

Novel ABA Triblock Copolymers With Pendant Carboxylic Acid Side Chain for Drug Delivery Systems

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INTRODUCTION

Recently, there has been an increasing interest in the design of self-assembling polymeric nano-containers for drug delivery purposes.¹ A variety of amphiphilic block copolymers have been studied. Although there has been much research on the use of polymeric materials for structural purposes, such as in drug delivery systems,^{3,4} biocompatible coatings and as matrices for reconstitution of biomolecules, there has been little attention paid to self-assembling polymeric membranes that incorporate functionality as an integral part of the membrane.⁵

In our previous work,² we have reported poly[(dimethylsiloxane-co-methylhydrosiloxane)-block-oxazoline] ABA triblock copolymers derivatized with methyl benzoate and 18-crown-6 ether supramolecules via hydrosilylation reactions. The pendant groups of 18-crown-6 are of interest in the biomedical realm for the recognition and transport of potassium ions. 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. In this study, we have synthesized a series of new triblock polymers by using a new tosyl-terminated ester siloxane end-blocker that serves as molecular weight control in the synthesis of polydimethylsiloxane (PDMS) and poly(dimethylsiloxane-co-methylhydrosiloxane) [P(DMS-co-MHS)] copolymers. The triblock polymers were further derivatized with undecanoic acid *tert*-butyl ester via hydrosilylation reactions and were converted to undecanoic acid by deprotection.

EXPERIMENTAL

Materials.

All reagents were used as received without further purification unless otherwise noted. 2-allyloxyethanol (98%), *p*-toluenesulfonyl chloride, methyl-2,4-dihydroxybenzoate (98%), 10-undecenoic acid (98%), 1,1,3,3-tetramethyldisiloxane (97%) and platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane were purchased from Sigma-Aldrich; 4-Dimethylaminopyridine (DMAP) from Fluka; and octamethylcyclotetrasiloxane (D₄), 1,3,5,7-tetramethylcyclotetrasiloxane (D₄H) and 1,3-bis(hydroxybutyl)tetramethyldisiloxane from Gelest, Inc. 2-Methyl-2-oxazoline (98%) and *p*-toluenesulfonic acid monohydrate (TsOH), were obtained from Alfa Aesar.

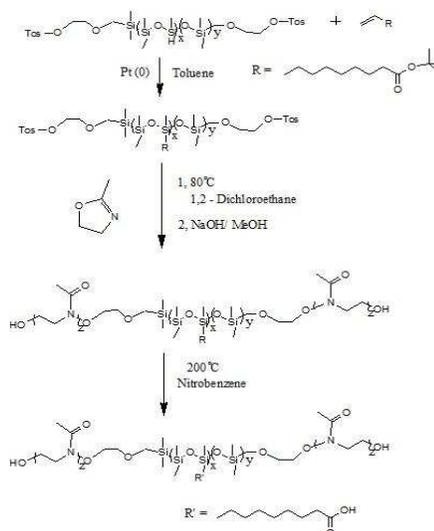
Synthesis of toluene-4-sulfonic acid 2-allyloxy-ethyl ester.

A 350 ml round-bottomed flask was charged with 2-allyloxy ethanol (3.57 g, 35 mmol), THF (20 ml) and cooled to 0°C (ice bath), *p*-toluenesulfonyl chloride (8.67 g, 46 mmol) was added and the solution stirred for 3 h while maintaining the bath temperature at 0°C. TLC indicated the disappearance of the starting alcohol. The reaction mixture was poured into ice water (25 ml). The organic phase was separated, washed with brine (3X20 ml) and dried over anhydrous magnesium sulfate. Solvents were removed under reduced pressure and residue was purified by distillation to give toluene-4-sulfonic acid 2-allyloxy-ethyl ester as a colorless oil (7.49 g, 88% yield).

Synthesis of tosyl-terminated ester siloxane end-blocker

1,1,3,3-tetramethyldisiloxane (3.03 ml, 17.12 mmol) in 5 mL of dry toluene was added to a solution of toluene-4-sulfonic 2-allyloxy-ethyl ester (7.52 ml, 39 mmol) and 100 μL of 0.1M platinum divinyltetrasiloxane complex (Karstedt's catalyst) in xylenes drop wise

and the resultant mixture was stirred for 24 h at room temperature. Activated charcoal was added to this mixture and the solution was filtered through Celite. The solvent was evaporated in vacuo and the resultant crude product was purified using a silica gel column with 4:1 hexanes/ethyl acetate as the eluent. The solvent was evaporated via rotary evaporation to yield pale oils of 5.4g. (49%)



Scheme 1. The scheme for the synthesis of the polymers.

Synthesis of poly(dimethylsiloxane-co-methylhydrosiloxane) [P(DMS-co-MHS)]

D₄ and D₄H were distilled over CaH₂ under reduced pressure and stored under nitrogen prior to use. 1.87 g (2.9 mmol) of end-blocker was used to control the molecular weight and was added to a round-bottom flask and degassed. 10.33 g (34.80 mmol) of D₄ and 4.55 g (18.80 mmol) of D₄H were added under a constant nitrogen flow with the amount of D₄H depending on the desired feeding ratio. The mixture was stirred for 1h at 80°C, and then 500 μL of TsOH in 1,4-dioxane (0.2M) was added 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 to give 8.0 g of the co-polymer.

Synthesis of undecylenic acid *tert*-butyl ester

Concentrated sulfuric acid (0.55 mL, 10 mmol) was added to a vigorously stirred suspension of anhydrous magnesium sulfate (4.81 g, 40 mmol) in 40 mL of CH₂Cl₂. The mixture was stirred for 15 minutes, after which undecylenic acid (1.64 g, 10 mmol) was added. Tertiary butanol (4.78 mL, 50 mmol) was added last. The mixture was stoppered tightly and stirred for 18 h at 25 °C. The reaction mixture was then quenched with 75 mL of saturated sodium bicarbonate solution and stirred until all magnesium sulfate had dissolved. The solvent phase was separated, washed with brine, dried (MgSO₄), and concentrated to afford the crude *t*-butyl ester, which was purified by distillation to give a colorless oil. (1.56 g, 65%)

General procedure for polymer analogous hydrosilylation reaction

A 1.62 g of undecylenic acid *tert*-butyl ester in 5 g toluene was added to 1.32 g of copolymer in 5mL of dry toluene. An amount of 60 μL of a 0.1mol 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 the functionalized polymer as a pale oil (2.24 g).

Synthesis of functionalized amphiphilic triblock copolymers

A freshly distilled 1 mL of 2-methyl-2-oxazoline was added to 0.72 g of functionalized telechelic polysiloxanes.⁶ Amounts of 1 to 5 mL of toluene was added and the resultant solution was stirred at room temperature for 0.5 h. The mixture was then heated to 80 °C for 24 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 gave 1.34 g of triblock copolymers. This polymer was dissolved in nitrobenzene and heated at 200 °C for 5 h to yield the deprotected triblock polymer.

RESULTS AND DISCUSSION

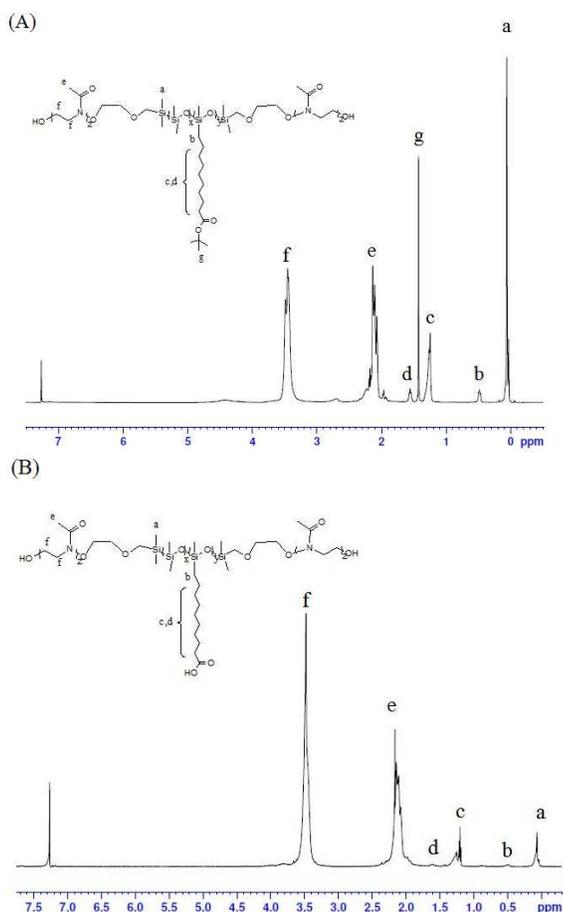


Figure 1. ¹H NMR analysis of the functionalized triblock polymer (A) and the deprotected triblock polymer (B) in CDCl₃.

In Figure 1, the ¹H NMR peak (g) corresponding to the *t*-boc group is sharp and more like a singlet. The NMR study showed that the triblock polymer with a protected side chain was successfully deprotected by heat at 200 °C in nitrobenzene. However, the ¹H peaks of **P(DMS-co-MHS)** and the side chain were reduced in height. This indicated that the deprotected triblock polymer formed vesicles and micelles in the solvent due to the minimization of the total energy of the system. The correlation time plays a key role in the features observed in the NMR spectrum. The factors that affect the correlation time are the temperature and the viscosity of the solvent and the molecular packing. A densely packed amphiphilic copolymer has a slow correlation time and fast spin-spin relaxation time, and hence, causes peak broadening.⁷

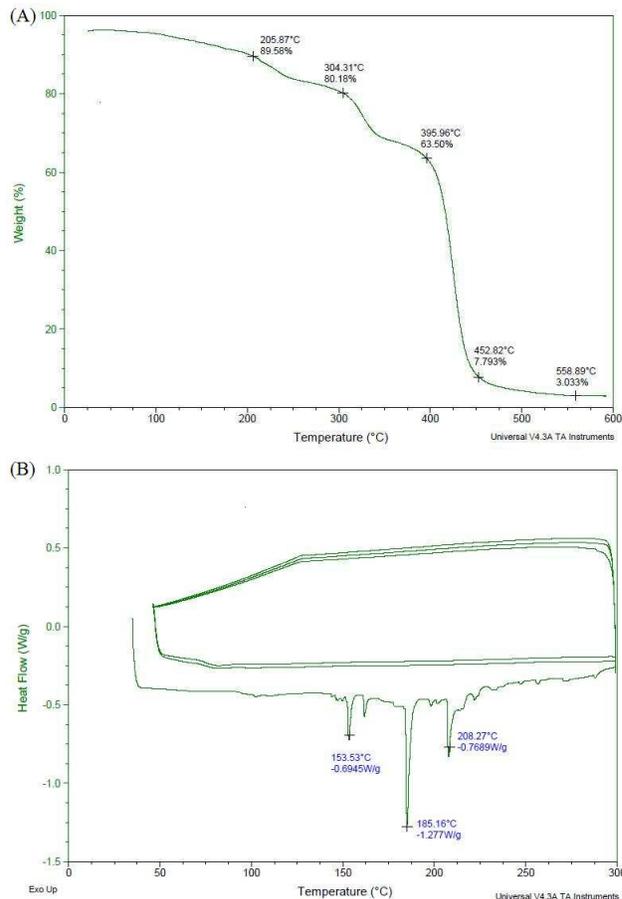


Figure 2. TGA (A) and DSC (B) analysis of the functionalized triblock polymer

Thermogravimetric analysis (TGA) showed that the triblock polymer lost approximately 10 % weight in the range of 100 to 205 °C. This weight change corresponds to the deprotection of *t*-boc groups. Differential scanning calorimetry (DSC) exhibited several sharp endothermic peaks in the range of 150 to 210 °C, which indicates the rearrangement of side chains on the polymer.

CONCLUSIONS

We have synthesized novel triblock polymer by using functional tosylates as initiator for the ring-opening polymerization of 2-methyl-1,3-oxazoline. The pendant *t*-boc side chains on the polymer were successfully converted to carboxylic acid.

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