Polymer 49 (2008) 5397–5404

Contents lists available at ScienceDirect

Polymer

journal homepage: www.elsevier.com/locate/polymer

Synthesis and characterization of poly(lactide-*b*-siloxane-*b*-lactide) copolymers as magnetite nanoparticle dispersants

R.T. Ragheb, J.S. Riffle*

Department of Chemistry and the Macromolecules and Interfaces Institute, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061-0344, USA

ARTICLE INFO

Article history:
Received 25 February 2008
Received in revised form 3 September 2008
Accepted 5 September 2008
Available online 26 September 2008

Keywords:
Polysiloxane
Polylactide
Magnetite

ABSTRACT

Poly(lactide-*b*-siloxane-*b*-lactide) triblock copolymers with pendent carboxylate groups have been synthesized to serve as dispersants for magnetite nanoparticles. Magnetic nanoparticles are of interest for potential biomedical applications including magnetic field-directed drug delivery and magnetic cell separations. For *in-vivo* applications, it is important that the magnetic particle be coated with biocompatible organic materials to afford dispersion characteristics or to further modify the surfaces of the complexes with biospecific moieties. Synthesis of the triblock copolymer dispersants comprises three reactions. First, difunctional, controlled molecular weight, telechelic, polymethylvinylsiloxane (PMVS) oligomers with 3-aminopropyl endgroups were prepared in ring-opening redistribution reactions. Secondly, these oligomers were utilized as macroinitiators for ring-opening L-lactide or D,L-lactide to provide triblock materials with PMVS central blocks and polylactide end blocks. Both the PMVS oligomers and the poly(lactide-*b*-siloxane-*b*-lactide) copolymers had the expected molecular weights and compositions. Thirdly, the vinyl groups on the polysiloxane center were functionalized with carboxylic acids by adding mercaptoacetic acid across the pendent double bonds. At neutral pH, the carboxylate-functional polysiloxane central block binds to the surfaces of magnetite nanoparticles, while the polylactides serve as tail blocks to provide dispersibility in polylactide solvents through interparticle steric repulsive forces. Analyses confirmed that the copolymers indeed adsorbed onto the surfaces of the magnetite nanoparticles, but fractionations of these materials suggested that the composition distribution of the components was somewhat inhomogeneous.

1. Introduction

For decades, polylactides have received enormous attention for biomedical applications due to their biocompatibility and biodegradability [1–6]. Their degradation into naturally occurring metabolites such as lactic acid is among several attractive characteristics [2]. Biodegradation occurs through hydrolytic or enzymatic cleavage of the acyl-oxygen ester bonds. The biocompatibility and safety of polylactides have been well established through extensive *in-vivo* studies [3,7–10].

Morphologies and biodegradation rates of polylactides depend on the stereoisomerism of the lactide monomers/polymers, molecular weights of the polymers, and functional endgroups [4,10–12]. Poly(L-lactide) (PLLA) is a semi-crystalline polymer with excellent mechanical properties. High molecular weight PLLA has a melt transition of ~180 °C and a glass transition temperature of 50–65 °C [5,13–16]. Poly(D,L-lactide) (PDLLA) is amorphous with a glass transition temperature of ~50 to 60 °C [5,13–16]. Polylactide homopolymers are commonly prepared by anionic or coordination-insertion ring-opening polymerization of the lactide monomer initiated by nucleophiles such as alcohols [17–19]. The coordination-insertion polymerization is often catalyzed by tin compounds such as stannous octoate [20–24].

Magnetic magnetite nanoparticles can be complexed with the carboxylate-functional poly(lactide-*b*-siloxane-*b*-lactide) copolymers described herein to yield dispersible magnetite–copolymer complexes (Fig. 1). Such complexes can then be fabricated into larger nano- or microspheres that are of potential interest for various biotechnological applications.

Potential applications for these magnetic materials include magnetic field-directed drug delivery, magnetic cell separations and magnetic hyperthermia therapy for treatment of tumors [25–30]. Current technology utilizing magnetic microspheres is limited by the lack of control over homogeneity of composition throughout the microspheres, and difficulty in achieving good dispersibility in various media. Advancements in preparing and understanding the structures of polymer-magnetic particle complexes may lead to the ability to localize high concentrations of drugs at a tumor site. These technologies could reduce the extreme side effects that occur with systemic cancer therapies.

---

* Corresponding author. Tel.: +1 540 231 8214.
E-mail address: judyriffle@aol.com (J.S. Riffle).

0032-3861/$ – see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.polymer.2008.09.020

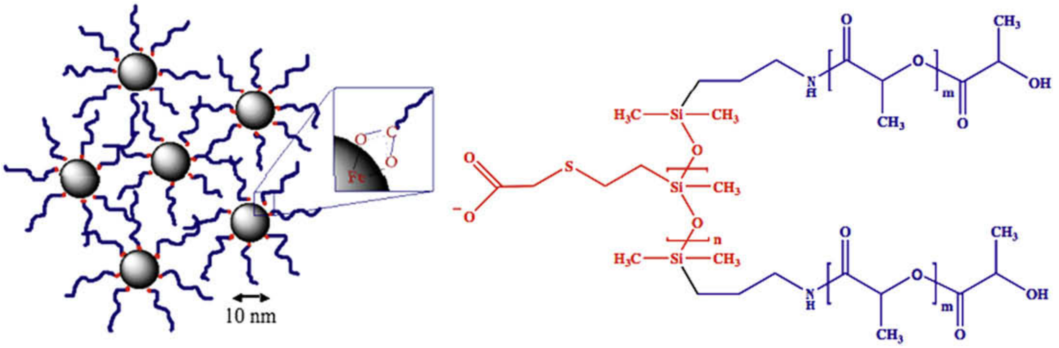

Fig. 1. Magnetite nanoparticles complex with carboxylate-functional poly(lactide-*b*-siloxane-*b*-lactide) copolymers.

This paper describes the synthesis and characterization of poly(lactide-*b*-methylvinylsiloxane-*b*-lactide) triblock copolymers, and their derivatization with carboxylic acid groups for complexation with magnetite nanoparticles. The magnetite–polymer complexes will later be incorporated into controlled-size microspheres for studies relative to various biomedical applications.

2. Experimental

2.1. Materials

1,3,5,7-Tetramethyl-1,3,5,7-tetravinylcyclotetrasiloxane (D_{4vi}), octamethylcyclotetrasiloxane (D_4), and bis(3-aminopropyl)tetramethyldisiloxane (all from Gelest) were fractionally distilled before use. Tetramethylammonium hydroxide pentahydrate ($TMAH \cdot 5H_2O$, Aldrich, 99%) was stored in a desiccator and used as received. Toluene (Aldrich, 98%) was washed twice with concentrated sulfuric acid and neutralized with water. It was dried over $MgSO_4$ for 1 h, then over calcium hydride overnight and distilled just before use. Chloroform, stannous octoate, diethyl ether, trifluoromethanesulfonic acid, and mercaptoacetic acid were obtained from Aldrich and used as received. Methanol (HPLC grade) was obtained from EM Science and used as received. L-Lactide and D,L-lactide (both from Purac) were recrystallized from ethyl acetate (Aldrich), filtered, dried at room temperature in a septum-sealed round-bottom flask under vacuum, and stored under nitrogen. Millipore water was obtained from Millipore and used as received. $FeCl_3 \cdot 6H_2O$ and $FeCl_2 \cdot 4H_2O$ (Aldrich) were used as received. Ammonium hydroxide, a 50% (v/v) aqueous solution (Alfa Aesar), was deoxygenated prior to reaction. Concentrated hydrochloric acid (EM Science) was diluted to 4 M with Millipore water.

2.2. Synthesis of tetramethylammonium disiloxanolate catalyst [31,32]

To prepare the tetramethylammonium disiloxanolate catalyst, a reaction flask was equipped with a mechanical stirrer, a nitrogen inlet running through the solution, and a Dean-Stark trap with a condenser linked to a drying tube. $TMAH \cdot 5H_2O$ (0.685 g, 0.0038 mol) was charged to the reaction vessel followed by addition of D_4 (13.7 g, 0.046 mol) via syringe to form a 4.8 wt% $TMAH \cdot 5H_2O$ dispersion in D_4. The mixture was reacted with rapid stirring and nitrogen bubbling through it for 24 h at 80 °C. The nitrogen flow was sufficiently high to aid in removing water via the Dean-Stark trap. After 24 h, the catalyst was syringed immediately from the reactor into the desired oligomeric reaction mixture to avoid moisture absorption by the hygroscopic catalyst.

2.3. Synthesis of 3-aminopropyl-terminated PMVS

PMVS was prepared via an anionic ring-opening equilibration of D_{4vi} in the presence of bis(3-aminopropyl)tetramethyldisiloxane as an endcapping reagent. A representative procedure is provided. All other oligomers were prepared with similar procedures, but with appropriately different ratios of endcapping reagent relative to cyclosiloxane monomer. D_{4vi} (50 g, 0.147 mol) and 1,3-bis(3-aminopropyl)tetramethyldisiloxane (6.21 g, 0.025 mol) were charged into a flame-dried, 500-mL, one-neck, round-bottom flask equipped with a magnetic stir bar and septum and heated to 80 °C. Once the mixture reached 80 °C, the tetramethylammonium disiloxanolate catalyst (0.337 g) was added via syringe. The reaction was heated for approximately 48 h at 80 °C to allow the oligomer to equilibrate. The oligomeric mixture was subsequently heated at 140 °C for 3 h while bubbling nitrogen through it to decompose the catalyst and evolve the trimethylamine by-product. Finally, the equilibrated mixture was heated at 125 °C under vacuum (1–2 mm pressure) for 5 h to remove cyclics. The polymer was stored under nitrogen in a flame-dried, sealed flask until used. ^1H NMR showed that the M_n of the PMVS oligomer was 2660 g mol^{-1} after isolation.

2.4. Synthesis of a poly[(L-lactide)-b-methylvinylsiloxane-b-(L-lactide)] copolymer (PLLA-b-PMVS-b-PLLA) utilizing 3-aminopropyl-terminated PMVS as a macroinitiator

The copolymerizations were conducted according to the following representative procedure for preparing a triblock copolymer with a central 2660 g mol^{-1} PMVS block and ~5000 g mol^{-1} PLLA tail blocks. L-Lactide (14.99 g, 0.13 mol) and toluene (30 mL) were charged to a flame-dried, nitrogen-purged, round-bottom flask equipped with a magnetic stir bar. The flask was placed in an oil bath at 65 °C to dissolve the lactide monomer. Aminopropyl-terminated PMVS (3.99 g, 1.50 mmol) was added and the reaction was stirred for 45 min at 65 °C. Stannous octoate (6.0 mg) was charged to the flask and the temperature of the oil bath was increased to 100 °C. Reaction progress was monitored with ^1H NMR. The copolymer was isolated by precipitation into hexanes followed by washing several times with hexanes. The copolymer was vacuum dried at 40 °C for 18 h. ^1H NMR showed that the triblock copolymer had an M_n of 11,540 g mol^{-1}.

2.5. Functionalization of a PLLA-b-PMVS-b-PLLA block copolymer with mercaptoacetic acid

The following is a representative procedure for derivatizing PDLLA-*b*-PMVS-*b*-PDLLA and PLLA-*b*-PMVS-*b*-PLLA triblock copolymers with pendent carboxylic acid groups. An 11,540 g mol^{-1} PLLA-*b*-PMVS-*b*-PLLA (10.31 g, 8.93×10^{-4} mol, average of 28 eq vinyl groups per mole) copolymer was weighed into a round-bottom flask equipped with a magnetic stir bar. Toluene (105 mL) was added via syringe and the solution was deoxygenated by bubbling dry nitrogen through the reaction mixture. AIBN (48.4 mg, 2.95×10^{-4} mol) was added and the reaction mixture was again purged with nitrogen. Mercaptoacetic acid (8.19 mL, 0.118 mol) was added via syringe and the reaction flask was placed in an oil bath at 80 °C. The reactions were monitored via ^{1}H NMR by following the disappearance of the peaks corresponding to the vinyl protons at 5.8 and 6.0 ppm. The copolymer was isolated by precipitation into cold hexanes and filtered. Additional cold hexanes were used to wash the filtered polymer, which was then vacuum dried at 40 °C for 18 h.

2.6. *Synthesis of magnetite–copolymer complexes*

Magnetite nanoparticles were prepared by a previously reported procedure [33,34]. Millipore water and an aqueous 50% NH_4OH solution were each deoxygenated by purging with N_2 for 30 min. The reaction apparatus was purged with N_2 prior to the reaction to ensure an anaerobic environment. Aqueous solutions of $FeCl_3 \cdot 6H_2O$ (2.0 g in 20 mL H_2O, 0.389 M) and $FeCl_2 \cdot 4H_2O$ (0.736 g in 20 mL H_2O, 0.195 M) were prepared separately under N_2 and syringed into a three-neck, 250-mL, round-bottom flask equipped with a mechanical stirrer and a pH electrode connected to a pH meter. The pH was adjusted to ~9.5 by adding ~10 mL of the NH_4OH solution while stirring. The solution immediately turned black indicating the formation of magnetite particles. The reaction mixture was stirred under N_2 for 1 h. The reaction was neutralized to pH ~7.0 using a 4 M HCl solution and stirred under a N_2 purge for an additional 30 min. The desired amount of carboxylic acid-functionalized triblock copolymer for the particular complex was dissolved in 90% CH_2Cl_2/10% MeOH v/v (25 mL) and the solution was added into the reaction flask and stirred for 18 h to adsorb the copolymer onto the nanoparticle surfaces. The mixture was transferred to a one-neck vessel. The reaction flask was washed with 90% CH_2Cl_2/10% MeOH v/v to ensure complete transfer of the product. The CH_2Cl_2/MeOH was removed under vacuum and the product was collected by holding a magnet against the bottom of the flask and decanting the water. The magnetite complex was washed with Millipore water three times to remove any salts. The complex was dried under vacuum at room temperature, then it was redispersed in 90% CH_2Cl_2/10% MeOH (100 mL). The dispersion was centrifuged to remove any aggregates. The CH_2Cl_2/MeOH was removed under vacuum and the complex was stored in a sealed vessel under nitrogen.

2.7. *Characterization*

^{1}H NMR spectra were obtained on either a Varian Unity 400 or a Varian Inova 400 NMR spectrometer operating at 400 MHz. The NMR parameters included a pulse width of 28.6° and a relaxation delay of 1.000 s at ambient temperature. The samples were dissolved in *d*-$CHCl_3$ for obtaining the spectra, with the exception of the acid-functionalized triblock copolymers that were dissolved in 90% *d*-$CHCl_3$/10% *d*-MeOH. ^{29}Si NMR spectra were obtained on a Varian Unity 400 NMR spectrometer operating at 80 MHz. The samples for ^{29}Si NMR were prepared with 0.30 g copolymer, 0.05 g Cr(Acac)$_3$, and 2.4 mL *d*-$CHCl_3$. Quantitative silicon NMR spectra were obtained with the aid of the relaxation agent, Cr(Acac)$_3$, with a pulse width of 168.0° and a relaxation delay of 10.000 s. Inverse gated proton decoupling was used with the number of scans ranging from 500 to 1500.

Gel permeation chromatography was employed to investigate the molecular weights and molecular weight distributions of the PMVS oligomers and the poly(lactide-*b*-methylvinylsiloxane-*b*-lactide) copolymers. A Waters 2690 GPC equipped with four Waters Styragel HR columns (HR4 7.8 × 300 mm, HR3 7.8 × 300 mm, HR2 7.8 × 300 mm, and HR0.5 7.8 × 300 mm) was used for chromatographic analysis. Chloroform was employed as the mobile phase at 25 °C and a flow rate of 1.0 mL min^{-1}. Polystyrene standards were used to construct a universal calibration to determine absolute molecular weights. A second GPC was also employed. This was a Waters GPC (515 pump, 717 autosampler) with an external 2410 refractive index detector, equipped with three PLgel 5 μm MIXED-C columns. ACS grade THF was used at a flow rate of 1.0 mL min^{-1} and 40 °C. Multi-angle laser light scattering was utilized with an in-line Wyatt Minidawn. Samples were filtered prior to all runs through a 0.2 μm PTFE filter.

DSC scans were performed on a TA Instruments DSC Q1000 under constant helium flow. The samples (10–15 mg) were ramped from −150 to 200 °C using hermetically sealed DSC pans. Two scans were performed on each sample and the T_gs were taken from the inflection points on the second scans.

Thermogravimetric analyses were performed on a TGA Q1000 from TA Instruments, Inc. TGA samples were ramped from 50 to 800 °C at 10 °C min^{-1} in a N_2 environment.

A Philips 420T TEM operated at 400 kV was used to obtain photomicrographs of the magnetite–copolymer complexes. The complexes were dispersed in chloroform, then deposited on carbon-coated copper grids and allowed to air dry.

Magnetic properties were measured in the solid state using a Standard 7300 Series Lakeshore Vibrating Sample Magnetometer. The reported magnetizations were determined from the plateau region of the magnetic flux density of a solid sample at 8000 Oe applied field with a sensitivity of 0.1 emu.

Surface analyses of the magnetite–copolymer complexes were investigated via X-ray photoelectron spectroscopy (XPS). The data was obtained on a Perkin–Elmer X-ray photoelectron spectrometer 5400 Series using a Mg anode operating at 300 W (14 kV) with the pressure of the system below 5×10^{-6} Pa.

3. Results and discussion

Poly(lactide-*b*-methylvinylsiloxane-*b*-lactide) triblock dispersants were prepared by synthesizing a telechelic PMVS oligomer

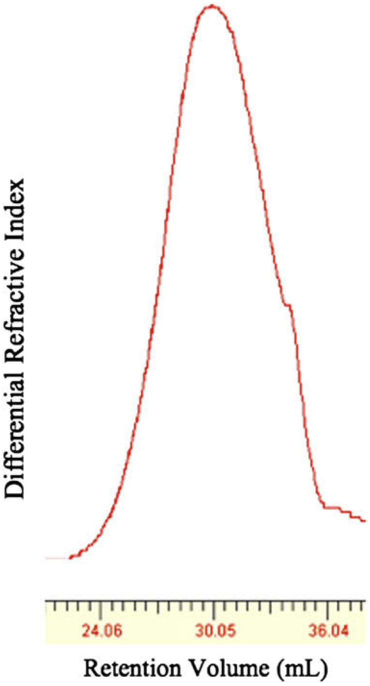

Fig. 2. GPC in THF was used to characterize a 2660 g mol^{-1} homopolymer revealing a PDI of 2.1.

having aminoalkyl endgroups, then initiating the ring-opening of lactide monomers with those endgroups (Fig. 2). The vinyl pendent groups on the PMVS central block were then derivatized with carboxylic acids. Thus, our approach was to utilize the central carboxylate-functional polysiloxane as the dispersant anchor block to adsorb carboxylates onto the magnetite nanoparticle surfaces, and allow the polylactide terminal blocks to extend into various solvents to impart dispersion stability. The magnetite–block copolymer complexes are excellent candidates for applications in biotechnology since both copolymer blocks and the magnetite are biocompatible. Although it is beyond the scope of this paper, it is desirable to fabricate controlled-size nano- and microspheres from these magnetite–block copolymer complexes without any additional polylactide carrier. It is anticipated that utilizing pre-formed polymer–magnetite complexes as the precursors for fabricating microspheres will result in highly homogeneous magnetic microspheres.

3.1. *Synthesis of aminopropyl-terminated PMVS oligomers*

The aminopropyl-terminated PMVS oligomers were prepared through a base-catalyzed redistribution reaction by a similar method to that typically utilized for polymerizing D_4 to form polydimethylsiloxane [35]. The base-catalyzed equilibration of D_{4vi} differs from D_4 in that the methylvinylcyclosiloxanes are more reactive toward the siloxanolate anions. A characteristic of base-catalyzed equilibrations of cyclosiloxanes is to achieve high molecular weight oligomers early in the reactions due to the high concentration of the cyclosiloxane relative to the linear chains [31,32]. As the equilibrations progress, the high molecular weight chains are reduced in molecular weight as they equilibrate, and the endcapping reagent also incorporates. In the present reactions, the build-up of viscosity early in the reactions is even more prevalent than for the 3(aminopropyl)-functional polydimethylsiloxane case since the D_{4vi} ring is more reactive than D_4 toward base and the same endcapping reagents have been employed.

The tetramethylammonium dimethylsiloxanolate equilibration catalyst that was utilized herein is known to efficiently catalyze equilibrations of D_4 [36]. The catalyst reacts with the methylvinylsiloxane through at least three different routes [31]. As the equilibration progresses, active chains react with cyclics, interchange with other chains, or experience backbiting. The chains become capped with the 3-(aminopropyl)dimethylsilyl endcapping agent during the polymerization, whereby the Si–C bonds remain intact during the redistribution reaction. A particularly desirable feature of the alkylammonium cation is that it can be thermally decomposed at ~140 °C and the trimethylamine by-product of the decomposition can be evolved with a nitrogen purge. After elimination of the catalyst by-product, the smaller cyclic species formed in the equilibration reaction can be removed by stripping the fluid oligomer under vacuum, and this can also remove very low molecular weight linear species. A typical polydispersity of ~2.0 is established due to the equilibration of chain lengths (Fig. 2).

Molecular weights of the aminopropyl-terminated PMVS oligomers were characterized through a combination of quantitative ^{29}Si and ^{1}H NMR, and GPC. ^{29}Si NMR has a wide frequency range, and thus provides a convenient means for distinguishing the environments of the backbone and endgroup silicon species. The silicon atoms of the methylvinylsiloxane repeat units are observed at −34 to −36 ppm, while the trialkylsilyl endgroups are observed at 9–10 ppm. Since there are two endgroups per chain, the relative integral values of these resonances were utilized to quantify the degrees of polymerization. ^{1}H NMR was also employed to confirm the compositions and molecular weights of the oligomers. The integrals of the methylene protons bonded to the terminal silicon atoms resonating at 1.1–1.2 ppm were compared to the vinyl proton sets in the repeat units. These values correspond well with the degrees of polymerization calculated from ^{29}Si NMR (Table 1).

Table 1
Molecular weights of 3-(aminopropyl)-terminated PMVS oligomers

M_n (g mol^{-1})			PDI
^{1}H NMR	^{29}Si NMR	GPC	
1370	1370	1400	2.1
1610	1850	1700	1.9
1960	1960	1600	2.6
2660	2660	2900	2.1

Absolute molecular weights were also obtained by GPC utilizing THF as the solvent with a universal calibration based on hydrodynamic volume. The aminopropyl-terminated PMVS oligomers were derivatized with benzophenone prior to the GPC measurements to avoid adsorption of the aliphatic amines on the column components [37].

3.2. *Triblock poly(lactide*-b-*siloxane*-b-*lactide) copolymers*

The aminopropyl-functional PMVS oligomers served as macroinitiators for polymerization of L-lactide or D,L-lactide rings to form the tail blocks of the triblock copolymers (Fig. 3 and Table 2). The primary amine is sufficiently nucleophilic to readily react with the carbonyl carbons on the lactide monomers, and at 65 °C this reaction opens one ring without the aid of a catalyst. Thus, the amine functional groups on the PMVS macroinitiators ensure efficient initiation of the lactide blocks. The resultant hydroxy endgroups can then propagate the polymerization of lactide through a coordination-insertion mechanism in the presence of stannous octoate. Initiation of lactide polymerizations with primary amines have been reported, but those investigations also included tin(II) catalysts in the initiation step [38,39]. To our knowledge, initiation without the catalyst to afford addition of one lactide ring, then subsequent addition of stannous octoate to promote propagation has not been reported previously.

The lactide polymerizations were monitored with proton NMR. After reaction of the aminopropyl-functional oligomer with monomer for 1 h at 65 °C, the lactide methine hydrogen peak corresponding to the open-chain structure appears at ~5.2 ppm. Integration confirmed that only one lactide cyclic dimer added onto each amine group. The amide hydrogen protons resonating at ~6.5 ppm also appear as the addition proceeds. Stannous octoate catalyst was added after the amine groups were quantitatively capped with monomer. ^{1}H NMR was employed to monitor the propagation of the lactide chain with the disappearance of the peaks corresponding to the methine and methyl protons on the lactide monomer [40]. The final copolymers were isolated by dissolution in chloroform and precipitation into methanol. This procedure removes residual lactide monomer.

The compositions of the triblock poly(L-lactide-*b*-methylvinylsiloxane-*b*-L-lactide) and poly(D,L-lactide-*b*-methylvinylsiloxane-*b*-D,L-lactide) copolymers, and the molecular weights of both the blocks and the copolymers were analyzed by proton NMR (Fig. 4 and Table 2). GPC also provided data on the molecular weights and distributions (Table 2). The integrals corresponding to the methine protons in the linear lactide repeat unit resonating at ~5.2 ppm were compared to the two terminal methine protons of the tail blocks resonating at ~4.4 ppm, and utilized to calculate the molecular weights of the tail blocks (Table 2). The data shows reasonable correlation between the targeted molecular weights and those calculated from NMR. Molecular weight averages obtained from GPC also correlated well with the targeted values. Polylactide homopolymers that are polymerized by similar conditions to those utilized in this work for forming the block

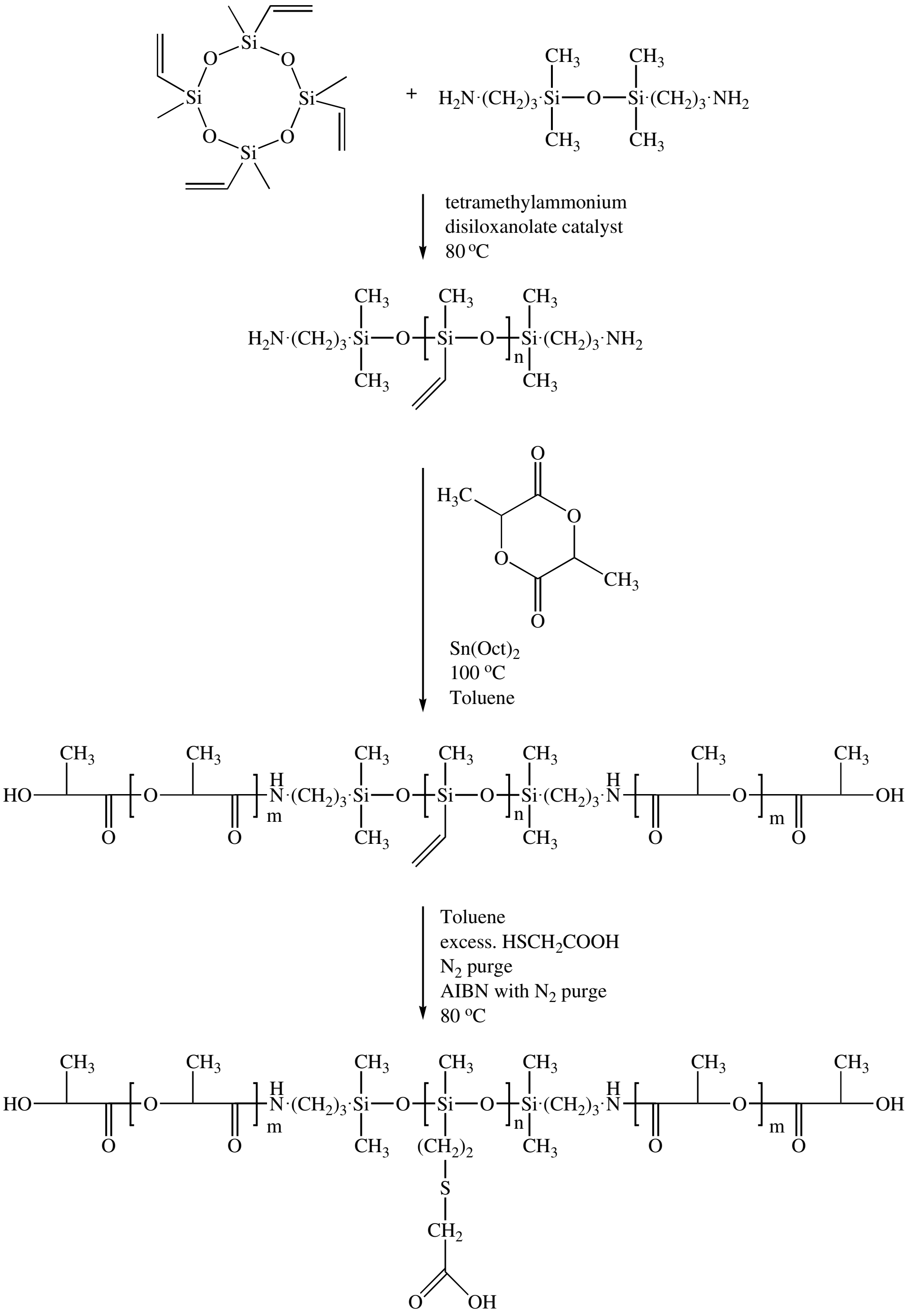

Fig. 3. Synthesis of poly(lactide-*b*-siloxane-*b*-lactide) triblock copolymers with pendent carboxylic acid groups.

copolymers have narrow molecular weight distributions (close to one). Thus, as expected the values for molecular weight distributions for these block copolymers are narrower than for the PMVS equilibrated macroinitiators.

It was desirable to functionalize the PMVS blocks with multiple carboxylate groups so that these blocks would bind to the surfaces of the magnetite nanoparticles. The thiol of mercaptoacetic acid was added across the vinylsilyl bonds in a free radical initiated chain reaction to obtain the desired functional copolymers. The vinylsilyl chemical structure provides an ideal substrate for ene-thiol additions since these vinyl groups do not readily polymerize by free radical reactions [41]. An excess of mercaptoacetic acid was utilized to avoid any propagation of the double bonds. The reactions were monitored by following the disappearance of resonances associated with the vinyl proton sets in the ^{1}H NMR spectra at ~6 ppm. The number of carboxylic acid groups per polymer chain was further verified by quantitative ^{29}Si NMR by analyzing a shift of the vinyl-substituted silicon resonances at ~ −30 ppm to silicons with carboxyalkyl substituents at ~ −23 ppm (Table 3). The data supports the premise that unwanted propagation of the vinyl groups had been essentially avoided during free radical addition of the thiols. To verify that the conditions of these functionalization reactions did not cause transesterification of the polylactide blocks, a PDLLA homopolymer was exposed to an analogous concentration of mercaptoacetic acid under the conditions utilized for functionalization. GPC chromatograms before and

Table 2
Molecular weights of a series of poly(lactide-*b*-methylvinylsiloxane-*b*-lactide) triblock copolymers

Target M_n (g mol^{-1})	M_n (g mol^{-1})		PDI
	^{1}H NMR	GPC	
PLLA-*b*-PMVS-*b*-PLLA			
2000-1610-2000	1810-1610-1810	7,400	1.05
5000-1610-5000	4950-1610-4950	12,400	1.01
2000-2660-2000	2090-2660-2090	7,400	1.16
5000-2660-5000	4440-26660-4440	15,600	1.10
8000-2660-8000	8140-2660-8140	16,600	1.23
PDLLA-*b*-PMVS-*b*-PDLLA			
50,000-1370-50,000	43,250-1370-43,250	121,000	1.28
5000-1960-5000	4630-1960-4630	12,000	1.19

after this process confirmed that the molecular weights and distributions did not change (before exposure – 11,200 g mol^{-1} with a PDI of 1.5; after exposure – 11,000 g mol^{-1} with a PDI of 1.6).

3.3. *Preparation and characterization of magnetite–copolymer nanoparticle complexes*

One goal of this research was to prepare magnetite–copolymer complexes with high compositions of magnetite and with compositional homogeneity across the particle distribution so that nano- and microspheres fabricated from these complexes would have high and consistent magnetic susceptibilities. We investigated a common and facile approach for synthesizing magnetite that consisted of treating an aqueous solution of Fe(III) and Fe(II) chlorides in the stoichiometric 2:1 molar ratio with hydroxide [33,34,42,43,44]. For example, Elmore reported the preparation of stabilized magnetite colloids by dissolving $FeCl_2 \cdot 4H_2O$ and $FeCl_3 \cdot 6H_2O$ in water and adding an aqueous NaOH solution while stirring [44]. The precipitate was rinsed with water and 0.01 N HCl and then refluxed in an aqueous surfactant solution to stabilize the colloidal particles.

The magnetite nanoparticles in the present study were coated with the carboxylate-functional poly(lactide-*b*-siloxane-*b*-lactide) copolymers in an interfacial adsorption process where the magnetite nanoparticles were dispersed in water and the copolymer was dissolved in dichloromethane/methanol (Fig. 5). The pH was adjusted to pH ~7 for this coating process to avoid any hydrolysis of the polylactide blocks. In this range, the magnetite surface has both cationic and anionic charges (the magnetite isoelectric point = pH 6.8), and the acid groups in the copolymer were in their anionic salt form [45]. Hence, it was reasoned that these conditions would promote adsorption of negatively charged carboxylates onto cationic magnetite surface sites.

Two complexes were fractionated using a copolymer having 4500 g mol^{-1} PLLA end blocks and a 5200 g mol^{-1} polysiloxane anchor block wherein 66 and 50 wt% magnetite were charged in the coating procedure in order to probe their compositional homogeneities/heterogeneities. After adsorption of the copolymer, the complexes were dispersed in dichloromethane and fractionated by centrifuging the dispersions. For the complex in which 50 wt% of magnetite was charged into the coating process, ~69% of the material remained in the supernatant, and ~27% of the complex that had been charged with 66 wt% magnetite remained dispersed. The magnetizations of the complexes that remained well dispersed in the supernatants were measured by VSM and compared to the bare magnetite, and this provided a means to estimate the concentrations of magnetite in those fractions to be between 20 and 30 wt%. The complexes in the supernatants, after isolation by evaporation of the solvent, had magnetizations at 8000 Oe applied field of 14 (for the complex in which 66 wt% magnetite was charged into the coating process) and 17 emu g^{-1} (for the complex in which 50 wt% magnetite was charged into the coating process). The bare magnetite nanoparticles had a magnetization of 66 emu g^{-1} at this field strength.

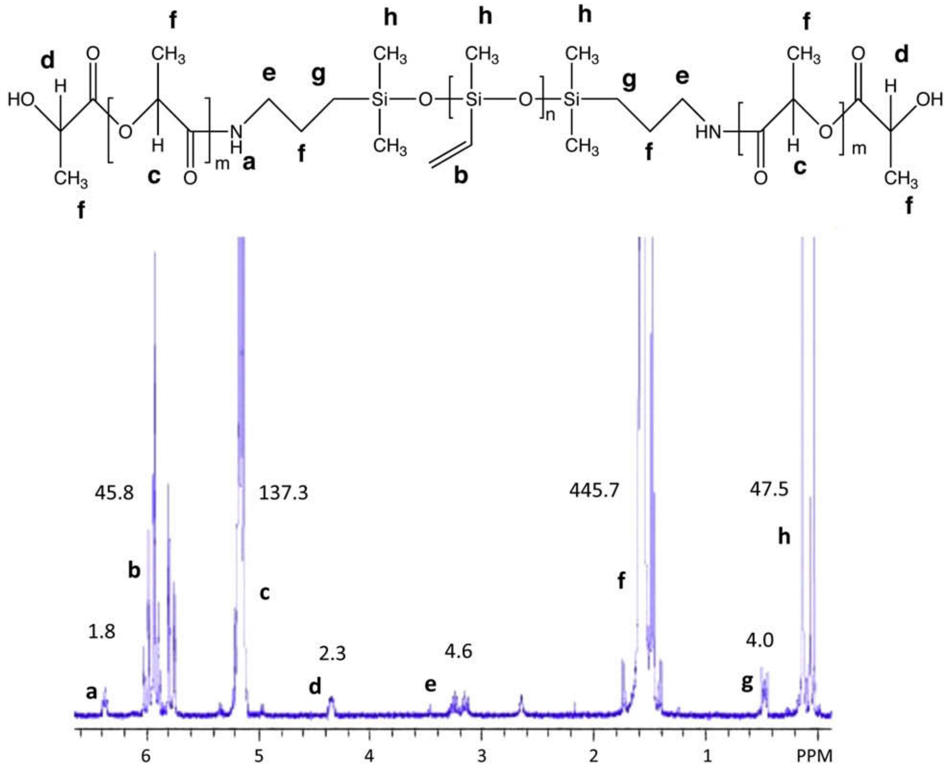

Fig. 4. ^{1}H NMR of a poly(L-lactide-*b*-methylvinylsiloxane-*b*-L-lactide) triblock copolymer with 5000-1600-5000 g mol^{-1} block molecular weights, respectively.

Table 3
Structural confirmation of the carboxylate functionality of poly(lactide-*b*-siloxane-*b*-lactide) triblock copolymers

M_n (^{1}H NMR) ($g\,mol^{-1}$)	Target no. of acid groups per mole	No. of acid groups per mole (^{29}Si NMR)
PLLA-*b*-PMVS-*b*-PLLA		
4950-1610-4950	16	15
2090-2660-2090	28	28
4440-2660-4440	28	23
PDLA-*b*-PMVS-*b*-PDLA		
43,250-1370-43,250	13	13
4630-1960-4630	20	19

The magnetite–copolymer complexes in the supernatants and centrifugates were also analyzed by TGA (Fig. 6). Eight wt% of char remained after pyrolysis of the block copolymer alone, suggesting that the polysiloxane block likely formed some siliceous species, so this was taken into account when calculating the compositions of the complexes. Bare magnetite nanoparticles had approximately 96% char. The supernatant fractions from the original complexes where 66 and 50 wt% magnetite had been charged contained 23 and 34 wt% magnetite, respectively, by this analysis. Thus, although the nanoparticles had formed complexes with the block copolymers, the compositional data on the fractions suggested that the composition distribution was broad across the particle distribution. This may be at least partially attributable to the interfacial coating process, but could also be a result of the magnetite particle precipitation method.

The magnetite–copolymer complexes could be dispersed in chloroform or dichloromethane but not in water. This suggested that the particles were indeed coated with the organo-soluble block copolymers having water-insoluble PLLA or PDLLA tail blocks. The surface compositions were probed using XPS to confirm that good surface coverage had been achieved (Table 4). Complexes of magnetite coated with an acid-functional PLLA-*b*-siloxane-*b*-PLLA triblock copolymer with 4440 $g\,mol^{-1}$ tail blocks and a 5200 $g\,mol^{-1}$ central block were compared to bare magnetite. The relative iron (27%) and oxygen (46%) compositions on the surfaces of the bare magnetite particles corresponded reasonably well with the expected bulk magnetite composition. Once the magnetite nanoparticles were coated with the copolymer, these surface compositions changed significantly. The iron content decreased from 27% to 2% suggesting that the particles were indeed coated with the triblock dispersion stabilizer. The presence of Si and S in the coated magnetite further confirmed the presence of the copolymer on the surface.

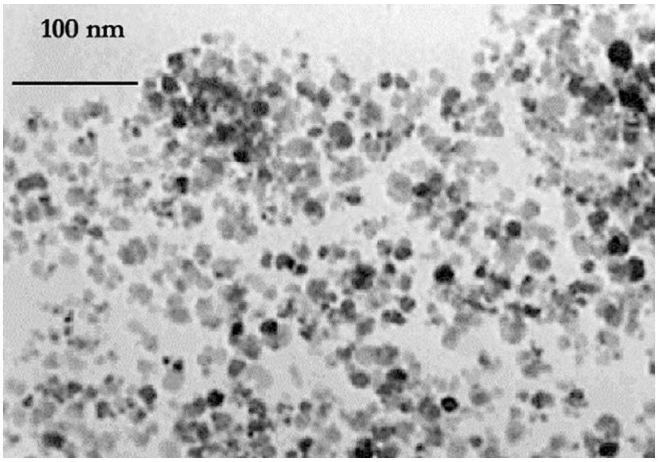

Fig. 5. TEM of a triblock copolymer–magnetite nanoparticle complex (the copolymer was a PLLA-*b*-siloxane-*b*-PLLA having 4440 $g\,mol^{-1}$ end blocks and a 5200 $g\,mol^{-1}$ carboxyfunctional polysiloxane central block) with 50 wt% magnetite.

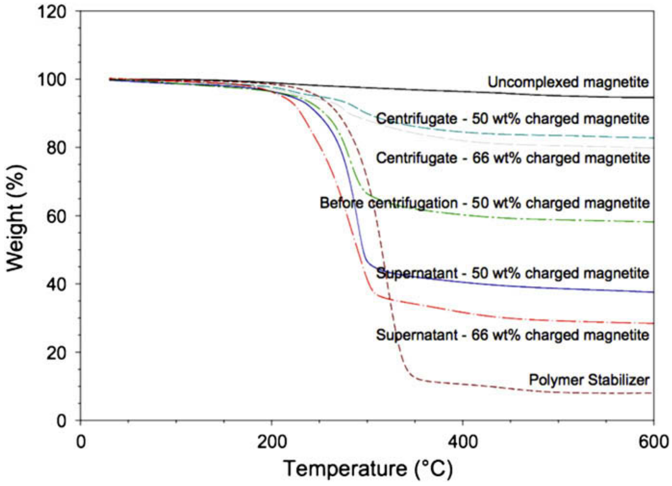

Fig. 6. Weight loss data after pyrolysis of magnetite–copolymer complexes by TGA (the copolymer was a PLLA-*b*-siloxane-*b*-PLLA having 4440 $g\,mol^{-1}$ end blocks and a 5200 $g\,mol^{-1}$ carboxyfunctional polysiloxane central block).

Table 4
Atomic surface compositions of magnetite–copolymer complexes prepared with a PLLA-*b*-siloxane-*b*-PLLA copolymer having a 5200 $g\,mol^{-1}$ central block and 4440 $g\,mol^{-1}$ end blocks

Elements (at%)	C	O	N	Fe	Si	S
Magnetite	23	46	0	27	–	–
Target 66 wt% magnetite (supernatant)	59	28	0	2	9	1
Target 50 wt% magnetite (supernatant)	58	25	0	0	16	0
Target 66 wt% magnetite (centrifugate)	34	41	0	18	4	2
Target 50 wt% magnetite (centrifugate)	29	46	0	19	3	2
Target 50 wt% magnetite (no centrifugation)	49	38	0	7	4	1

4. Conclusions

Telechelic aminopropyl-terminated PMVS homopolymers were equilibrated utilizing a pre-formed polydimethylsiloxanolate basic catalyst by similar methods to those typically utilized for forming analogous aminopropyl-terminated polydimethylsiloxane oligomers [35]. These oligomers offer substantial versatility for components of block copolymers due to their functional endgroups combined with the pendent vinyl groups that can be further derivatized. In this work, they were utilized as macroinitiators for polymerizing polylactide blocks from their termini, then the vinyl substituents were converted to carboxylic acids through an ene-thiol free radical addition reaction. It is envisioned that many different thiol reagents could also be appended using similar conditions for the reactions. Both the PMVS oligomers and the poly(lactide-*b*-siloxane-*b*-lactide) copolymers had the expected molecular weights and compositions.

A method for adsorbing the carboxylate-functional triblocks onto magnetite nanoparticles was investigated. The magnetite was formed in an aqueous process by reacting stoichiometric ratios of iron chlorides with hydroxide, neutralized, and then a dichloromethane/methanol solution of the copolymer was added into the aqueous mixture so that it could adsorb onto the nanoparticle surfaces. It is important that the mixture be near neutral pH to avoid any hydrolysis of the relatively labile lactide ester bonds during the nanoparticle adsorption process. While the copolymer did adsorb onto the magnetite, analysis of the complexes showed that their composition distribution was inhomogeneous. It is not clear whether this is a result of the interfacial nature of the coating method or whether the process for making the magnetite results in too many aggregates to yield optimum results. We recommend that processes for both synthesis of magnetite nanoparticles and for coating these copolymers be investigated by alternative methods.

Acknowledgements

The authors gratefully acknowledge the financial support of the Division of Materials Research of NSF under contract number DMR-0312046.

References

[1] Weir NA, Buchanan FJ, Orr JF, Farrar DF, Boyd A. Biomaterials 2004;25:3939–49.
[2] Sodergard A, Nasman JH. Polymer Preprints (American Chemical Society, Division of Polymer Chemistry) 1994;35:431–2.
[3] Sodergard A, Selin JF, Nasman JH. Polymer Degradation and Stability 1996;51:351–9.
[4] Chu CC. Polymer 1985;26:591–4.
[5] Hu DSG, Liu HJ. Journal of Applied Polymer Science 1994;51:473–82.
[6] Tokiwa Y, Jarerat A. Biotechnology Letters 2004;26:771–7.
[7] Scott G, Gilead D. Degradable polymers: principles and applications. London: Chapman and Hall; 1995.
[8] Li S, Anjard S, Rashkov I, Vert M. Polymer 1998;39:5421–30.
[9] Rashkov I, Manolova N, Li SM, Espartero JL, Vert M. Macromolecules 1996;29:50–6.
[10] Saltzman WM. Drug delivery: engineering principles for drug therapy. Oxford, New York: Oxford University Press; 2001.
[11] Kricheldorf HR. Chemosphere 2001;43:49–54.
[12] Shinno K, Miyamoto M, Kimura Y, Hirai Y, Yoshitome H. Macromolecules 1997;30:6438–44.
[13] Fukushima K, Kimura Y. Polymer International 2006;55:626–42.
[14] MacDonald RT, McCarthy SP, Gross RA. Macromolecules 1996;29:7356–61.
[15] Tsuji H, Ikada Y. Macromolecules 1992;25:5719–23.
[16] Tsuji H, Ikada Y. Macromolecular Chemistry and Physics 1996;197:3483–99.
[17] Spassky N, Wisniewski M, Pluta C, Borgne AL. Macromolecular Chemistry and Physics 1996:197.
[18] Dubois P, Jacobs C, Jerome R, Teyssie P. Macromolecules 1991;24:2266–70.
[19] Stridsberg K, Ryner M, Albertsson AC. Macromolecules 2000;33:2862–9.
[20] Loefgren A, Albertsson AC, Dubois P, Jerome R, Teyssie P. Macromolecules 1994;27:5556–62.
[21] Stridsberg K, Albertsson AC. Journal of Polymer Science, Part A: Polymer Chemistry 1999;37:3407–17.
[22] Schenck HV, Ryner M, Albertsson AC, Svensson M. Macromolecules 2002;35:1556–62.
[23] Schindler A, Hibionada YM, Pitt CG. Journal of Polymer Science, Polymer Chemistry Edition 1982;20:319–26.
[24] Zhang X, Wyss UP, Pichora D, Goosen MFA. Polymer Bulletin 1992;27:623–9.
[25] Gomez-Lopera SA, Plaza RC, Delgado AV. Journal of Colloid and Interface Science 2001;240:40–7.
[26] Liu X, Yueping G, Zhiya M, Liu H. Langmuir 2004;20:10278–82.
[27] Roullin VG, Deverre JR, Lemaire L, Hindre F, Venier-Julienne MC, Vienet R, et al. European Journal of Pharmaceutics and Biopharmaceutics 2002;53:293–9.
[28] Kim KD, Mikhaylova M, Wang FH, Kehr J, Bjelke B, Zhang Y, et al. Chemistry of Materials 2003;15:4343–51.
[29] Kusaka M, Takegami K, Sudo A, Yamazaki T, Kawamura J, Uchid A. Journal of Orthopaedic Science 2002;7:354–7.
[30] Honda H, Kawabe A, Shinkai M, Kobayashi T. Journal of Fermentation and Bioengineering 1998;86:191–6.
[31] Mazurek M, Chojnowski J. Macromolecular Chemistry 1977;178:1005–17.
[32] Kawazumi K, Maruyama H, Hashi K. Kogyo Kagaku Zasshi 1963;66:628–31.
[33] Zhang Q, Thompson MS, Carmichael-Baranauskas AY, Caba BL, Zalich MA, Lin Y-N, et al. Langmuir 2007;23:6927–36.
[34] Harris LA, Goff JD, Carmichael AY, Riffle JS, Harburn JJ, St. Pierre TG, et al. Chemistry of Materials 2003;15:1367–77.
[35] McGrath JE. ACS symposium series #286. Washington, DC: ACS; 1985. pp. 1–22.
[36] Hurd DT, Osthoff RC, Corrin ML. Journal of the American Chemical Society 1954;76:249–52.
[37] Elsbernd CS, Spinu M, Krukonis VJ, Gallagher PM, Mohanty DK, McGrath JE. In: Zeigler JM, Fearon FWG, editors. Advances in chemistry series No. 224. Washington, DC: ACS; 1990. p. 145–64.
[38] Kowalski A, Libiszowski J, Biela T, Cypryk M, Duda A, Penczek S. Macromolecules 2005;38:8170–6.
[39] Goffin A-L, Duquesne E, Moins S, Alexandre M, Dubois P. European Polymer Journal 2007;43:4103–13.
[40] Zhong Z, Dijkstra PJ, Feijen J. Journal of the American Chemical Society 2003;125:11291–8.
[41] Scibiorek M, Gladkova NK, Chojnowski J. Polymer Bulletin 2000;44:377–84.
[42] Welo LA, Baudisch O. Philosophical Magazine 1925;50:399–408.
[43] Schwertmann U, Cornell RM. Iron oxides in the laboratory: preparation and characterization. New York: VCH; 1991.
[44] Elmore WC. Physical Review 1938;54:309–10.
[45] Tewari PH, McLean AW. Journal of Colloid and Interface Science 1972;40:267–72.