crystalline phase was observed for the copolymer obtained in run 21, whereas the sample obtained in run 23 should have shorter glycolide blocks, in agreement with the presence of the GLG sequences. The whole picture is compatible with the formation of copolymer samples with a blocky structure showing a first sequence comprising glycolidyl blocks separated by short lactyl and lactidyl groups and a second part of the chain with a complementary distribution of the two monomers.

Copolymers obtained by complex **2** at higher temperature showed lower L_{GG} and L_{LL} values, and higher second mode of transesterification values (Table 4, runs 25−26). In particular, average lactide and glycolide block lengths for the copolymer obtained in run 26 was close to 2, the value expected for a completely random copolymer. Accordingly, these samples

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Table 4. Copolymerization of *rac*-Lactide and Glycolide Promoted by Complexes 1 and 2 in Solution[a]

run	catalyst	solvent	T (°C)	yield (%)	F_{GA}[b]	L_{GG}[c]	L_{LL}[c]	T_{LGL}[d]	T_{GLG}[d]
19	**1**	toluene	90	45	99	n.d.	n.d.	n.o.	n.o.
20	**1**	chlorobenzene	90	68	72	5.91	2.32	0.28	0.05
21	**1**	chlorobenzene	120	66	54	2.94	2.50	0.63	n.o.
22	**1**	xylenes	90	43	90	7.23	0.80	n.o.	0.94
23	**1**	xylenes	130	66	59	2.96	2.06	0.73	0.13
24	**2**	toluene	90	41	89	n.d.	n.d.	n.o.	n.o.
25	**2**	chlorobenzene	120	67	66	2.75	1.32	1.39	0.08
26	**2**	xylenes	130	79	49	1.94	2.02	0.95	0.09

[a]Polymerization conditions: precatalyst = 25 μmol; MeOH = 25 μmol (0.25 mL of a 0.1 M toluene solution); solvent = 5 mL; glycolide = 2.50 mmol, *rac*-lactide = 2.50 mmol, t = 180 min. [b]F_{GA}, content of glycolide in copolymer (mol %), as determined by ^{1}H NMR (DMSO-d_6, 100 °C). [c]Average sequences length of glicolidyl (GG) and lactidyl (LL) blocks in the copolymer; as calculated by ^{13}C NMR (DMSO-d_6, 100 °C). [d]Yield of the second mode of transesterification (%) of glycolidyl (LGL) and lactydyl (GLG) sequences; calculated from ^{1}H NMR (DMSO-d_6, 100 °C). n.d. = not determined; n.o. = not observed.

Table 5. Molecular Characterization and Thermal Analysis of PLGAs Prepared with Complexes 1 and 2 in Solution[a]

run	$M_{n,th}$ (kDa)[b]	$M_{n,NMR}$ (kDa)[c]	$M_w/M_{n,GPC}$[d]	T_g (°C)[e]	T_m (°C)[e]	ΔH_m (J g^{-1})[e]
20	21.4	22.3	1.3	41.3; 51.1	199.0	36.7
23	23.6	22.8	1.3	42.0; 52.7	n.o.	n.o.
25	21.0	14.9	1.3	42.7	187.7	6.9
26	26.0	21.4	n.d.	45.9	n.o.	n.o.

[a]General conditions: precatalyst = 25 μmol; MeOH = 25 μmol (0.25 mL of a 0.1 M toluene solution); solvent = 5 mL; glycolide, 2.50 mmol, *rac*-lactide = 2.50 mmol; t = 180 min. [b]Theoretical molecular weight. [c]Molecular weight determined by ^{1}H NMR (DMSO-d_6, 100 °C). [d]Determined by gel permeation chromatography (GPC) vs polystyrene standards, elution solvent mixture: chloroform/HFIP 99/1. [e]Values reported for the second heating cycle. n.d. = not determined; n.o. = not observed.

displayed unique glass transition temperature (Table 5, runs 25−26; *see* also Supporting Information), as observed in the copolymerizations performed in bulk (*see* above).

To get more insights on the copolymerization behavior of catalyst **2**, the effect of the polymerization time was studied. A polymerization run, performed in the same conditions (f_{GA} = 50) than run 26 in Table 4, was quenched at low conversion (t = 0.5 h). Comparison of the two products showed that in the beginning of the polymerization the L_{GG} (2.95) are higher than L_{LL} (0.89), thus indicating that glycolide is polymerized first (F_{GA} = 70). At higher conversion the L_{GG} and L_{LL} values were close to 2, as expected for a random copolymer. Thus, the transesterification reactions, taking place during the polymerizations, are mainly responsible of the random structure.

End group analysis performed by ^{1}H NMR spectroscopy on the obtained copolymers showed polymer chains end-capped with a methyl ester and a hydroxyl group.

The molecular weights of selected samples were evaluated by GPC in the chloroform/HFIP 99/1 solvents mixture. As discussed above, the GPC analysis is not reliable for the assessment of the real molecular weight of the glycolide/lactide copolymers. Nevertheless, the GPC results indicated fine dispersities (M_w/M_n = 1.3), narrower than those of the copolymers prepared in bulk (M_w/M_n = 1.1−2.4; see Table 2). Molecular weights calculated from ^{1}H NMR spectra are in good agreement with the theoretical values for the samples obtained with catalyst **1**, while they are lower for the samples obtained with catalyst **2**.

Block Copolymerization. The synthesis of block copolymers was attempted by using catalyst **1** in xylenes at 130 °C. The block copolymer was obtained by sequential addition of the two monomers, polymerizing first the *rac*-lactide. After 4.5 h an aliquot was withdrawn from the reaction mixture to assess the molecular weight of the poly(lactide) block by NMR (2.5 kDa). The addition of the glycolide monomer to the mixture yielded the product in 10 min, and the precipitated polymer was analyzed by NMR.

The ^{13}C NMR analysis showed the exclusive presence of the carbonyl signals attributed to the homosequences LLLL and GGGG. Signals due to transesterification processes were negligible. The ^{1}H NMR analysis of the copolymer confirmed the reflection of the feed in the copolymer composition (*see* Supporting Information). The lengths of the glycolidyl and lactidyl blocks were determined by evaluation of the integrals of the main signals, and were found to be as follows: L_{GG} = 15; L_{LL} = 31. The ^{1}H NMR analysis, moreover, showed the exclusive presence of end groups LL−OCH_3 (at 3.70 ppm), derived from the insertion step of the *rac*-lactide monomer into the Al−OCH_3 bond, and the HOGG− end group (at 4.13 ppm), generated by hydrolysis of the growing poly(glycolide) block.

Formation of the poly(*rac*-lactide-*block*-glycolide) copolymer was definitely proved by DOSY NMR experiment (Figure 5).

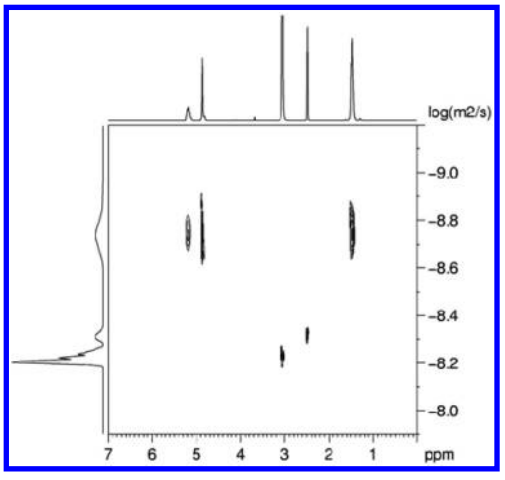

Figure 5. 2D DOSY NMR (400 MHz, DMSO-d_6, 80 °C) of the block copolymer obtained with compound **1**. Signals at 2.50 and 3.06 ppm are relative to the deuterated solvent (DMSO-d_6) and adventitious water, respectively.

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This experiment, indeed, providing diffusion coefficients of molecules related to hydrodynamic radius and molecular weight, is becoming a very powerful tool in investigating polymer properties.[31] In our case, the DOSY spectrum of the sample obtained by the block copolymerization reaction showed that the multiplets of the poly(*rac*-lactide) block (centered at 5.20 and 1.49 ppm) and the singlet of the poly(glycolide) block (at 4.87 ppm) lied at the same diffusion coefficient, and therefore belonged to the same polymeric chains.

The molecular weight estimated by NMR was found to be close to the theoretical one ($M_{n,NMR}$ = 3.7 kDa *vs* $M_{n,th}$ = 3.1 kDa). DSC analysis (*see* Supporting Information) evidenced the presence of only one T_g at 45.4 °C, attributable to the *rac*-lactide block, while no T_g was observed for the homoglycolide block, as observed above for the poly(glycolide) (*see* Figure 4a; Table 3, run 3).

Thus, the sequential addition of the two monomers leads to the achievement of a poly(*rac*-lactide-*block*-glycolide) copolymer, which represents an experimental evidence of the tendentially *living* behavior of the polymerization promoted by this class of initiators.

It was found, moreover, that, in order to obtain the block copolymer, glycolide had to be added to living PLA chains. The opposite sequence of monomers addition led mainly to poly(glycolide) and a low amount of the block copolymer. The importance of the order of the monomer addition in the block copolymerization was previously underlined in the literature.[10,32]

CONCLUSIONS

The copolymerization of glycolide and *rac*-lactide produces biocompatible and biodegradable materials, which have long been of interest for biomedical application. In this regards the search for efficient ROP initiators for the synthesis of PLGA copolymers having controlled composition and microstrure is a very stimulating field.

We have shown that salicylaldiminato aluminum compounds are efficient initiators in the homo- and copolymerization of *rac*-lactide and glycolide. A highly versatile behavior has been recognized, and PLGAs having different microstructures, from random to blocky to multiblock, have been obtained as the polymerization conditions have been changed.

Copolymerization in bulk produced random copolymers, whose average block lengths linearly increase with the monomer feed ratio. The copolymers were amorphous, and their T_g could be nicely modulated by the feed.

The copolymer microstructure reasonably should result from transesterification processes taking place together with the main copolymerization reaction. Interestingly, the values of the coefficients of the second mode of transesterification T_{LGL} were higher than the T_{GLG} ones of 1 order of magnitude, thus indicating that the transterification reaction involving the attack of active lactidyl chain end on preformed glycolidyl segments was preferred. On the contrary, as previously observed, the tendency of these complexes to break the lactidyl unit into two lactyl fragments was low. Such a behavior is in contrast with previously reported ROP initiators for the synthesis of PLGAs.

On the contrary, copolymerization performed in several solvents afforded mainly blocky copolymers, with sequence blocks lengths higher than 2. Finally, the sequential addition of the two monomers afforded diblock copolymers, thus indicating a certain living character of the polymerization.

In all the cases, GPC analysis disclosed monomodal molecular weight distribution with narrow dispersities. A reasonable agreement between the theoretical molecular weights and the experimental ones evaluated by NMR analysis was observed. As a result a controlled polymerization behavior can be recognized in the polymerization, and the copolymers molecular weight could be adjusted by regulating the monomers/initiator feed ratio.

We can envisage that these results should be of interest in applications where modulated thermal, physical and degradation properties of PGA/PLA based materials are required.

ASSOCIATED CONTENT

Supporting Information

NMR spectra of complexes **1** and **2**, NMR spectra and DSC thermograms of selected polymers, plot of L_{LL} vs L/G, data of copolymerization of L-LA and GA. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to Prof. Adolfo Zambelli, on the occasion of his 80th birthday

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