Synthesis and Characterization of Polyphosphazene-*block*-polyester and Polyphosphazene-*block*-polycarbonate Macromolecules

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ABSTRACT: Amino end-terminated poly(L-lactic acid), poly(trimethylene carbonate), and polycaprolactone were synthesized via ring-opening polymerization techniques. The amino terminus was used to form a covalent link to poly(dichlorophosphazene), itself synthesized using a living cationic polymerization. The chlorine atoms in the polyphosphazene blocks were subsequently replaced by trifluoroethoxy groups. This is the first reported synthesis of block copolymers of polyphosphazenes linked to polyesters or polycarbonates. The molecular structure of each copolymer was established using multinuclear NMR techniques. Molecular weight analysis was used to provide confirmatory evidence that the two polymers chains were covalently linked. Thermal analysis results showed evidence that in the solid state the two blocks were phase-separated because the parent thermal transitions were detectable for each copolymer.

Introduction

Various polyphosphazene architectures can be synthesized by changes in the reagents used to replace chlorine atoms in poly(dichlorophosphazene) to optimize many different properties. Numerous polyphosphazenes have been synthesized, with applications that range from fire retardants to tissue engineering scaffolds.[1] The classical synthesis of poly(dichlorophosphazene) utilizes a thermal ring-opening polymerization of the cyclic trimer, hexachlorocyclotriphosphazene, $(NPCl_2)_3$.[2−4] However, although this route is convenient for the synthesis of linear, single- or mixed-substituent polymers, it is not appropriate for the assembly of more elaborate architectures, such as block copolymers, that involve linear polyphosphazenes connected to other polyphosphazenes or to organic polymers.

In 1995, a new synthetic route was introduced that allows the synthesis of polyphosphazenes via a living cationic polymerization pathway.[5] This route has led to the development of new macromolecules with block copolymer structures and with novel properties derived from the organic polymer component as well as the polyphosphazene. The process described here begins with telechelic organic polymers, with an amino end group. Two variants have been developed. First, a trifluoroethoxy-substituted phosphoranamine monomer is linked to the organic polymer via its amino terminus, and a polyphosphazene chain is then grown from this site using a chlorophosphoranamine monomer. Alternatively, as used in the present work, the phosphoranamine-terminated organic polymer can be used to terminate a preformed living poly(dichlorophosphazene) chain. The final polyphosphazene structure is then produced in the final step by chlorine replacement reactions by the appropriate organic nucleophiles. The living cationic route yields polymers with well-defined molecular weights.

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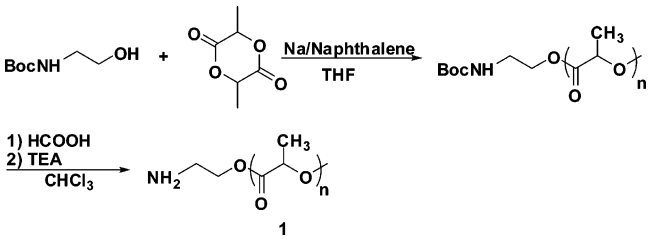
Scheme 1. Preparation of Amine-Terminated Poly(L-lactic acid) (PLA), Polymer 1[20]



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Since the development of this living polymerization route, polyphosphazenes have been synthesized with a range of different polymer block structures, such as polyphosphazene-*block*-polyphosphazene copolymers,[6−8] poly(ethylene oxide)-*block*-polyphosphazene copolymers,[9−11] polystyrene-*block*-polyphosphazene copolymers,[12−14] poly(methyl methacrylate)-*graft*-polyphosphazene copolymers,[15] polysiloxane-*block*-polyphosphazene copolymers,[16] and poly(propylene glycol)-*block*-polyphosphazene copolymers.[17] Developing uses for these macromolecules include lithium ion conduction membranes and micelles for drug delivery.

In this work, we report the synthesis of polyphosphazene-*block*-polyesters and polyphosphazene-*block*-polycarbonates. Poly(lactic acid) (PLA), polycaprolactone (PCL), and poly(trimethylene carbonate) (PTMC) were synthesized by ring-opening polymerization techniques. These organic polymers were prepared with a single amino terminus and a phosphoranamine end unit that was later utilized as a termination point for the cationically polymerized polyphosphazene chain. Molecular structure determination and molecular weights were used to verify the synthesis of the target block copolymers. The objective of this study was to develop reaction conditions that would lead to well-defined block copolymers with one block (the phosphazene component) that is hydrolytically stable. This would then serve as a model system for other, more challenging polymers in which both blocks are hydrolytically sensitive.

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Table 1. Reaction Quantities for the Synthesis of Polymers 4−6

polymer	amine-terminated polymers **1**−**3**	$Br(CF_3CH_2O)_2P{=}N{-}SiMe_3$	Et_3N
4	2.0 g, 0.4 mmol[a]	40 mg, 0.4 mmol	57 mg, 0.6 mmol
5	2.0 g, 0.1 mmol[a]	58 mg, 0.1 mmol	37 mg, 0.4 mmol
6	1.0 g, 0.07 mmol[a]	32 mg, 0.08 mmol	20 mg, 0.2 mmol

[a] Determined as the millimoles of end groups as calculated based on the M_n.

Table 2. Reaction Quantities for the Synthesis of Polymers 7−9

polymer	PCl_5	$(CF_3CH_2O)_3P{=}N{-}SiMe_3$	$(Cl)_3P{=}N{-}SiMe_3$	Na^0	CF_3CH_2OH
7	167 mg, 0.8 mmol	166 mg, 0.4 mmol	1.8 g, 8.0 mmol	405 mg, 18 mmol	2.0 g, 20 mmol
8	50 mg, 0.2 mmol	50 mg, 0.1 mmol	2.7 g, 12.1 mmol	557 mg, 24 mmol	2.7 g, 27 mmol
9	28 mg, 0.1 mmol	28 mg, 0.07 mmol	1.5 g, 6.7 mmol	300 mg, 14 mmol	1.5 g, 15 mmol

Table 3. Molecular Characterization Data for Polymers 7−9

		mol wt (kg/mol)		
polymer	^{31}P NMR (ppm)	M_w	M_n	T_g (°C)
7	8.4	27	15	−40,[a] 48[b]
8	8.1	56	30	−40,[a] −21[c]
9	8.1	53	30	−40,[a] −60[d]

[a] Glass transition temperature for the polyphosphazene block. [b] Glass transition temperature for the poly(L-lactide) block. [c] Glass transition temperature for the poly(trimethylene carbonate) block. [d] Glass transition temperature for the polycaprolactone block.

Experimental Section

Materials. All reactions were carried out under a dry argon atmosphere using standard Schlenk line techniques. Dichloromethane, tetrahydrofuran, toluene, and triethylamine (EMD) were dried using solvent purification columns.[18] Phosphorus pentachloride was purified by sublimation before use. 2,2,2-Trifluoroethanol and caprolactone were distilled from CaH_2. All other materials were used as received, unless otherwise noted. The synthesis of (dimethylamino)pyridine−toluenesulfonate (DPTS),[19] $Cl_3P{=}NSiMe_3$[17], and $Br(CF_3CH_2O)_2P{=}NSiMe_3$[17] were carried out using procedures described in the literature.

Equipment. ^{31}P and ^1H NMR spectra were obtained with use of a Bruker 360 WM instrument operated at 145 and 360 MHz, respectively. Gel permeation chromatograms were obtained using a Hewlett-Packard HP 1100 gel permeation chromatograph equipped with two Phenomenex Phenogel linear 10 columns and a Hewlett-Packard 1047A refractive index detector. The samples were eluted at 1.0 mL/min with a 10 mM solution of tetra-*n*-butylammonium nitrate in THF. The molecular weight determinations were obtained after comparison to the elution times of calibrated polystyrene standards. Glass transition temperatures were measured with a TA Instruments Q10 differential scanning calorimetry apparatus with a heating rate of 10 °C/min and a sample size of ca. 10 mg.

Synthesis of Boc−Aminoethanol-Terminated Poly(L-lactic acid) (PLA). This synthesis was adapted from previous reports.[20] The following procedure was carried out in an inert atmosphere glovebox. Naphthalene (128 mg, 1.0 mmol) and sodium (230 mg, 1.0 mmol) were mixed in THF (1 mL) at room temperature for 20 min. This mixture was added to a solution of Boc−aminoethanol (40 mg, 0.25 mmol) in THF (1 mL), and the mixture was stirred for 20 min at room temperature. The initiator solution (1 mL) was added to a solution of L-lactide (7.2 g, 49.6 mmol) in THF (14 mL). The solution turned opaque white and became viscous. Termination of the polymerization after 30 min was accomplished by the addition of acetic acid. The polymer solution was concentrated and precipitated into hexanes. Purification was achieved by two additional precipitations from THF into hexanes. ^1H NMR ($CDCl_3$): δ (ppm) 1.38 (s, 9H, CH_3), 1.69 (d, 3H, CH_3), 3.30 (br, 2H, CH_2), 4.22 (br, 2H, CH_2), 4.30 (q, 1H, CH), 5.11 (q, 3H, CH_3).

Deprotection of Boc−Aminoethanol-Terminated Poly(L-lactic acid) (Polymer 1).[20] Boc−aminoethanol-terminated poly(L-lactic acid) was dissolved in trifluoroacetic acid, and the solution was stirred at room temperature for 8 h. The polymer was then concentrated and precipitated into diethyl ether. Further purification involved dissolution of the polymer in THF followed by precipitation into diethyl ether three times. ^1H NMR ($CDCl_3$): δ (ppm) 1.62 (d, 3H, CH_3), 3.25 (br, 2H, CH_2), 4.27 (br, 2H, CH_2), 4.35 (q, 1H, CH), 5.07 (q, 3H, CH_3). M_n = 6500 g/mol.

Synthesis of 4-Nitrophenethanol-Terminated Poly(trimethylene carbonate) (PTMC). This synthesis was adapted from previous reports.[21] The following procedure was carried out in a glovebox. A 1.9 M solution of triethlyaluminum in toluene (2.06 mL, 3.92 mmol) was added slowly to tetrachloroethane (TCE) (25 mL) over 20 min. 4-Nitrophenethanol (655 mg, 3.91 mmol) in TCE was added to this solution. 1,3-Dioxan-2-one (15.0 g, 147 mmol) was dissolved in 30 mL of TCE and was added to the initiator solution. This mixture was removed from the glovebox and heated to 85 °C for 2 h. The polymer was then precipitated into methanol, then redissolved in dichloromethane, and precipitated into methanol two more times. ^1H NMR ($CDCl_3$): δ (ppm) 2.01 (m, 2H, CH_2), 4.12 (t, 4H, CH_2), 7.18 (d, 2H, aromatic), 8.11 (d, 2H, aromatic).

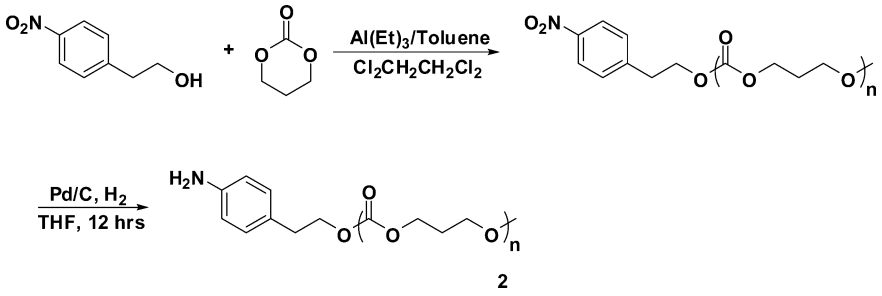
Deprotection of 4-Nitrophenethanol-Terminated Poly(trimethylene carbonate) (Polymer 2).[21] 4-Nitrophenethanol-terminated PTMC (15.0 g) was dissolved in 100 mL of THF, and 10% palladium/carbon (0.6 g) was added. This solution was charged with 45 psi of hydrogen and agitated for 12 h in a Parr hydrogenator. The solution was filtered and centrifuged to remove the catalyst. The solution was then concentrated and precipitated into methanol:water (1:1). ^1H NMR ($CDCl_3$): δ (ppm) 2.11 (m, 2H, CH_2), 4.17 (t, 4H, CH_2), 7.16 (d, 2H, aromatic), 8.22 (d, 2H, aromatic). M_n = 15 000 g/mol.

Synthesis of Boc−Glycine−Polycaprolactone (PCL). This procedure was also adapted from previous reports.[22] Caprolactone (10.3 g, 97.1 mmol) was dissolved in toluene (10 mL), and the solution was cooled to 0 °C. Aluminum triisopropoxide (1.02 g, 5.0 mmol) was dissolved in toluene (40 mL), and the solution was cooled to 0 °C and then added to the caprolactone solution. This mixture was stirred for 2 h at 0 °C, and the reaction mixture was warmed to room temperature before toluene (80 mL) was added. The solution was washed with 20 mL aliquots of 0.3 M aqueous HCl (three times), then dried over $MgSO_4$, concentrated, and precipitated into hexanes. Polycaprolactone (8.0 g, 3.3 mmol), dicyclohexylcarbodiimide (DCC) (1.0 g, 9.4 mmol), and DPTS (0.6 g, 2.0 mmol) were dissolved in chloroform (200 mL). Boc−glycine (0.7 g, 4.0 mmol) was added to this mixture, which was stirred at room temperature for 48 h. The solution was filtered, concentrated, and precipitated into cold methanol. Purification involved dissolution of the polymer in $CHCl_3$ and precipitation into cold methanol (twice). ^1H NMR ($CDCl_3$): δ (ppm) 1.1 (s, 9H, CH_3-end group), 1.3 (b, 2H, CH_2), 1.5 (b, 4H, CH_2), 2.1 (b, 2H, CH_2), 3.3 (b, 2H, CH_2), 4.6 (s, 2H, CH_2 end group).

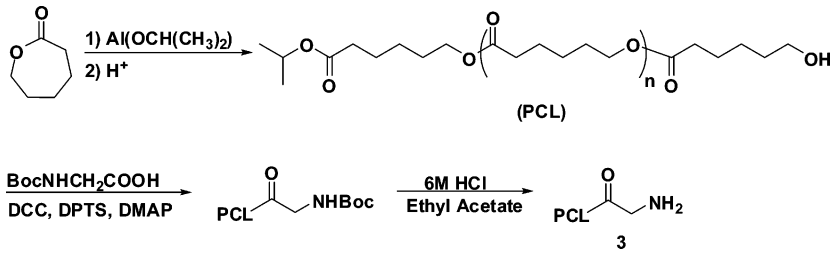
Deprotection of Boc−Glycine−Polycaprolactone (Polymer 3). Boc−Gly−PCL was dissolved in ethyl acetate, and 6 M HCl in ethyl acetate was added. This solution was stirred at room temperature for 4 h, and the solvent was removed. The residue was dissolved in $CHCl_3$ and precipitated into cold methanol (three times). ^1H NMR ($CDCl_3$): δ (ppm) 1.3 (b, 2H, CH_2), 1.5 (b, 4H, CH_2), 2.1 (b, 2H, CH_2), 3.3 (b, 2H, CH_2), 4.6 (s, 2H, CH_2 end group). M_n = 15 000 g/mol.

Polycaprolactone Functionalization with $Br(CF_3CH_2O)_2P{=}NSiMe_3$ (Polymers 4−6). A similar procedure was used to react $Br(CF_3CH_2O)_2P{=}N{-}SiMe_3$ with the amino end terminus of

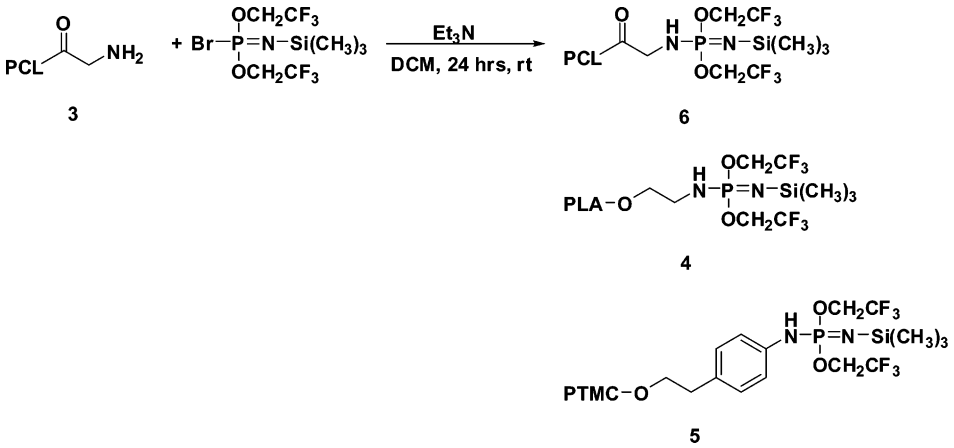
Scheme 2. Preparation of Amine-Terminated Poly(trimethylene carbonate) (PTMC), Polymer 2[21]



Scheme 3. Synthesis of Amine-Terminated Poly(caprolactone) (PCL), Polymer 3[22]



Scheme 4. Synthesis of Polymer 6[a]



[a] The synthesis of polymers **4** and **5** were produced with similar procedures as previously outlined.

polymers **1**−**3**. The attachment of $Br(CF_3CH_2O)_2P{=}N{-}SiMe_3$ to polymer **3** is given as an example. Polymer **3** (1.0 g, 0.07 mmol of end groups) was dissolved in THF (50 mL). Triethylamine (20 mg, 0.2 mmol) was added to this solution, followed by $Br(CF_3CH_2O)_2P{=}N{-}SiMe_3$ (32 mg, 0.08 mmol). The reaction mixture was then stirred at room temperature for 24 h. The solvent was removed under vacuum and the solid product used without further purification. The reactant amounts for polymers **4** and **5** are listed in Table 1.

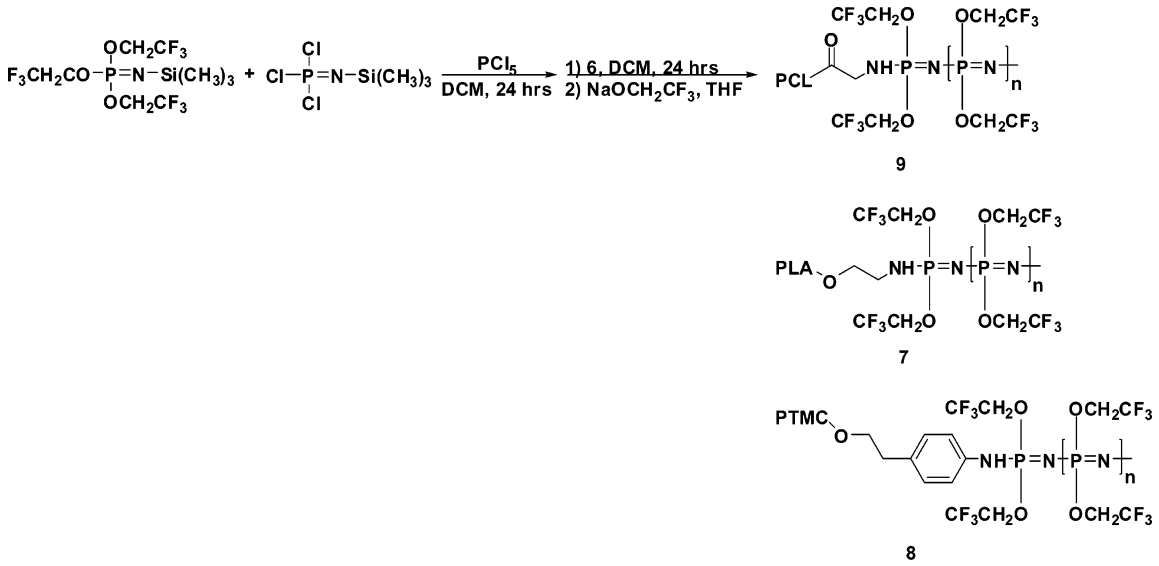
Preparation of Polycaprolactone-*block*-poly[bis(trifluoroethoxy)phosphazenes] (Polymers 7−**9).** To a stirred solution of PCl_5 (28 mg, 0.1 mmol) in dichloromethane (20 mL) was added $(CF_3CH_2O)_3P{=}N{-}SiMe_3$ (28 mg, 0.07 mmol), and the reagents were allowed to react for 8 h. The monomer, $(Cl)_3P{=}N{-}SiMe_3$ (1.50 g, 6.7 mmol), was added to this reaction solution, which was stirred at 25 °C for 16 h. A solution of polymer **4** in dichloromethane (25 mL) was added to terminate the reaction, and the solution was then stirred for 24 h. The dichloromethane was removed under vacuum, and the residual polymer was redissolved in THF. In a separate reaction vessel, sodium (0.30 g, 14.0 mmol) was suspended in THF (20 mL) and trifluoroethanol (1.5 g, 14.7 mmol) was added dropwise. The sodium trifluoroethoxide salt was then added to the block copolymer solution, and the mixture was stirred at room temperature for 24 h. The solvent was then removed. The crude copolymer was purified by dialysis in an 80:20 mixture of THF:H_2O using 6000−8000 MCO tubing. The product amounts and conditions for polymers **7** and **8** are given in Table 2. The molecular characterization data are described in Table 3. The ^1H NMR data remained the same for the organic blocks as previously described, and the protons on the polyphosphazene side group were evident at 4.3 ppm.

Results and Discussion

Synthesis of Polymers 1−**3.** Amine-terminated poly(L-lactic acid)[20] (**1**), poly(trimethylene carbonate)[21] (**2**), and polycaprolactone[22] (**3**) were synthesized via ring-opening polymerization following earlier literature techniques. Poly(L-lactic acid) was synthesized as shown in Scheme 1. The alcohol terminus of Boc-amino ethanol was used to initiate the anionic ring-opening polymerization of the L-lactide with a monomer/initiator (M:I) ratio of 50:1. GPC analysis of the protected PLA showed a molecular weight of M_n = 6500 g/mol. Polymer **1** was isolated after removal of the Boc-protecting group with acetic acid. The final polymer structure was analyzed with ^1H NMR techniques. The acidic deprotection conditions did not affect the molecular weight of polymer **1**, with M_n remaining at 6500 g/mol.

The synthesis of polymer **2** is outlined in Scheme 2. The initiation of trimethylene carbonate was induced by 4-nitrophenethanol and $AlEt_3$ with a monomer:initiator ratio of 75:1. The molecular weight was measured to be 15 000 g/mol (M_n). The nitro end function was reduced by hydrogenation (H_2 and Pd/C) to yield the desired amino end-functionalized polymer

Scheme 5. Synthesis of Polycaprolactone-*block*-poly[bis(trifluorethoxy)phosphazene] (Polymer 9)[a]



[a] A similar procedure was followed for the synthesis of polymers **7** and **8**.

2. The final structure was characterized by ^{1}H NMR techniques. The hydrogenation procedure had no effect on the final molecular weight (M_n = 15 000 g/mol) of polymer **2**.

The synthetic procedure for the synthesis of polymer **3** is shown in Scheme 3. The polymerization of caprolactone was accomplished with use of the initiator, aluminum triisopropoxide, with a monomer:initiator ratio of 50:1. This polymerization produced hydroxyl-terminated polycaprolactone with a molecular weight (M_n) of 15 000 g/mol. The hydroxyl-terminated polymer was end-functionalized with Boc−glycine, followed by removal of the Boc protective group with hydrochloric acid. This produced the amine-terminated polymer **3** that was subsequently used for block copolymer synthesis. Removal of the Boc protection group did not affect the final molecular weight of polymer **3** (M_n = 15 000 g/mol).

Synthesis of Polymers 7−9. The amino end functionality of polymers **1**−**3** was utilized as an attachment point for Br-$(CF_3CH_2O)_2P{=}NSiMe_3$ via nucleophilic replacement of bromine linked to the phosphorus atom. Scheme 4 describes the synthetic procedure for the synthesis of polymers **4**−**6**. The phosphoranamine end unit was used to terminate a living poly(dichlorophosphazene) chain, as shown in Scheme 5, to yield the chloropolyphosphazene block covalently attached to the organic polymer block. The design of the polyphosphazene chain was intended to achieve an equal number of repeat units to that in the corresponding organic polymer block. The chlorine atoms in the polyphosphazene block were then subsequently replaced by trifluoroethoxide side groups to yield polymers **7**−**9**. This yielded a block copolymer with one block that is hydrolytically sensitive (PLA, PTMC, or PCL) and the other block water-stable (trifluoroethoxyphosphazene).

Molecular characterization of polymers **7**−**9** was conducted using multinuclear NMR techniques. The ^{31}P NMR spectra contained a peak at −8 ppm that corresponded to a polyphosphazene with trifluoroethoxide side groups. The ^{1}H NMR spectra of the copolymers showed the presence of the organic blocks as previously detailed, together with a broad peak at 4.4 ppm. This corresponds to the $-CH_2CF_3$ of the polyphosphazene side groups. Molecular weight analysis showed polymer **7** with M_n = 15 000 g/mol and polymers **8** and **9** with M_n = 30 000 g/mol. DSC analysis of the block copolymers revealed phase separation between the two blocks. For polymers **7**−**9**, the polyphosphazene block gave a transition at −40 °C, with a second transition for the parent organic polymers. Polymer **7** showed a transition at 48 °C, polymer **8** at −21 °C, and polymer **9** at −60 °C.

Conclusions

This is the first reported synthesis of polyphosphazene-*block*-polyester or polycarbonate macromolecules. The organic blocks poly(L-lactic acid), poly(trimethylene carbonate), and polycaprolactone were synthesized with amino end functions that were subsequently used to terminate the living cationic polymerization of poly(dichlorophosphazene). After chlorine replacement by trifluorethoxy groups, the final polymers were analyzed with multinuclear NMR, GPC, and DSC techniques to confirm the molecular structures. These new block copolymer architectures are prototypes for the further development of this system. The use of side groups other than trifluoroethoxy in the polyphosphazene blocks is expected to lead to totally bioerodible block copolymers with hydrolysis profiles and physical properties that can be optimized for a variety of biomedical uses, including tissue engineering and controlled drug delivery.

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