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Versatile synthesis of self-assembling ABA triblock copolymers with polymethyloxazoline A-blocks and a polysiloxane B-block decorated with supramolecular receptors

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Abstract

BACKGROUND: Self-assembling amphiphilic block copolymers with incorporated, biologically relevant functionalities have received limited attention, partly due to the fact that biomolecules are not robust enough to synthetic manipulation, do not lend themselves readily to systematic studies due to their complexity and leach rather quickly from a vesicle or membrane when physically incorporated. Synthetic supramolecules are used as biomolecule mimics in functional membranes.

RESULTS: Reaction conditions were established for the synthesis of a tosyl-terminated siloxane end-blocker, which serves as molecular weight control in the synthesis of polydimethylsiloxane (PDMS) and poly(dimethylsiloxane-*co*-methylhydrosiloxane) [P(DMS-*co*-MHS)] copolymers. Hydrosilylation reactions were investigated for the covalent coupling of synthetic supramolecules (18-crown-6 ether, hydroxybenzoate) to the polymer backbone using the methylhydrosiloxane repeat units as the anchor moiety. Using P(DMS-*co*-MHS) or derivatized P(DMS-*co*-MHS) copolymers as macroinitiator for the ring-opening polymerization of 2-methyl-4-hydroxy-oxazoline led to the formation of poly[(dimethylsiloxane-*co*-methylhydrosiloxane)-*block*-oxazoline] [P(DMS-*co*-MHS-*b*-Ox)] ABA triblock copolymers with defined PDMS to PMHS ratios and controlled molecular weights.

CONCLUSION: Derivatized P(DMS-*co*-MHS-*b*-Ox) ABA triblock copolymers synthesized using a novel versatile procedure undergo vesicle formation upon electroformation with vesicle diameters ranging from 2 to 10 μm. The size of the vesicle depends on the overall polarity of the macromolecule.
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Keywords: poly(dimethylsiloxane-co-oxazoline); triblock copolymers; self-assembly; hydrosilylation; vesicle

INTRODUCTION

Recently there has been a renewed interest in the design of self-assembling polymeric nano-containers mainly for drug delivery purposes. A variety of amphiphilic block copolymers have been employed and excellent reviews are available.[1] Though there has been much research on the use of polymeric materials for structural purposes as in stealth devices, drug delivery systems, biocompatible coatings[2–5] and as matrices for reconstitution of biomolecules,[6,7] there has been little attention paid to self-assembling polymeric membranes that incorporate functionality as an integral part of the membrane.

Some attempts have been made where functionality is conferred to the polymeric membrane by incorporation of biomolecules such as channel proteins.[7] Unfortunately, the long-term stability of such systems is generally poor. Furthermore, though biomolecules offer exquisite levels of functionality, usually they are not robust to synthetic manipulations and are not simple enough for systematic investigations as part of a macromolecular assembly. Supramolecules are synthetic counterparts to biomolecules and offer similar levels of functionality. They provide a variety of functions from ion channels to enzyme mimics.

This is the first report on a poly[(dimethylsiloxane-*co*-methylhydrosiloxane)-*block*-oxazoline] ABA triblock copolymer that was further derivatized with methyl benzoate and 18-crown-6 ether supramolecules via hydrosilylation reactions (Fig. 1). Pendant groups

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of 18-crown-6 are of interest in the biomedical realm for the recognition and transport of potassium ions. The design of this triblock copolymer was driven by the following requirements: (1) biocompatibility of all blocks and (2) liquid-like membrane properties that will be achieved through the presence of the polysiloxanes, which have very low glass transition temperatures, hence making the use of plasticizers or rheological modifiers unnecessary. Syntheses of such triblock membranes reported in the literature[8] do not lend themselves easily to receptor functionalization. We report here a facile and versatile route towards the synthesis of both functionalized and non-functionalized triblock copolymers and show that they retain their self-assembling properties, and self-assemble into vesicles upon electroformation.

EXPERIMENTAL

Materials

All reagents were used as received without further purification unless otherwise noted. 11-Bromo-1-undecene (97%), methyl-2,4-dihydroxybenzoate (98%), 10-undecenoic acid (98%), 2-methyl-2-oxazoline (98%), *p*-toluenesulfonic acid monohydrate (TsOH), lithium iodide and platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane were purchased from Sigma-Aldrich; 2-hydroxymethyl-18-crown-6 (≥90%) and 4-dimethylaminopyridine (DMAP) from Fluka; and octamethylcyclotetrasiloxane (D_4), 1,3,5,7-tetramethylcyclotetrasiloxane (D_4H) and 1,3-bis(hydroxybutyl)tetramethyldisiloxane from Gelest, Inc. Potassium carbonate and triethylamine were obtained from Alfa Aesar and synthesis-grade toluene

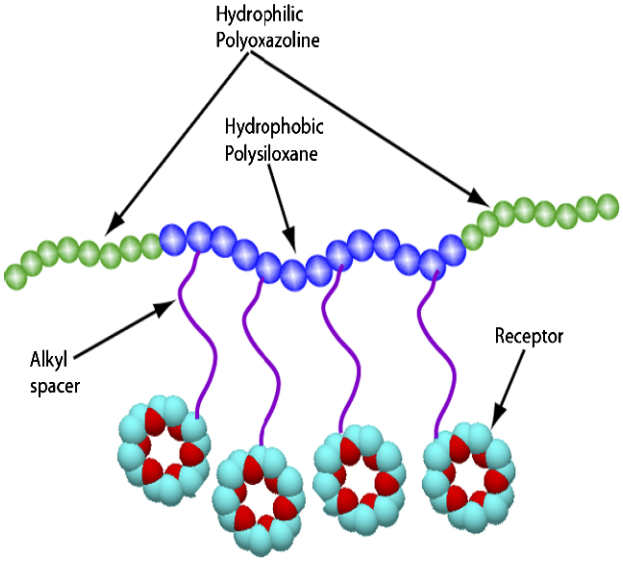

Figure 1. Schematic representation of functionalized triblock copolymers, consisting of hydrophilic polyoxazoline and hydrophobic polysiloxane. The polysiloxane copolymer is derivatized via a hydrosilylation reaction to carry an active supramolecular moiety. The long alkyl spacer gives the supramolecule translational mobility but prevents it from leaving the membrane phase. To ensure transport the backbone needs to contain a minimum density of carriers enabling a 'hopping' mechanism to occur.

(Drisolv) from EMD Chemicals. Dimethylformamide, 1,2-dichloroethane and dichloromethane with low moisture content and stored over molecular sieves were purchased from Sigma-Aldrich.

Instrumentation

^{1}H NMR spectra were recorded with 300 and 500 MHz Varian spectrometers using 5 mm outer diameter tubes. Sample concentrations were approximately 10 mg mL^{-1} in either $CDCl_3$ or CD_3OD.

Electroformation of vesicles was performed on indium tin oxide (ITO) slides purchased from SPI, Inc. using an Agilent 33 220A function generator. Vesicles were imaged using a Zeiss inverted microscope (Zeiss Axiovert 200M) fitted with a ×63 phase objective.

Gel permeation chromatography (GPC) studies were performed using a Waters 1525 binary HPLC pump (Waters, Milford, MA) equipped with an R410 differential refractometer as a detector.

Synthesis of 1,3-bis(tosyloxybutyl)tetramethyldisiloxane

To a solution of 1,3-bis(hydroxybutyl)tetramethyldisiloxane (5.6 g, 20 mmol) cooled to 0 °C, *p*-toluenesulfonyl chloride (9.5 g, 50 mmol) and DMAP (0.61 g, 5 mmol) were added, both dissolved in 200 mL of dry CH_2Cl_2. Triethylamine (8.15 g, 80 mmol) was added to this solution dropwise over 10 min. The mixture was stirred for 1 h at 0 °C; subsequently the temperature was raised to room temperature and the solution stirred for another 24 h, and washed with 1 mol L^{-1} HCl, saturated $NaHCO_3$ and distilled water. The organic layer was dried over $NaSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, 40–63 mesh) using hexanes/ethyl acetate (4:1) to yield 1,3-bis(tosyloxybutyl)tetramethyldisiloxane (5 g, 8.6 mmol) as a pale yellow oil. See Fig. S1(a) and Table S1 for yields.

^{1}H NMR ($CDCl_3$, 300 MHz): 0 ppm (Si–CH_3, s, 12H), 0.3–0.5 ppm (Si–CH_2–, m,4H), 1.2–1.4 ppm (Si–CH$_2$–CH_2–, m, 4H), 1.6–1.8 ppm (–CH_2–CH$_2$–OTs, m, 4H), 2.45 ppm (*p*-CH_3–Ar–SO$_3$–, s, 6H), 4.0 ppm (–CH_2–OTs, t, 4H), 7.3 ppm (ArH, d, 4H), 7.8 ppm (ArH, d, 4H).

General procedure for the synthesis of telechelic α,ω-butyltosyloxy-terminated poly(dimethylsiloxane-*co*-methylhydrosiloxane) [P(DMS-*co*-MHS)]

D_4 and D_4H were distilled over CaH_2 under reduced pressure and stored under argon prior to use. 1,3-Bis(tosyloxybutyl)tetramethyldisiloxane was used to control the molecular weight and respective amounts (Table S2) were added to a round-bottom Schlenk vessel fitted with a reflux condenser and degassed. D_4 and D_4H were added under a constant nitrogen flow, the amount of D_4H depending on the desired feeding ratio (Table S3). The mixture was stirred for

1 h at 50 °C, and then 100 μL of TsOH in 1,4-dioxane (125 mg mL^{-1}) was added. The temperature was raised to 70 °C and the mixture was stirred for 48 h. Subsequently, the reaction mixture was concentrated *in vacuo* to remove cyclic side-products and the polymer was isolated by precipitating in methanol and extracted with hexanes. The polymer was dried and characterized using ^{1}H NMR (Figs S1(b) and S1(c)). ^{1}H NMR ($CDCl_3$, 300 MHz): 4.7 ppm, –Si–*H*. See Tables S2 and S3 for yields.

Synthesis of methyl-(2-hydroxy-4-undecenyloxy) benzoate

Dry dimethylformamide (100 mL) was added via a syringe to a mixture of potassium carbonate (5.53 g, 30 mmol), lithium iodide (0.8 g, 6 mmol), 18-crown-6 (1.6 g, 6 mmol) and methyl-2,4-dihydroxybenzoate (30 mmol, 6.5 g; 95% pure), under a constant nitrogen flow. The resulting solution was stirred for 30 min. 11-Bromoundecene (30 mmol, 7 g) was added dropwise to this homogenous mixture via an addition funnel. The solution was heated to 85 °C and stirred overnight. After cooling to room temperature the solvent was removed via rotary evaporation. Deionized water was added, and the mixture was extracted three times with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent removed via rotary evaporation. The crude product was purified using a short silica gel column with 10:1 hexanes/ethyl acetate as the eluent (Fig. S2, Scheme I). The solvent was evaporated via rotary evaporation to give a clear oil that crystallized upon standing (6.4 g, 20 mmol, 66%), m.p. 39.5–40 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.1–1.4 ppm (–C*H*$_2$–, m, 12H), 1.6–1.8 ppm (Ar–O–CH$_2$–C*H*$_2$–, m, 2H), 1.9–2.1 ppm (CH$_2$=CH–C*H*$_2$–, m, 2H), 3.9 ppm (Ar–COO–C*H*$_3$, s, 3H), 4.0 ppm (Ar–O–C*H*$_2$–, 2H, t), 4.9–5.1 ppm (C*H*$_2$=CH–, m, 2H), 5.8–5.9 ppm (CH$_2$=C*H*–, m, 1H), 6.4–6.5 ppm (Ar*H*, m, 2H), 7.7 ppm (Ar*H*, d, 1H), 11 ppm (Ar–O*H*, s, 1H).

Synthesis of (undec-10-enoyloxy)methyl 18-crown-6

The synthesis was adapted from a procedure for the production of a sodium-chelating 15-crown-5 ether.[9] For the synthesis of the potassium-chelating crown 18-crown-6 ether, 10-undecenoic acid (10.556 g, 57.2 mmol), *N*,*N*′-dicyclohexylcarbodiimide (DCC; 10.98 g, 53.2 mmol) and DMAP (5.74 g, 47 mmol) were added to a solution of 2-hydroxymethyl-18-crown-6 (10.445 g, 35.5 mmol). Dry CH_2Cl_2 (150 mL) was added and the solution was stirred for 24 h at room temperature. The solution was then filtered to remove the dicyclohexyl urea, and the resulting solution was washed three times with a saturated $NaHCO_3$ solution. The solvent was removed by rotary evaporation and the crude product purified by column chromatography (silica gel deactivated with 0.4% w/w triethylamine) using hexanes/ethyl acetate (1:1) to yield (undec-10-enoyloxy)methyl 18-crown-6 as a pale yellow oil (9.4 g, 20.4 mmol, 57%) (see Fig. S2, Scheme II).

^{1}H NMR ($CDCl_3$, 300 MHz): 1.1–1.4 ppm (–C*H*$_2$–, m, 10H), 1.6–1.8 ppm (–COO–CH$_2$–C*H*$_2$–, m, 2H), 1.9–2.1 ppm (CH$_2$=CH–C*H*$_2$–, m, 2H), 2.2–2.4 ppm (–COO–C*H*$_2$–CH$_2$–, t, 2H), 3.6–3.9 ppm (–O–C*H*$_2$–C*H*$_2$–O, 23H, t), 4.9–5.1 ppm (C*H*$_2$=CH–, m, 2H), 5.8–5.9 ppm (CH$_2$=C*H*–, m, 1H).

General procedure for polymer analogous hydrosilylation reaction

To a 1.75 g solution of the corresponding telechelic polymer, a calculated amount of the ω-alkenyl receptor [(methyl-(2-hydroxy-4-undecenyloxy) benzoate or (undec-10-enyloxy)methyl 18-crown-6)] and 5 mL of dry toluene were added. An amount of 100 μL of a 0.1 mol L^{-1} platinum divinyltetrasiloxane complex in xylenes was added to this solution and the resultant mixture was stirred for 24 h. The solvent was evaporated *in vacuo* and the resultant solution was washed with distilled water and extracted with diethyl ether. The solvent was evaporated via rotary evaporation to yield pale yellow to brown oils. Activated charcoal was added to this mixture and the solution was filtered through Celite to yield either colorless or yellow oils which were characterized using ^{1}H NMR. See Fig. 2 for the methyl(2-hydroxy-4-undecenyloxy) benzoate derivative. ^{1}H NMR: ($CDCl_3$, 300 MHz), 0.5 ppm, –Si–C*H*$_2$–.

Synthesis of functionalized amphiphillic triblock copolymers

Functionalized telechelic polysiloxanes were weighed in and 1 mL of 2-methyl-2-oxazoline, freshly distilled from CaH_2, was added. Amounts of 1 to 5 mL of solvent (Table S4) were added and the resultant solution was stirred at room temperature for 0.5 h. The mixture was then heated to 50 °C for 15 h and to 75 °C for an additional 20 h. The solution was allowed to cool to room temperature and 1 mL of 0.1 mol L^{-1} NaOH in MeOH was added and the solution was stirred for an additional hour. The mixture was washed with diethyl ether/hexane to remove side-products and the solvent was removed by rotary evaporation to yield the functionalized triblock polymers and characterized using ^{1}H NMR (Fig. S3). ^{1}H NMR: ($CDCl_3$, 300 MHz), 3.4–3.6 ppm (–N–C*H*$_2$–C*H*$_2$–N), 2.0–2.2 ppm (C*H*$_3$–CO–N–). See Table S4 for yield data.

Electroformation of vesicles

Vesicles were electroformed using a modified literature procedure.[10] Briefly, solutions of triblock copolymer in chloroform (c = 20 mg mL^{-1}) were applied to ITO slides and allowed to dry. To one of the slides a silicone gasket was affixed to create a solution reservoir. Sucrose solution (100 mmol L^{-1}) containing 200 μg mL^{-1} fluoroscein salt was gently placed into the reservoir and the gasket was then sandwiched between

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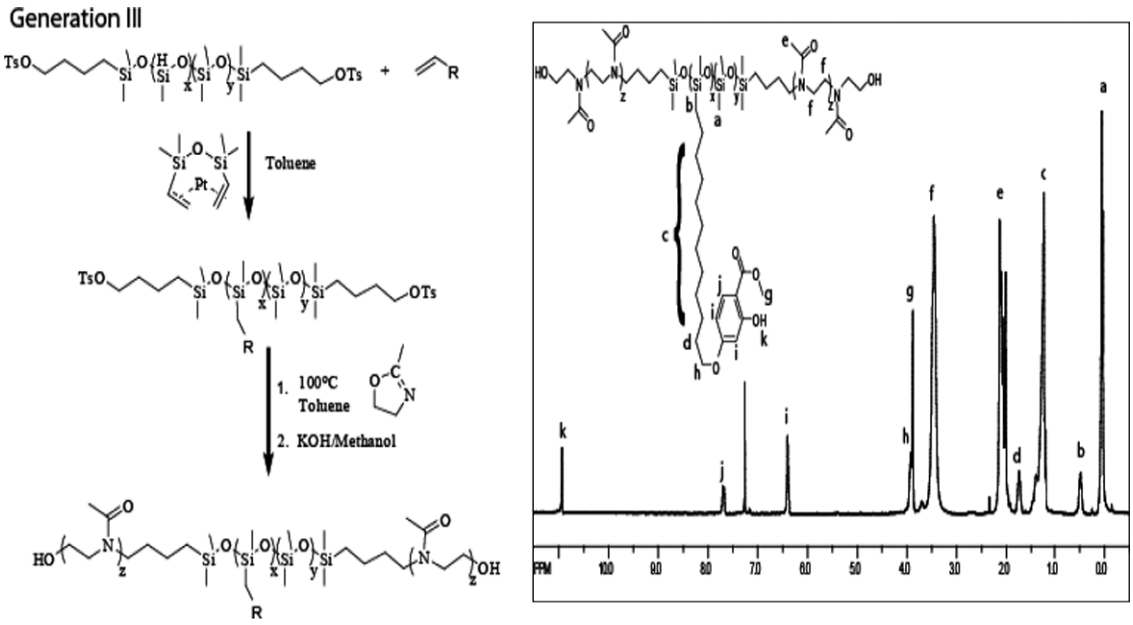

Figure 2. Generation III shows a modification to the earlier scheme to yield an active nanostructure. Here the backbone was first derivatized and then used as a macroinitiator for the ring-opening polymerization of 2-methyl-2-oxazoline. As evidenced by ^{1}H NMR analysis, this route is successful and is the preferred one for the synthesis of functionalized triblock copolymers.

two ITO plates. The plates were then connected to an Agilent function generator and subjected to a 10 Hz AC sinusoidal waveform, with peak-to-peak amplitude of 2 V, for 2 h and then 5 Hz for another hour. Afterwards, the sucrose solutions were gently dispersed into 2 mL of a 100 mmol L^{-1} glucose solution. The resultant solution was allowed to settle and imaged under phase contrast using a Zeiss microscope.

RESULTS AND DISCUSSION

Structure–function relationships play a key role in the biomedical arena. Designing polymeric materials that function as cellular mimics can lead to advances in prosthetic applications. Key properties for such membranes are host–guest recognition, selectivity and transport. Molecular recognition can be effected by covalent binding (e.g. glucose binding by phenylboronic acids[11]) or non-covalent complexing, as observed in crown ethers. Though simple physical incorporation of these supramolecules can yield a functional membrane, they do not posses long-term stability due to leaching of the supramolecules from the membrane. In a biological medium the leachate can be toxic; for example, lipophilic crowns have been shown to cause cell death.[12]

Long alkyl spacers can be used as a tether to covalently bind such supramolecules to a polymeric backbone and thus achieve improved long-term stability by suppressing the leaching process.[9] The cost for the increase in robustness is the reduction in mobility of the carrier in the membrane phase. However, this can be offset by increasing the carrier concentration along the polymeric backbone. The transport mechanism is now mainly through a hopping mechanism[13] rather than simple diffusion (Fig. 1).

Previously reported syntheses of non-functionalized poly(siloxane-*block*-oxazoline) triblock copolymers relied on one of two major strategies. One approach is to convert a commercially available α,ω-bishydroxypoly(dimethylsiloxane) into a macroinitator by converting the hydroxyl group into a trifluoromethanesulfonic acid ester (triflate),[8] which initiates the ring-opening polymerization of 2-methyl-2-oxazoline. The second approach is to synthesize the polysiloxane with reactive end-groups, namely benzyl chloride, and use those as a macroinitiator for the ring-opening polymerization of 2-ethyl-2-oxazoline with sodium iodide as catalyst.[14] Another approach to the synthesis of a diblock copolymer that merits attention is based upon the hydrosilylation of a SiH-terminated polydimethylsiloxane (PDMS) with allyl alcohol. The hydroxyl end group thus obtained is converted into a tosylate[15] and used as the macroinitiator as in the syntheses described above. The central theme of all the reported syntheses has been to generate a macrointiator capable of initiating the ring-opening polymerization of oxazolines. A wide variety of initiators have been reported of which the triflates are the most effective since they are highly electrophilic.[16]

Our main goal is to produce triblock copolymers with the P(DMS-*co*-MHS) block (B-block) being available for further derivatization, specifically the attachment of biologically active supramolecules. Hence, the syntheses described in the literature were unsuitable for our purposes since they limit the functional groups that could be attached in polymer analogous reactions to the ones that are stable towards electrophilic attack. Furthermore, triflates are generally less air and moisture stable, requiring very

careful handling. The approach of using chlorides was also not very attractive since it needed fairly high temperatures (130 °C) and the use of iodide as a catalyst can cause unwanted side-reactions in the functional groups. Tosylates offer a good balance between the required leaving group ability, tolerance to other functional groups and stability. Since we require a copolymer of dimethylsiloxane and methylhydrosiloxane, P(DMS-*co*-MHS), reported schemes like the one mentioned earlier[14] cannot be used since it involves a hydrosilylation step. Also, post-derivatization of a hydroxyl end-group was not attractive since the termination may be neither quantitative nor bi-functional, and may lead to very tedious work-up strategies to isolate the bi-functional tosylates. Additionally, hydroxybutyl- and hydroxypropyl-terminated polysiloxanes degrade upon heating, through the loss of end-groups.[17] Recently, we reported[18] a novel and facile route to synthesizing quantitatively terminated bi-functional P(DMS-*co*-MHS) tosylated telechelics, which is a modification of a reaction reported by Yilgor *et al*.[14,19] This reaction concept was applied throughout this work (see Figs S1(c) and S4).

Polysiloxanes are generally prepared from cyclic monomers by cationic ring-opening polymerization using an acid or base catalyst. Though the Si–O bond is highly stable under neutral conditions it is readily cleaved in highly acidic or basic conditions. Siloxane bonds are constantly broken and reformed in both linear and cyclic species, until the reaction reaches its thermodynamic equilibrium. Hence, this polymerization is often termed an equilibration or redistribution polymerization. Unlike the Si–O bond, the Si–C bond is stable under these reaction conditions and if molecules containing Si–C bonds are present, they will terminate the growing chain and serve as end-blockers.[19] The remaining cyclic non-functional side-products can be removed by vacuum distillation or precipitation. If the end-blocker is a siloxane dimer it will yield bi-functional siloxane telechelics and simultaneously provide a method for the control of the molecular weight.

Synthesis of bistosylate siloxane telechelic

A linear siloxane dimer terminated on both ends with tosylate groups was synthesized by converting a commercially available 1,3-bis(hydroxybutyl)tetramethyldisiloxane into the ditosylate. The reaction scheme is shown in Fig. S1(a) along with the ^{1}H NMR spectrum showing complete conversion of hydroxyl groups into tosylate end groups. Reaction conditions for the tosylation are listed in Table S1. DMAP proved to be the most successful tosylation catalyst. Since the siloxane bonds cleave readily under tosylation conditions, 4 equivalents of triethylamine are necessary as proton scavenger, thus guaranteeing yields of approximately 40%. Reactions were conducted in methylene chloride for 1 h at 0 °C followed by 24 h at room temperature. Using sodium hydroxide with benzyltrimethylammonium chloride as catalyst in a 75:25 THF:H_2O v/v mixture, a procedure that works well for ditosylations of glycols, did not yield tosylated bis(hydroxybutyl)tetramethyldisiloxane, and reactions with NaOH as base were terminated after 4 h, since disiloxane bonds were cleaved. Substituting potassium carbonate for sodium hydroxide prevents this cleavage but the tosylated product was obtained in very low yields (Table S1).

Synthesis of P(DMS-*co*-MHS)

Reaction conditions for the copolymer synthesis were established by first investigating the PDMS homopolymer synthesis. Bistosylate disiloxane was used as an end-blocker in the acid (*p*-TsOH)-catalyzed ring-opening polymerization of D_4, as shown in Fig. S1(b). The associated ^{1}H NMR spectrum shown alongside Fig. S1(b) clearly shows the bi-functional termination of the PDMS homopolymer. Entries one through three in Table S2 describe reactions in which the monomer concentration was kept constant and end-blocker concentration was varied to control the molecular weight. In those reactions monomer and end-blocker were added to the toluene solution containing the acid catalyst. The obtained polymers show a significant difference between the expected and actual molecular weight. End-blocker and monomer form a suspension rather than a solution in toluene. It was determined that a stable homogeneous monomer–end-blocker suspension must be formed prior to adding the acid catalyst. When the acid catalyst was added to a stable suspension (entry 4 of Table S2) α,ω-butyltosyloxyl-terminated PDMS was obtained with a molecular weight as predetermined by the end-blocker-to-initiator ratio. Since the end-blocker and monomer are initially immiscible, reaction progress can be monitored visually by the change from a heterogeneous suspension to a homogenous mixture.

The yields of the PDMS synthesis are generally low; the molarity of the D_4 concentration in toluene affects the ratio of cyclics to linear polymers. As shown in Table S2 (entry 1), if the D_4 concentration in toluene is 1.58 mol L^{-1}, the yield is only 8%, which is in good agreement with work reported by Buese, which states that the polymerization of D_4 in concentrations below 2 mol L^{-1} yields 80–95% cyclic products.[20] Increasing the concentration to 21 mol L^{-1} D_4 in toluene results in yields of 20–30%. The yield can be improved if the product is recovered by solvent extraction rather than precipitation in methanol due to the low molecular weights involved. If extraction in hexanes in used, as for the case of copolymers (Table S3), yields improve to 40–75%.

A P(DMS-*co*-MHS) copolymer will constitute the B-block in the final derivatized triblock copolymers (Fig. 1). These copolymers were synthesized using the reaction conditions that were most suitable for the PDMS homopolymer synthesis (Table S2, entry 4). The reaction scheme is shown in Fig. S1(c) and the corresponding ^{1}H NMR spectrum shows

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the incorporation of methylhydrosiloxane by the appearance of the Si–H protons at 4.7 ppm. To further investigate the versatility of the approach we varied the Si–H content by altering the D_4 : D_4H feed ratio to see if the ratio charged would be the ratio obtained. Again, the monomers and the end-blocker were stirred prior to the addition of the acid catalyst, thus obtaining a stable suspension. Best results were obtained when the acid catalyst (TsOH) was dissolved in dioxane and added after stirring the suspension for 1 h (entries 2–4 in Table S3). It was determined that catalytic amounts of TsOH should not exceed 0.001 eq. The methyl protons of the toluenesulfonate moiety (protons e) were used as internal reference during ^{1}H NMR analyses and served as reference for the determination of the Si–H content, and molecular weights (Fig. S4). Molecular weights ranged between 4000 and 5000 g mol^{-1}, as predetermined by the monomer-to-end-blocker ratio, proving that the molecular weight can be controlled by the feed ratio of the end-blocker to the cyclic monomers. GPC analysis (data not shown) of these polymers yielded a polydispersity index of 2.1, typical for siloxane polymers synthesized using the acid-catalyzed ring-opening polymerization approach.[9]

Derivatization of P(DMS-*co*-MHS) with supramolecules

2-Hydroxy-4-undecenyloxymethyl benzoate was studied as the model receptor and used to establish reaction conditions for hydrosilylation that yield derivatized P(DMS-*co*-MHS) copolymers. The synthesis scheme for this model receptor is shown in Fig. S2 (Scheme I). Initially, a strong base (sodium hydride) was used; however, this approach led to low yields, and better results were obtained when K_2CO_3 activated by catalytic amounts of 18-crown-6 was used along with lithium iodide as a co-catalyst (*in situ* Finkelstein reaction). The product was purified by column chromatography, giving a total product yield of 70%. ^{1}H NMR spectroscopy was used to verify the structure.

The receptor of interest, potassium-chelating 18-crown-6-ether, was synthesized by adapting a method of Klok *et al*.[9] originally developed for the synthesis of sodium-chelating 15-crown-5-ether. An 11-carbon undecenyl spacer was first attached to the hydroxymethyl 18-crown-6-ether via a DCC coupled esterification catalyzed by DMAP, followed by the hydrosilylation reaction (Fig. S2, Scheme II).

The receptor (18-crown-6-ether or methyl benzoate) was attached to the P(DMS-*co*-MHS) backbone using a polymer analogous hydrosilylation reaction. The functionalization was quantitative and can be identified by the disappearance of the vinyl protons (5.9 and 5.4 ppm) and the appearance of the Si–CH_2 peaks at 0.5 ppm (^{1}H NMR spectrum in Fig. 2). The presence of the hydroxyl group in the 2-position did not adversely affect the polymerizations and shows the versatility of the synthetic route used. The hydrosilylated siloxane polymer was purified following a literature procedure[17] using a silica column. Briefly, the reaction product was loaded onto a silica column and unreacted benzoate was eluted with toluene. ^{1}H NMR analysis of the eluate revealed the presence of trace amounts of P(DMS-*co*-MHS) copolymer. Subsequently, diethyl ether was used to recover the derivatized copolymer, and the product was obtained by solvent evaporation. Unlike the hydrophobic benzoate side chain containing siloxane telechelics, the crown ether containing siloxanes could not be purified using a silica column. In order to make the method more general we developed a simple procedure to purify these copolymers using activated carbon (see experimental section). This method leads to purified telechelics that can be used for the ring-opening polymerization of 2-methyl-2-oxazoline. ^{1}H NNMR spectroscopy was used to verify the structure.

Synthesis of triblock copolymers

Triblock copolymers were synthesized by cationic ring-opening polymerization of 2-methyl-2-oxazoline using the bistosylate-terminated siloxane telechelics as macroinitiators. As in the telechelic synthesis, reaction conditions were first determined using the PDMS homopolymer. The reaction scheme (Generation I) is shown in Fig. S3 along with the ^{1}H NMR spectrum of the triblock copolymer. The spectrum exhibits the classic polyoxazoline segment peaks of the side-chain methyl protons between 2.0 and 2.3 ppm, and the protons connected to the nitrogen appear at 3.3–3.5 ppm. Similarly, triblock copolymers were formed when P(DMS-*co*-MHS) was used as macroinitiator (Fig. S3, Generation II). The ^{1}H NMR spectrum verifies the structure of the triblock copolymer, clearly indicating the presence of the polyoxazoline, Si–CH_3 and Si–H moieties. The presence of the fairly reactive Si–H groups does not seem to hinder the block polymerization under the reaction conditions used.

We synthesized the triblock copolymers described above with the methylhydrosiloxane moieties containing B-block in an effort to further derivatize the B-block using hydrosilylation reactions. The effect of the reaction order was investigated by (i) first forming the triblock copolymers followed by the hydrosilylation reaction, or (ii) the hydrosilylation was conducted first, followed by the ring-opening polymerization of 2-methyl-2-oxazoline. One of the most important outcomes of the work presented was the discovery that the hydrosilylation reaction, i.e. the attachment of the tethered supramolecules to the P(DMS-*co*-MHS) block, needs to be conducted prior to the block copolymer formation with 2-methyl-2-oxazoline, that is, option (ii). Reactions in which the triblock copolymer was formed first, option (i), and the supramolecules were tethered later met with failure. We believe this is due to the interaction of the platinum metal catalyst with the polyoxazoline block. We have not investigated the use of platinum catalyst other than Kardsedt's catalyst since it is the most widely used and gentle method

of hydrosilylation. Hence, the reaction scheme was modified so that after the copolymerization of D_4 and D_4H, a hydrosilylation reaction was performed yielding a P(DMS-*co*-MHS) copolymer derivatized with an appropriate side chain (Fig. 2, Generation III).

Best results were obtained when PDMS homopolymer was used as macroinitiator without solvent, i.e. the polyoxazoline A-blocks were obtained in the expected molecular weight, and the overall yield was 94%. Using the P(DMS-*co*-MHS) copolymer, or derivatized copolymers, necessitated the use of a solvent. Toluene was used for the copolymer and the benzoate-derivatized copolymers, while dichloroethane was used for the crown-ether-derivatized copolymer. Hydrosilylation of the P(DMS-*co*-MHS) copolymer derivatized with the 18-crown-6 supramolecule led to a low yield when the side-chain density was low (Table S4, 8% MHS). The reason for that is believed to be in the purification steps. Current work focuses on optimizing this procedure.

Research focused on 18-crown-6-ether, since this supramolecule is expected to coordinate and potentially translocate potassium ions. Potassium ions are both biologically relevant and play an important role in maintaining membrane potentials in neural tissue. One of our long-term goals is to modulate the ionic gradient around the neural tissue to elicit a response. The first step towards this goal is to produce a synthetic membrane capable of self-assembling into vesicles and sequestering potassium ions from the extracellular fluid. Currently, research is underway that focuses on the translocation of potassium ions using the self-assembled triblock copolymers described here. Moreover, the question as to whether the triblock polymeric membranes would retain their self-assembling properties when the side-chain mesogen was the hydrophilic crown ether rather than the hydrophobic benzoate that was used initially as a model receptor could additionally be answered.

GPC analyses of triblock copolymers were unsuccessful in common GPC solvents. This is believed to be due to the amphiphilic nature of these polymers. Current efforts are focused on finding appropriate matrices for MALDI-TOF molecular weight studies.

Self-assembling properties of triblock polymers

Though the self-assembling properties of poly (oxazoline-*co*-polysiloxane) triblock copolymers have been established,[1,8] the self-assembly properties of copolymers with Si–H repeat units or copolymers with long side chains have not yet been demonstrated. In order to ensure that the synthesized copolymers retain their self-assembling properties, copolymers were assembled into vesicular structures before and after derivatizations. Electroformation was chosen, since this method yields large-sized vesicles that can be readily imaged using conventional light microscopy. The resulting vesicles are shown in Fig. 3.

Vesicle size is determined by the composition of the main chain as well as by the nature of the side chains.

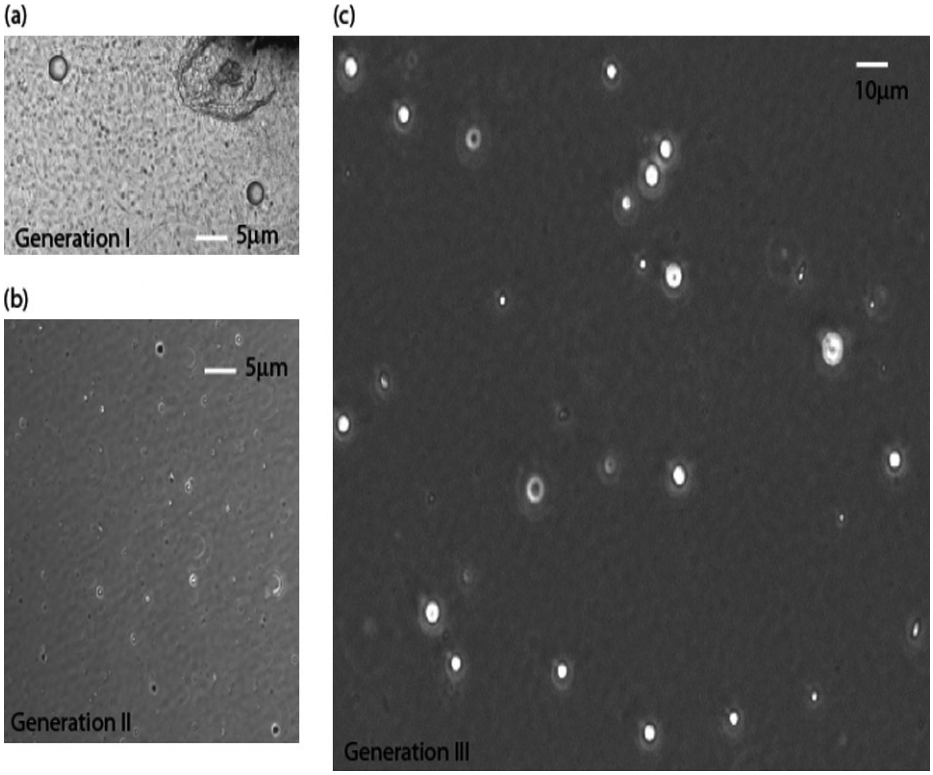

Figure 3. Vesicles obtained by electroformation and imaged by conventional light microscopy. Vesicles are in the range 1–5 μm. The size distribution correlates with the backbone lipophilicity. (a) Vesicles of size between 2 and 3 μm formed by copolymers that have a PDMS hydrophobic core. (b) Vesicles of size between 1 and 2 μm formed by copolymers that have a P(DMS-*co*-MHS) hydrophobic core. (c) Vesicles of size between 3 and 5 μm formed by copolymers that have a methyl(2-hydroxy-4-undecenyloxy) benzoate-derivatized siloxane hydrophobic block.

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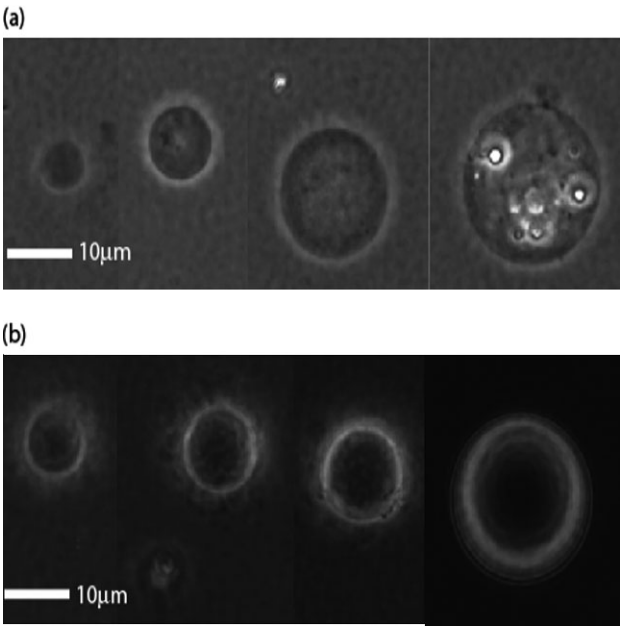

Figure 4. Electroformed vesicles using the two functionalized triblocks with different receptor densities; both images are montages of individually cropped images. (a) Vesicles formed with the triblock containing 8% 18-crown-6 receptor side chains. (b) Vesicles formed with the triblock containing 32% 18-crown-6 receptor side chains.

Conventional triblock copolymers (Generation I) form vesicles of 2–3 μm in diameter. Converting the B-block into a random copolymer of dimethylsiloxane and hydroxymethylsiloxane results in smaller sized vesicles with a diameter between 1 and 2 μm, which is believed due to the increased polar character of Si–H bonds. This hypothesis is further validated by the fact that the vesicles formed by the copolymers containing the lipophilic 2-hydroxy-4-undecenyloxymethyl benzoate forms larger sized vesicles, with diameters between 2 and 5 μm. Even larger diameter vesicles (*ca* 10 μm) were formed with the crown ether-derivatized triblock copolymers. The density of receptors also seems to play a role in the vesicle size distribution. Vesicles formed using the crown ether-derivatized triblock copolymers with 32% side-chain density exhibit a larger fraction of large-diameter vesicles than triblock copolymers with 8% side-chain density. The side-chain density does not adversely affect the self-assembling properties of these polymers as seen by the vesicles shown in Fig. 4.

CONCLUSIONS

A novel and facile route to synthesizing both functionalized and non-functionalized self-assembling triblock copolymers has been demonstrated. One of the most important results of this work has been the identification that hydrosilylation of the hydrophobic siloxane core needs to be performed prior to block copolymerization. The derivatized siloxane with pendant side groups still retains its macrointiating ability. The synthesized triblocks have been electroformed into vesicles. Vesicle size seems to correlate with side-chain lipophilicity. Side-chain receptor density does not seem to affect the self-assembling properties of these polymeric membranes.

Supplementary material

Supplementary electronic material for this paper is available in Wiley InterScience at: http://www.interscience.wiley.com/jpages/0959-8103/suppmat/.

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