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Biodegradable Ionomers

Björn Atthoff, Fredrik Nederberg, Jöns Hilborn, and Tim Bowden*

Department of Materials Chemistry, Uppsala University, Box 538, 75121 Uppsala, Sweden

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ABSTRACT: Several telechelic anionic or cationic ionomers were synthesized starting from poly(trimethylene carbonate) diols (PTMC) of different molecular weight, ranging from 1000 to 12 000 g/mol. In the synthesis of the anionomer, addition of sulfur trioxide trimethylene complex to the PTMC end-group hydroxyls and subsequent ion exchange afforded a disulfate monoester sodium salt. The cationomer was synthesized in two steps. Acylation of the PTMC diol using 4-chlorobuturyl chloride was followed by displacement of the alkyl chloride with trimethylamine to give a quaternary ammonium salt. These ionomers showed excellent swelling properties, up to around 500% in H_2O, while the unfunctionlized PTMC did not swell at all. The lowest molecular weight ionomers were soluble in both water and chloroform. The physical properties of the ionomers were analyzed with oscillating rheological experiments. Interestingly, the ionomers displayed “rubbery plateau”. The mechanical and swelling properties may be linked to phase separation resulting in ionic aggregates within the bulk, which may function as physical cross-links. At ambient temperatures, the PTMC starting material behaved like a highly viscous fluid, while the ionomers behaved as elastomers. In a hydrophilic environment, the ionomers displayed a surface rearrangement making the surface of the ionomer hydrophilic by allowing the ionic end groups to appear at the water ionomer interface. In air or vacuum all the ionic groups were found in the bulk of the material as analyzed by XPS or contact angle measurements. Finally, we showed that with the specific ionic groups it was possible to complex specific molecules to the ionomers.

Introduction

This paper reports the synthesis of telechelic low-molecular-weight ionomers based on poly(trimethylene carbonate) (PTMC) to provide biomimetic, rubberlike, and biodegradable materials.

Polymers prepared from glycolic acid and lactic acids have found a multitude of uses in the medical industry, beginning with the biodegradable sutures in the 1970s.[1] Since that time, diverse products based on lactic and glycolic acid and also other materials, including poly(dioxanone),[2] poly(trimethylene carbonate), and copolymers,[3] and poly(ϵ-caprolactone) homopolymers and copolymers,[4] have been accepted for use as medical devices. In addition to these approved devices, research is conducted to extent the scope of use including polyanhydrides,[5] poly(ortho ester)s,[6] polyphosphazenes,[7] and other biodegradable polymers. Besides eliminating the need for a second surgery, the biodegradation is useful for applications such as carriers for controlled drug delivery. In general, synthetic biodegradable polymers offer specific advantages to natural materials in that they can be tailored to give a wider range of mechanical properties and more predictable lot-to-lot uniformity than materials from natural sources. A drawback is, however, the lack of specific biochemical interactions.

Strategies to provide such interactions involving the introduction of specific functional groups,[8] hydrophilic segments,[9] or biomimetic functionalities have been reported.[10] Synthetically, this requires consideration of the inherent labile nature of the biodegradable polymer backbone. When reactivity and solubility allow, the introduced moiety being the initiator ensures incorporation into all chains. Many of the interactions in vivo, however, occur in an aqueous environment with water-soluble compounds. Introduction of these requires the use of protective groups or mild and efficient postmodification reactions.

A noticeable biomimetic motif is the zwitterionic water-soluble head of the phospholipid phosphatidylcholine being a major component of the cell membrane. Polymers carrying phosphorylcholine (PC) provides both cell membrane mimicry and amphiphilicity, allowing for applications as for instance coatings by hydrophobic interactions and micellar particles.[11] Such materials have in general demonstrated excellent prevention of nonspecific protein adsorption. A recent extension of the PC polymers has been toward biodegradable materials. Quantitative postmodification reactions with simple workup procedures have given materials that spontaneously enrich at water interfaces,[12] form ionomers by zwitterions association in the bulk,[13] swell in water, and may encapsulate and release protein.[14] As such, they may be applicable for blood contacting application where prevention of interactions with the blood may be desired.[13]

Nature uses various means of controlling interactions, including prevention of unspecific interactions and promotion of specific interactions where among the simplest means is by charge. Negatively charged heparin[15] is abundant in the human body and is rich in sulfate groups responsible for a myriad of interactions. Positively charged entities in biological molecules include the trimethylammonium functionality. As an example, D- and L-carnitite functions as a complexing carrier for the transport of long-chain Acyl Coenzyme A in and out from the mitochondrial matrix.[16] To extent the capabilities of synthetic biodegradable polymers, we suggest postmodification strategies of preformed polymers to introduce specific charges. Thereby interactions in an aqueous environment could be promoted between synthetic materials and natural biomolecules.

Specifically in this paper, poly(trimethylene carbonate) diols with molecular weights ranging from 1000 to 12 000 g/mol have been synthesized and quantitatively functionalized with biomimetic cationic and anionic end groups. These biodegradable ionomers exhibit rubberlike elasticity at physiological temperatures. In addition, they are capable of adsorbing significant amounts of water with spontaneous surface enrichment of the charged groups, enabling selective adsorption of complementary charged molecules.

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* To whom correspondence should be addressed. E-mail: Bowden@polymer.uu.se.

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Experimental Section

Materials. Prior to use, pyridine, acetonitrile, and 1,4-butanediol (Aldrich) were refluxed over calcium hydride, distilled, and stored under argon. Chloroform and dichloromethane (VWR) were washed with water, dried with magnesium sulfate, and distilled over calcium hydride. Stannous 2-ethylhexanoate (∼95%), sulfur trioxide−trimethylamine complex, malachite green carbinol hydrochloride, sodium hydrogen carbonate (99.7%), 4-chlorobutyryl chloride, 1,3-dicyclohexylcarbodiimide (99%), *p*-toluenesulfonic acid monohydrate (>98.5%), 4-(dimethylamino)pyridine (99%), trimethylamine, (3-carboxypropyl)trimethylammonium chloride (techn. grade), *N*,*N*-dimethylformamide (DMF) (99.5%) (Aldrich), benzyl alcohol (99%) (Lancaster Synthesis), diethyl ether (analytical grade), methanol (>98.5%), phosphate buffered saline (PBS) (VWR), and trimethylene carbonate (Boehringer Ingelheim), Tropaeolin OO (Riedel-de Haën), were used as received.

Instrumentation. ^{1}H NMR spectra were recorded using a JEOL ECP 400 MHz spectrometer with the solvent proton signal as an internal standard. Rheological behavior was analyzed with an AR2000 rheometer from TA Instruments equipped with parallel plate geometry with a diameter of 8 mm. An oscillating torque experiment was performed at 1 Hz, 0.1 mrad displacement, and a heating ramp with 1 °C/measurement point from −50 to 90 °C. For contact angle measurements a FTÅ goniometry equipment with FTÅ 200 Video software from First Ten Ångström Inc. was used. A 10 μL drop of air was applied to the upside-down polymer film submerged in water, and the inverse contact angle was determined. XPS analysis was performed on a Phi Electronics Quantum 2000, using a monochromatic Al X-ray source ($h\upsilon = 1486.86$ eV). An initial survey spectrum was recorded followed by a depth sputter profile (1.8 s, 20.8 W, 100 μm, 45.6°, 58.7 eV) where sulfur, chlorine, and nitrogen were recorded. Size exclusion chromatography (SEC) was performed on a Waters Alliance GPCV2000 with three Styragel columns (HR1−HR3−HR5E), the detectors used were the viscometer and the RI, and Empower was the software used to evaluate the results.

Synthesis of Poly(trimethylenecarbonate) Diol (PTMC) (1). The procedure for the 4000 g/mol oligomer is given as example. A 50 mL two-necked Schlenk flask equipped with a stir bar was carefully flame-dried under vacuum and purged with nitrogen before 5.0 g (49.0 mmol) of trimethylene carbonate, 25 mg (61 μmol) of $Sn(Oct)_2$, and 0.11 g (1.225 mmol) of 1,4 butanediol were added inside the glovebox for a DP of 40 (20/arm). The closed reaction mixture was stirred at 110 °C for 4 h in an oil bath. Following completion of the reaction, the PTMC was dissolved in chloroform and precipitated in 1 L of cold methanol. The precipitate was allowed to sediment and washed repeatedly with methanol and dried under vacuum at 40 °C until constant weight. Yield: 97%. ^{1}H NMR ($CDCl_3$) = 1.73 (m, 2H, $-CH_2-$, initiator), 1.86 (m, 2H, $-\mathit{CH_2}-CH_2-OH$, end group,), 2.05 (m, 2H, $-CH_2-$, poly), 3.73 (t, 2H, $-\mathit{CH_2}-OH$, end group), 4.22 (t, 4H, $-CH_2-$, poly).

Synthesis of α,ω-Di(3-sulfoxypropoxycarbonyl)poly(trimethylene carbonate) Trimethylammonium Salt (2). The procedure for the 4000 g/mol oligomer is given as example. A 50 mL two-necked Schlenk flask equipped with a stir bar was carefully flame-dried under vacuum and purged with nitrogen before 5.0 g (1.22 mmol) of polymer **1**, 1.70 g (12.2 mmol) of sulfur trioxide−trimethylamine complex, and 20 mL of DMF was added to the flask inside the glovebox. The closed reaction mixture was stirred at 50 °C for 16 h on an oil bath. Aliquots were withdrawn from time to time to monitor the progress of the reaction by ^{1}H NMR analysis. Following completion of the reaction the solution was precipitated into 2 L of diethyl ether. The precipitate was redissolved in dichloromethane, filtered, and precipitated in 1 L of cold methanol. This was done twice. The precipitate was allowed to sediment and washed repeatedly with methanol and then dried under vacuum at 40 °C until constant weight. Yield: 81%. ^{1}H NMR ($CDCl_3$) = 1.73 (m, 2H, $-CH_2-$, initiator), 2.05 (m, 2H, $-CH_2-$, poly), 2.93 (d, 9H, $HN^+(\mathit{CH_3})_3$, counterion), 4.22 (t, 4H, $-CH_2-$, poly).

Ion Exchange of 2 to α,ω-Di(3-sulfoxypropoxycarbonyl)poly(trimethylene carbonate) Sodium Salt (Anionomer) (3). The procedure for the 4000 g/mol oligomer is given as example. A 50 mL two-necked Schlenk flask equipped with a stir bar was carefully flame-dried under vacuum and purged with nitrogen before 5.0 g (1.22 mmol) of polymer **2**, 1.0 g (11.9 mmol) of solid sodium hydrogen carbonate, and 20 mL of DMF were added. The reaction mixture was stirred at room temperature for 16 h. Aliquots were withdrawn from time to time to monitor the progress of the reaction by ^{1}H NMR analysis. Following completion of the reaction the solution was precipitated into 2 L of diethyl ether. The precipitate was redissolved in dichloromethane filtered and precipitated in 1 L of cold methanol. This was done twice. The precipitate was allowed to sediment and washed repeatedly with methanol and then dried under vacuum at 40 °C until constant weight. Yield: 89%. ^{1}H NMR ($CDCl_3$) = 1.73 (m, 2H, $-CH_2-$, initiator), 2.05 (m, 2H, $-CH_2-$, poly), 4.22 (t, 4H, $-CH_2-$, poly).

Synthesis of α,ω-Di(4-chlorobutanoyl) Poly(trimethylene carbonate) (4). The procedure for the 4000 g/mol oligomer is given as example. A 50 mL two-necked Schlenk flask equipped with a stir bar was carefully flame-dried under vacuum and purged with nitrogen before 5.0 g (1.22 mmol) of polymer **1**, 0.31 g (2.94 mmol) 4-chlorobutyryl chloride, and 0.46 g (5.87 mmol) of pyridine were dissolved in 20 mL of dichloromethane. The closed reaction mixture was stirred at room temperature for 24 h before precipitation into 1 L of cold methanol twice. The precipitate was allowed to sediment and washed repeatedly with methanol and then dried under vacuum at 50 °C until constant weight. Yield: 94%. ^{1}H NMR ($CDCl_3$) = 1.73 (m, 2H, $-CH_2-$, initiator), 2.05 (m, 2H, $-CH_2-$, poly), 2.47 (t, $R-O_2C-CH_2-$, end), 3.55 (t, $-CH_2-Cl$, end), 4.22 (t, 4H, $-CH_2-$, poly).

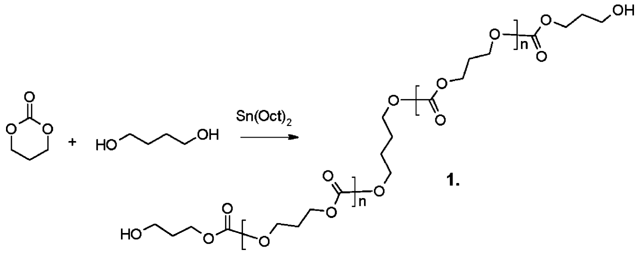
Synthesis of α,ω-Di(*N*,*N*,*N*-trimethyl-4-oxobutane-1-amonium) Poly(trimethylene carbonate) (Cationomer) (5). The procedure for the 4000 g/mol oligomer is given as example. A 50 mL round-bottom flask equipped with a stir bar was carefully flame-dried under vacuum and purged with nitrogen before it was cooled to −20 °C and charged with 5.0 g (1.2 mmol) of polymer **4**, 0.1 mL of trimethylamine, and 20 mL of acetonitrile. The closed reaction mixture was stirred at 60 °C for 24 h before precipitation into 1 L of cold methanol twice. The precipitate was allowed to sediment and washed repeatedly with methanol and then dried under vacuum at 50 °C until constant weight. Yield: 91%. ^{1}H NMR ($CDCl_3$) = 1.73 (m, 2H, $-CH_2-$, initiator), 2.05 (m, 2H, $-CH_2-$, poly), 2.51 (t, $-CO-CH_2-$, end), 3.44 (s, $-N^+(CH_3)_3$, end), 3.75 (m, $-\mathit{CH_2}-N^+(CH_3)_3$, end), 4.22 (t, 4H, $-CH_2-$, poly).

One-Step Synthesis of α,ω-Di(*N*,*N*,*N*-trimethyl-4-oxobutane-1-amonium) Poly(trimethylene carbonate) (Cationomer) (5). A 50 mL round-bottom flask equipped with a stir bar was carefully flame-dried under vacuum and purged with nitrogen before it was charged with 2.0 g (0.5 mmol) of polymer **1**, 0.35 g (1.9 mmol) of (3-carboxypropyl)trimethylammonium chloride, 0.99 g (4.8 mmol) of 1,3-dicyclohexylcarbodiimide, 85.7 mg (0.29 mmol) of DPTS, 10 mL of DMF, 5 mL of pyridine, and 5 mL of chloroform before the flask was closed, and the mixture was allowed to stir at ambient conditions for 24 h before precipitation into diethyl ether twice, followed by precipitation into 1 L of cold methanol. The precipitate was allowed to sediment and then dried under vacuum at 50 °C until constant weight. Yield: 87%. ^{1}H NMR ($CDCl_3$) = 1.73 (m, 2H, $-CH_2-$, initiator), 2.05 (m, 2H, $-CH_2-$, poly), 2.51 (t, $-CO-CH_2-$, end), 3.43 (s, $-N^+(CH_3)_3$, end), 3.75 (m, $-\mathit{CH_2}-N^+(CH_3)_3$, end), 4.22 (t, 4H, $-CH_2-$, poly).

Synthetic protocols for the variations in molecular weight are available in the Supporting Information.

Swelling Behavior. The swelling behavior was determined on compression-molded polymer disks with a diameter of 6 mm and a thickness of 1 mm. In the experiments PBS at pH 7.4 and deionized water were used at 22 °C. The disks were immersed, and the swelling degree was determined at different times using the following formula: swelling (%) $= ((m_t - m_0)/m_0) \times 100$, in which m_0 is the original weight and m_t is the weight at time t.

Scheme 1. Synthesis of Poly(trimethylene carbonate) Diols



Complexation of Complementary Charged Dyes. Ionic interaction was investigated using casted films of the polymers which were submerged into either of the two chosen dyes for 1 min. The dyes malachite green carbinol hydrochloride (cationic) and tropaeolin OO (anionic) were dissolved in deionized water at a concentration of 1 mg/mL. After dyeing the films were washed five times in deionized water.

Results and Discussion

Nature often employs ionic interaction to assemble various functional molecules. For example, in the cell membrane, the positively charged phosphorylserine complexes with negatively charged heparin;[8] heparin in turn may complex proteins.[17] Inspired by nature, we have developed techniques to functionalize biodegradable polymers with the aim of producing materials that ionically can bind oppositely charged molecules to extend the possibilities of tailoring biointeractions. Specifically, we have synthesized telechelic ionomers of poly(trimethylene carbonate) diols (PTMC) and quantitatively equipped these with anionic and cationic functionalities. The starting PTMC diols with molecular weights ranging from 1000 to 12 000 g/mol were synthesized using ring-opening polymerization in bulk with stannous octoate as the catalyst and 1,4-butanediol as the initiator, as shown in Scheme 1.

To prepare the anionic moiety having sulfate salts at both chain ends, the PTMC diol was employed as a nucleophile to the electrophilic sulfur trioxide trimethylamine complex to give the PTMC disulfate (Scheme 2). The reaction was monitored by ^{1}H NMR to reveal shifting of the methylene triplet centered at 3.73 ppm for compound **1** (Figure 1) to 4.22 ppm for compound **2**, in which it is overlapped with resonances from the polymer backbone protons. This indicates complete conversion of the starting ω-hydroxy-terminated PTMC to the desired intermediate PTMC-SO$_3$ NH(CH$_3$)$_3$. A new resonance arising from the methyl groups in trimethylammonium ion was also visible at 2.93 ppm; the area of this peak correlates well with a fully substituted PTMC diol. The yield after isolation for this transformation was 81%, which is slightly low considering complete conversion. It was, however, slightly difficult to precipitate the formed amphiphiles leaving residues in the methanol, lowering the overall yield. This was especially observed for the lower molecular weights, M_w 1000 and 2000 g/mol. This did not, however, affect the average number molecular weight as judged by ^{1}H NMR, and hence no fractionation seems to take place.

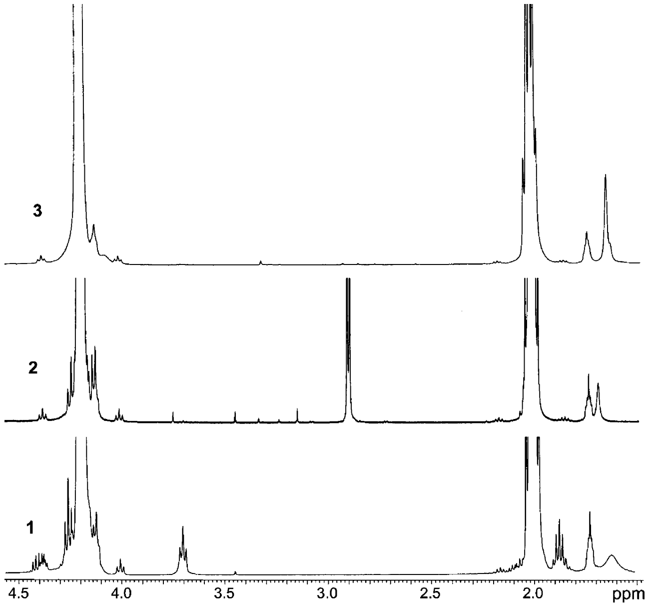
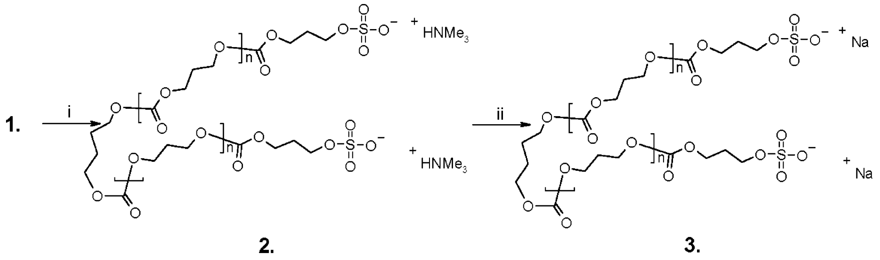


Figure 1. ^{1}H NMR of the starting poly(trimethylene carbonate) diol (**1**), the intermediate sulfate functionalized PTMC with the trimethylammonium counterion (**2**), and the final anionomer with sodium as counterion (**3**).

To prepare sulfate end groups resembling those found in biological systems, for example those in heparin, the trimethylammonium counterion was exchanged to sodium by simply stirring a solution of the polymer in DMF with solid NaHCO$_3$. Deprotonation of the ammonium salt yields trimethylamine that is evaporated from the reaction mixture. Also, this step is clearly visible in the ^{1}H NMR spectra **3** in Figure 1. The methylene resonance from the trimethylammonium counterion at 2.93 ppm disappears, driven by the evaporation of trimethylamine (g) when replaced by sodium. Initially, acetonitrile was unsuccessfully surveyed as polar solvent for the sulfatation reaction. It was shown that DMF, being a strong enough dipolar aprotic solvent, was required to dissolve the sulfate salts. In similarity the ion exchange was initially attempted in THF with the aim to allow easy purification and isolation procedure. Surprisingly, THF turned out to cleave the sulfate ester, returning to the starting materials. Also, for this step DMF was finally selected.

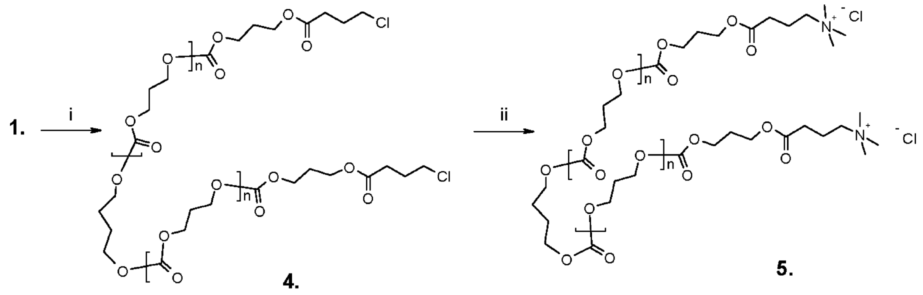
The cationic ionomer was synthesized using two different approaches. The first approach was a one-step procedure condensing (3-carboxypropyl)trimethylammonium chloride with PTMC diol to form an ester with the help from DCC/DPTS. The other, and preferred route, is a two-step synthesis (Scheme 3), where in a first step 4-chlorobutyryl chloride is reacted with the ω-hydroxyl end group of the PTMC mediated by pyridine,

Scheme 2. Synthesis of Difunctional Anionic Ionomer



i) SO$_3$•NMe$_3$ ii) NaHCO$_{3(s)}$

Scheme 3. Synthesis of Difunctional Cationic Ionomer



i) 4-Chlorobutyryl chloride, Pyridine ii) $NMe_{3(g)}$

and in a second step trimethylamine displaces the chloride to introduce the cationic ammonium group. Both these steps were followed by precipitating the products into cold methanol twice to give 90% yields. The two step route is the preferred route because of the ease of purification and the absence of allergenic compound such as DCC used in the one-step procedure. Also for this synthesis, ^{1}H NMR end-group analysis was an easy way of ensuring complete conversion (Figure 2). For the acylation, the ^{1}H NMR revealed disappearance of the methylene triplet centered at 3.73 ppm, shifting to 4.22 ppm but hidden under the polymer backbone resonances as for the anionic compound. Two new resonances appear in the intermediate as triplets: one at 3.55 ppm attributed to the methylene adjacent to the chloride and the other corresponding to protons at the α-position to the carbonyl at 2.55 ppm. Again this demonstrated the complete conversion of the starting ω-hydroxy-terminated PTMC to the intermediate PTMC-Cl. This acylation step resulted in an isolated yield of 94%. The second reaction is the introduction of the cationic end group. This is accomplished by displacing the alkyl chloride with trimethylamine (gas) under pressure. Also, this step was monitored by ^{1}H NMR. The methylene triplet at 3.55 ppm shifted downfield to 3.75 ppm and loses its distinctiveness due to reduced mobility of charged groups in chloroform, leading to aggregation and thus peak broadening. A new singlet peak from the 18 methyl protons present in the two ammonium groups appears at 3.43 ppm.

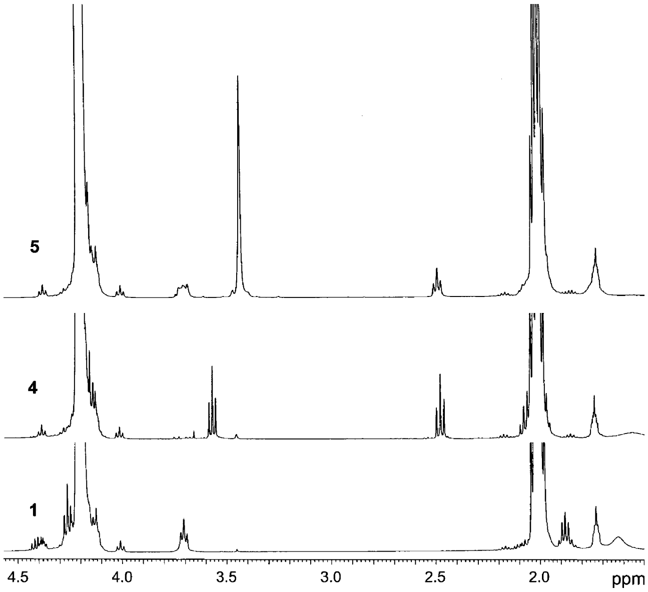


Figure 2. ^{1}H NMR of the starting poly(trimethylene carbonate) diol (**1**), the intermediate PTMC with chloride as end group (**4**), and the final cationomer (**5**).

Table 1. Selection of Backbone PTMC Diols Synthesized

sample	M/I ratio	M_n(theory)	M_n(NMR)	PDI	yield (%)
PTMC 1000	10	1110	1329	1.21	96
PTMC 2000	20	2130	2240	1.30	95
PTMC 4000	40	4170	4088	1.33	97
PTMC 12 000	120	12 330	12 626	1.30	96

Table 2. Selection of Ionomers Synthesized

material	M_n(theory)	M_n(NMR)	yield (%)
anion 1000	1520	1506	45
anion 2000	2540	2387	92
anion 4000	4580	5212	89
anion 12000	12740	12536	93
cation 1000	1853	1508	<5
cation 2000	2873	2616	87
cation 4000	4913	4824	91
cation 12000	13073	15797	92

Using the developed synthetic procedures, four different molecular weights of the starting polymer (Table 1) and eight cationomer and anionomers (Table 2) were prepared on a 5 g scale. Because of the high yields in all the reactions and final products with molecular weight close to those of the starting materials, one may exclude fractionation upon precipitation. The only really problematic substance was the ionomers with molecular weight of 1000 g/mol. Both of them were soluble in water and methanol as well as chloroform, rendering isolation difficult, especially in the case of the cationomer where we only were able to isolate a couple of percent. The ionomers with molecular weight of 2000 g/mol were also found soluble in water as well as organic solvents at room temperature. They could however be isolated by precipitation at −20 °C. Molecular weight characterization using SEC was only performed on the starting material, since the charges of the ionomers cause agglomeration in solution and strong interactions with the columns, resulting in inaccurate data.

Agglomeration of the charged end groups also occurs in the bulk. The rheological behavior of the ionomers was compared with that of the starting PTMC (Figure 3), revealing an interesting phenomenon. For ionomers the T_g shifts to higher temperatures compared to the corresponding PTMC diols. Above T_g PTMC behaves as an amorphous melt while the ionomers display a rubbery plateau-like region retaining mechanical integrity. These observations corroborate with the behavior of non-biodegradable ionomers where the ionic functionalities aggregate, forming ionic domains in the bulk.[18] These ionic inverse micellar domains create physical cross-links in the PTMC matrix. Figure 3 shows the rheological behavior for Anion 4000 and PTMC 4000 and is representative for all the ionomers, with variations depending on charge and molecular weight as summarized in Table 3. Because of the difficulties in

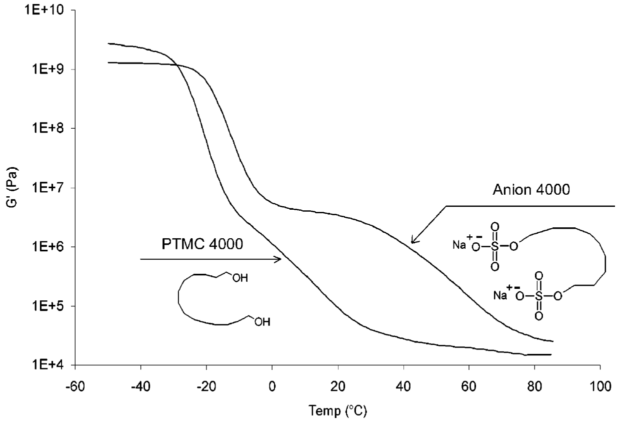


Figure 3. Rheological behavior of the Anion 4000 in comparison with PTMC 4000.

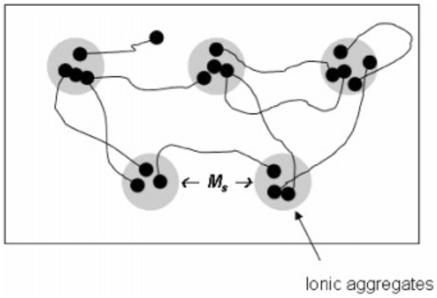


Figure 4. Schematic representation of ionic domains present in the hydrophobic bulk of the PTMC. These hydrophilic inverted micelles function as physical cross-links with mean distances between aggregates given by the average molecular weight between cross-links M_s.

Table 3. Rheological Data of All Ionomers and Their Corresponding PTMC Diols; T_g and the Modulus of the Plateau Are Presented

material	T_g (°C)	plateau (Pa)
PTMC 1000	−48	
anion 1000	−40	1.17×10^6
cation 1000	N.D.	N.D.
PTMC 2000	−34	
anion 2000	−27	1.81×10^6
cation 2000	−30	4.66×10^6
PTMC 4000	−18	
anion 4000	−11	4.09×10^6
cation 4000	−13	5.42×10^6
PTMC 12000	−15	
anion 12000	−13	3.34×10^6
cation 12 000	−14	4.44×10^6

isolation of the lowest molecular weight polymers, the rheological behavior could not be determined for the Cation 1000. The higher the molecular weight, the more extended is the rubbery plateau (data not shown).

If the equation $M_s = \rho RT/G'$, suggested by Wall,[19] Treolar,[20] and Flory,[21] is applied for these ionomers, the average segment molecular weight, M_s, may be estimated. Albeit the equation is not truly valid under the applied conditions, the results are qualitatively in agreement with the molecular weight of each segment. For all materials, the calculated segments have lower molecular weight than the formed oligomers, and the deviation is between 10 and 50%. The original equation is valid for a cross-linked rubber, and here we are dealing with physically cross-linked material that when heated loses their cross-links. For example, Anion 4000 gives an M_s of around 2400 g/mol. It also supports the suggested structure of phase-separated ionic domains functioning as cross-links, as schematically shown in Figure 4.

The ionic aggregates in the anionomer contain sodium ions and the cationomer chlorine ions that may be probed by XPS. By performing a depth profile analysis, it is clearly visible that the surface is depleted of the ionic domains that are found only in the bulk of the material (Figure 5). The ultrahigh vacuum in the XPS instrument behaves like a very hydrophobic surrounding.

If the bulk of the ionomers consists of hydrophilic domains, should not these then be able to swell in water? A swelling study was performed, and it does indeed display considerable swelling (Table 4). All of the ionomers formed soft organic−water hybrid gels, except for the lowest molecular weight compound, which dissolved. The degree of swelling and the time until constant weight varied considerably from around 40% to 560% and 2 to 1500 h. With the aim of potential applications in vivo, swelling was also performed in phosphate buffer solution (PBS) at pH 7.4. Neither of the ionomers swelled as much in PBS as in water, which can be attributed to a lower driving force for osmosis when the difference in ion concentration is smaller. To give some idea of swelling rates, which is dependent on sample size, both the time to one-third of maximum and the time to constant weight were determined. Initially swelling is rapid due to osmosis. Soon, however, the morphology is likely to change from isolated water droplets to an open cocontinuous structure with a loss of the osmotic pressure. Swelling is now driven only by the desire of the ionic end groups to gain entropy. This is, however, counterbalanced by unfavorable water contacts to the hydrophobic PTMC i.e., the hydrophobic effect.[22] When the 2000 and 4000 g/mol molecular weight ionomers were swollen to their maximum, they turned into fragile gels rather than rubbery materials. An exception was the anionomer 4000 in PBS which still displayed rubberlike behavior. The 12 000 molecular weight ionomers were swollen to soft but robust gels.

At room temperature these ionomers are above their T_g, within the so-called rubbery plateau region, and at the same time displaying hydrophilicity in the bulk. This should stimulate spontaneous surface migration of the hydrophilic end groups when subjected to a hydrophilic surrounding, as depicted by Figure 6.

Surface properties from cast films were therefore characterized by universal static contact angle measurement, both water drop on surface in air and air bubble on surface in water. The reference PTMC has a universal contact angle of 85° in air and 82° in water. Conversely, the ionomers display a quite different behavior. Representative are the 4000 anionomer and cationomer where the contact angle in air is the same as for the reference PTMC, while for the angle in water is very low with a contact angle of 28° for the anionomer and 25° for the cationomer (Table 5). The other polymers with varying molecular weights show similar behavior. Hence, when in air the nonpolar PTMC is oriented toward the air surface with the end group buried in the bulk, likely forming inverted micellar domains. Treatment in water rearranges the film and enriches ionic end groups at the polymer−water interface, as schematically shown in Figure 6.

PTMC itself is completely stable in water and degrades solely by enzymatic hydrolysis exhibiting clean surface erosion;[3b] therefore, one could assume that these types of ionomers would display similar biodegradability. Exactly how similar is difficult to say considering that the molecular weight is very low, which should increase the degradation rate; on the other hand, the surface is "shielded" by the ionic groups that potentially would make it more difficult for enzymatic degradation to take place.

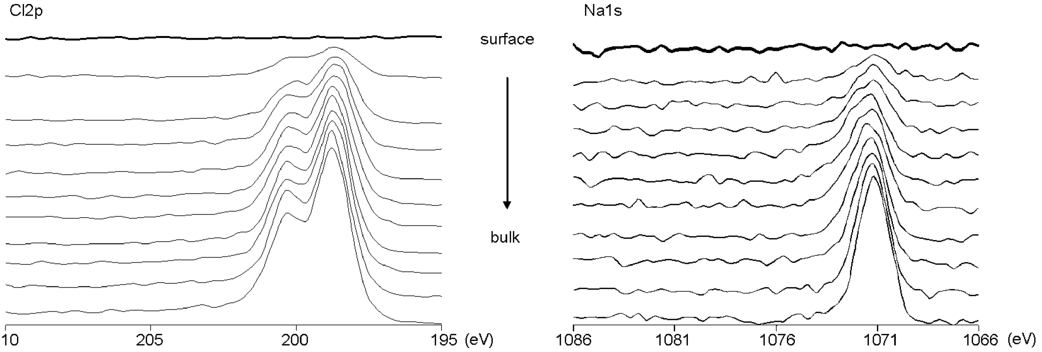


Figure 5. XPS depth profiles of biodegradable ionomers with the Cl 2p signal from the counterion of the cationomers to the left and Na 1s signal from the anionomer to the right.

Table 4. Swelling in Water and PBS at 22 °C[a]

material	swelling in PBS (wt %)	t_{max} (h)	$t_{1/3}$ (h)	swelling in H_2O (wt %)	t_{max} (h)	$t_{1/3}$ (h)
anion 1000	dissolved			dissolved		
anion 2000	dissolved			dissolved		
anion 4000	42	900	6	390	400	24
anion 12000	45	1500	100	49	1300	75
cation 1000	dissolved			dissolved		
cation 2000	590	650	15	560	2	0.08
cation 4000	251	76	3	405	6	0.2
cation 12000	37	600	35	88	850	100

[a] t_{max} = time until constant weight, and $t_{1/3}$ = time until one-third of constant weight.

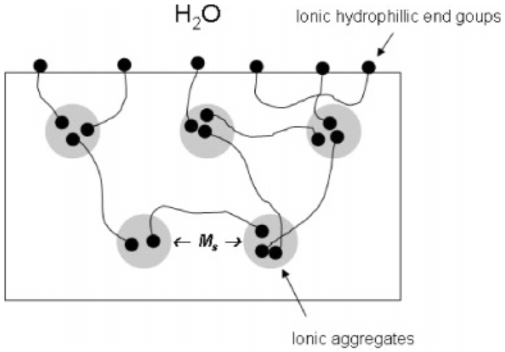


Figure 6. Surface migration of ionomer end groups in hydrophilic media.

Table 5. Water Contact Angles and under Water Contact Angles Measured with Air Bubble

	contact angle (deg) H_2O in air	contact angle (deg) air in H_2O
glass	90 ± 3.6	91 ± 4.7
PTMC 4000	85 ± 1.5	82 ± 1.5
anionomer 4000	86 ± 2.4	28 ± 1.8
cationomer 4000	85 ± 2.1	25 ± 2.1

Further, swelling of the material increases the surface area exposed to water, which could increase the degradation rate.

The aim of the study was to develop materials inspired from nature with control of the charge interactions to complex complementary charged molecules. To verify this concept, films of the anionomer 4000 and the cationomer 4000 were prepared. Unfunctionalized PTMC 4000 was used as reference. These films were then immersed into water solutions containing cationically or anionically charged dyes. A yellow anionic dye, Tropaeolin OO (Scheme 4a), and a blue cationic dye, malachite green carbinol hydrochloride (Scheme 4b), were used as demonstrators to electrostatically functionalize the surfaces. Figure 7 displays the pictures of the reference PTMC that is unaffected by the dyes and the cationomer that adsorbs only the yellow anionic dye while anionomer only adsorbs its complementary blue cationic dye.

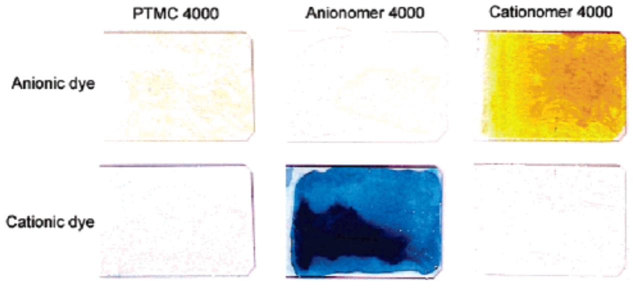
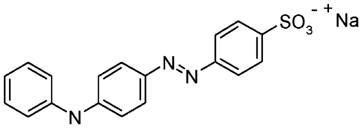
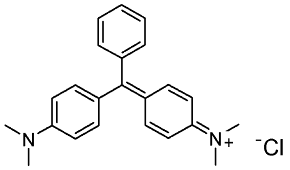


Figure 7. Specific uptake of charged dye, a yellow anionic dye, Tropaeolin OO, and a blue cationic dye, malachite green carbinol hydrochloride, of the anionomer and cationomer.

Scheme 4. Structure Showing the Structures of the Anionic (a) and Cationic (b) Dyes Used



a) anionic dye, Tropaeolin OO



b) cationic dye, malachite green carbinol hydrochloride

Conclusion

A general synthetic procedure to produce anionic or cationic functional biodegradable polymers from their diols has been developed. In this paper it was applied to poly(trimethylene carbonate) diols for quantitative conversion of the alcohols to either sulfate or trimethylammonium functionalities. The synthesis of α,ω-di(3-sulfoxypropoxycarbonyl poly(trimethylene carbonate) trimethylsodium salt (anionomer) was accomplished by reacting the PTMC diol with sulfur trioxide trimethylamine complex followed by an ion exchange to give the final product with the in vivo acceptable sodium counterion. A simple two-step procedure gave the α,*ω*-di(*N*,*N*,*N*-trimethyl-4-oxobutane-1-amonium) poly(trimethylene carbonate) (cationomer) involving the reaction of the PTMC diol with 4-chlorobutyryl chloride and followed trimethylamine to displace the chloride to introduce the cationic ammonium group. In a hydrophilic environment the ionic groups was shown to spontaneously enrich at the surface. Therefore, when the polymer degrades to expose a new surface, the system has the potential to re-form bioactive surface through migration of ionic groups present in the bulk. It has been shown that these materials behave rubbery, attributed to the association of ionic groups to form physical cross-links in the bulk. Finally, immersed into water these ionomers swell up to 5−6 times their own weight, creating possibilities for cargo space within the material. Functionalization of these materials at the surface and in the bulk with charged hydrophilic molecules can now be performed by simple immersion into its aqueous solution. Possible molecules to complex into these materials include charged drugs, peptides, and full proteins.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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