Supporting Information

Consequences of Isolated Critical Monomer Sequence Errors on the Hydrolysis Behaviors of Sequenced Degradable Polyesters

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1. Optical Profilometry Measurements

Figure S1

Figure S1. Optical profilometry film thickness measurements.
2. Scanning Electron Microscopy Imaging

Figure S2. Scanning electron microscopy images (100x) of lyophilized films during hydrolysis.
Figure S3. Scanning electron microscopy images (100x) of lyophilized films during hydrolysis.
3 Experimental
3.1 General Information

All reactions were performed in an inert atmosphere under N\textsubscript{2} unless otherwise stated. Methylene chloride and ethyl acetate were purchased from Fisher Scientific, stored in a solvent system, and passed through an activated alumina column prior to use. DCC was purchased from Oakwood Chemicals and used without further purification. Nucleophilic catalyst DPTS was prepared by neutralization of p-toluene sulfonic acid with pyridine and purified by recrystallization in dichloroethane. Silica gel for column chromatography was purchased from Sorbent Technologies.

The detailed synthesis of Cyc-SyLMLGLGL was previously reported.\textsuperscript{1}

Scheme S1

Scheme S2.

Scheme S2. Steglich esterification to Bn-SyLMLGGL-Si.
Scheme S3. Benzyl and silyl deprotections to yield SyLMLGGGL and subsequent macrolactonization reaction to prepare Cyc-SyLMLGGGL.

Spectra for all compounds/polymers begin on page S19.
Bn-GGL-Si

**Bn-G** (5.12 g, 30.8 mmol) and **GL-Si** (11.35 g, 31.9 mmol) were dissolved in 290 mL DCM. DPTS (1.71 g, 5.8 mmol) was added and allowed to dissolve before the addition of DCC (6.58 g, 31.9 mmol). The reaction vessel was capped and the reaction was allowed to stir at RT overnight. The solution was filtered, concentrated in vacuo, and purified by column chromatography using 5% ethyl acetate in hexanes. Product eluted in fractions 5-11 (250 mL fractions). 10.3 g (66%).
GGL-Si

Bn-GGL-Si (10.3 g, 19.3 mmol) was dissolved in 190 mL ethyl acetate in a Schlenk flask to prepare a 0.1 M solution. Pd/C (1.03 g, 10% by mass) was added, and two balloons of H\(_2\) (g) were passed through the flask. A third balloon was attached to serve as a source of excess H\(_2\) (g). The reaction was stirred at RT overnight. The solution was then filtered through a thick pad of celite and concentrated to provide the pure product, 7.3 g yield (85%).
Bn-GGGL-Si

**Bn-G** (1.91 g, 11.5 mmol) and **GGL-Si** (4.64 g, 10.4 mmol) were dissolved in 104 mL DCM. DPTS (0.612 g, 2.1 mmol) was added and allowed to dissolve before the addition of DCC (2.37 g, 11.5 mmol). The reaction vessel was capped and the reaction was allowed to stir at RT overnight. The solution was filtered, concentrated in vacuo, and purified by column chromatography using 5-10% ethyl acetate in hexanes. Product eluted in fractions 4-9 (250 mL fractions). 3.31 g, 59%.

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GGGL-Si

Bn-GGGL-Si (3.31 g, 5.59 mmol) was dissolved in 55 mL ethyl acetate in a Schlenk flask to prepare a 0.1 M solution. Pd/C (0.330 g, 10% by mass) was added, and two balloons of H₂ (g) were passed through the flask. A third balloon was attached to serve as a source of excess H₂ (g). The reaction was stirred at RT overnight. The solution was then filtered through a thick pad of celite and concentrated to provide the pure product, 2.60 g yield (93%).
Bn-LGGGL-Si

Bn-L (1.02 g, 5.69 mmol) and GGGL-Si (2.367 g, 4.01 mmol) were dissolved in 50 mL DCM. DPTS (0.305 g, 1.04 mmol) was added and allowed to dissolve before the addition of DCC (1.17 g, 5.17 mmol). The reaction vessel was capped and the reaction was allowed to stir at RT overnight. The solution was filtered, concentrated in vacuo, and purified by column chromatography using 10% ethyl acetate in hexanes. Product eluted in fractions 10-18 (250 mL fractions). 2.90 g yield (84%).

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δ (ppm) + Assignment

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δ (ppm)

1H-NMR (400 MHz, CDCl3)

Composition

C₃₅H₄₆O₁₁Si
LGGGL-Si

1H-NMR (400 MHz, CDCl3)

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13C-NMR (400 MHz, CDCl3)  

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HRMS (ESI)  

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LGGGL-Si  

Bn-LGGGL-Si (2.90 g, 4.36 mmol) was dissolved in 45 mL ethyl acetate in a Schlenk flask to prepare a 0.1 M solution. Pd/C (0.290 g, 10% by mass) was added, and two balloons of H2 (g) were passed through the flask. A third balloon was attached to serve as a source of excess H2 (g). The reaction was stirred at RT overnight. The solution was then filtered through a thick pad of celite and concentrated to provide the pure product, 2.33 g yield (Quantitative Yield).
Bn-SyLMLGGGL-Si

Bn-SyLM (0.725 g, 1.53 mmol) and LGGGL-Si (0.966 g, 1.68 mmol) were dissolved in 16 mL DCM. DPTS (0.090 g, 0.31 mmol) was added and allowed to dissolve before the addition of DCC (0.378 g, 1.68 mmol). The reaction vessel was capped and the reaction was allowed to stir at RT overnight. The solution was filtered, concentrated in vacuo, and purified by column chromatography using 10% ethyl acetate in hexanes. Product eluted in fractions 10-18 (250 mL fractions). 0.947 g yield (60%).
SyLMLGGGL-Si

A 0.60 M solution of Bn-SyLMLGGGL-Si (0.947 g, 0.92 mmol) was prepared in DCM. A 0.60 M solution of palladium (II) acetate (0.0093 g, 0.041 mmol), triethylamine (16 μL, 0.0124 mmol), and triethylsilane (205 μL, 1.29 mmol) was prepared and allowed to stir for 30 min. The solution of Bn-SyLMLGGGL-Si was then added dropwise over the course of five minutes. The reaction was allowed to stir at RT overnight. The solution was quenched with 10 mL saturated aqueous ammonium chloride solution and the organic layer was extracted 3x with DCM. The organic phase was dried with magnesium sulfate, filtered, and concentrated in vacuo to yield the crude product as a yellow oil. The product was purified by column chromatography using 10% ethyl acetate in hexanes to yield pure product as a white solid (0.332 g, 38%).
SyLMLGGGL

SyLMLGGGL-Si (0.332 g, 0.331 mmol) was dissolved in 3.3 mL THF to prepare a 0.1 M solution. The flask was cooled to 0 °C. TBAF (0.50 mL as a 1.0 M solution in THF, 0.50 mmol) was added to a vial and acetic acid (35 μL, 0.60 mmol) was added. The vial was vortexed briefly and this solution was added steadily to the solution of starting material. The reaction was warmed to RT over the course of 1 h and the reaction was quenched with 5 mL brine. The organics were extracted 3x with ethyl acetate, were dried with magnesium sulfate, filtered, and concentrated in vacuo to provide the crude product as a yellow oil. The product was purified by column chromatography (25% ethyl acetate in hexanes increased gradually to 90% ethyl acetate in hexanes). The product was a white solid (0.151 g, 65%).
Cyc-SyLMLGGGL

SyLM(L₃G₂) (0.113 g, 0.16 mmol) was dissolved in 2.5 mL dichloroethane and injected to a solution of DCC (0.066 g, 0.32 mmol) and DPTS (0.023 g, 0.08 mmol) in 2.5 mL dichloroethane at 60°C over a span of 16 hours. The solution was allowed to stir for an additional 24 hours before being filtered and concentrated to obtain the crude product. A column loaded with 15% ethyl acetate in hexanes was used to purify the product (0.070 g, 64%), a white solid.
Grubbs II was prepared and the appropriate volume was pipetted into each vial such that the reaction concentration was 0.7 M and 1.50 mol% catalyst was used. The vials were purged with nitrogen and the solutions were concentrated.

Polymerizations were performed with dry DCM obtained from a solvent system. A stock solution of Grubbs II was prepared and the appropriate volume was pipetted into each vial such that the reaction concentration was 0.7 M and 1.50 mol% catalyst was used. The vials were purged with nitrogen and the solutions were concentrated.

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Polymerizations to prepare LGLGL, LGGGL-2.5, LGGGL-5, LGGGL-10, and LGGGL-20

Each monomer was dissolved in chloroform to prepare a 100 mg/mL solution. Each solution was pipetted using a micropipetter into a dram vial to prepare five 1,500 µL solution mixtures (Base sequence : Erromer = 1,500 µL : 0 µL, 1462 µL : 37 µL, 1425 µL : 75 µL, 1350 µL : 150 µL, and 1200 µL : 300 µL). The solutions were concentrated in vacuo to produce the solid mixtures ready for polymerization.

The polymerizations were performed with dry DCM obtained from a solvent system. A stock solution of Grubbs II was prepared and the appropriate volume was pipetted into each vial such that the reaction concentration was 0.7 M and 1.50 mol% catalyst was used. The vials were purged with nitrogen and
sealed. Within 20 minutes, both solutions became very viscous. The reactions were left to react for 2 hours before quenching with 0.05 mL of ethyl vinyl ether. The vials were then concentrated in vacuo and placed in a vacuum chamber overnight. NMR spectra and SEC traces were collected on the following day. The polymers were reprecipitated in 500 mL cold methanol and allowed to stir for a half hour before filtering.

**Solution Casting of Thick Polymer Films**

The polymers were dissolved in methylene chloride to make 100 mg/mL solutions. On the bottom of flat differential scanning calorimetry pans, 28 uL of this solution was cast onto each (with a 10-200 uL micropipettor), very carefully to create a convex droplet that covered the entire surface. The best films were prepared by first coating the perimeter of the slide and then filling in the middle. The solution was allowed to dry on the slides for 3 hours before being placed in a vacuum chamber. After 2 days, those films that contained bubbles were removed from the glass slides using a razor blade and re-dissolved to prepare a 100 mg/mL solution. Films used for the hydrolysis study contained no bubbles, tears, or noticeable defects. The films were tan and transparent.

Film thicknesses were measured on representative films cut through the center using optical profilometry. A Bruker Contour Elite I optical profilometer was used. Samples were sliced to create a step indicative of film thickness and then analyzed.

**Hydrolysis Study**

Polymer films, removed from glass slides, were placed in dram vials followed by the addition of 2 mL 10x phosphate buffer solution, pH = 7.4 The vials were capped and placed in an incubator set at 37 °C. The films were placed on a rotating platform with a slow speed of 8 rpm to promote gentle mixing and to prevent localized concentration of acidic monomer around the films. The pH of the buffer solution was monitored over time and showed no distinguishable change. When timepoints were collected, the appropriate films were removed from the incubator, removed from the buffer solution, and blotted dry with a paper towel. Photographs were taken of each film at this point. The films were then rinsed with deionized water, blotted dry again and placed in new vials. Liquid N₂ was poured over the films and the films were placed in a lyophilizer for several hours. A full film was used for SEC analysis (~3 mg) and DSC analysis on weeks 2, 4, 6, 8, and 10.
3. Experimental Spectra

Figure S4. $^{13}$C NMR spectra of the L-carbonyl region.
Figure S5. $^1$H NMR spectral comparisons of the L/G/M region for Cyc-SyLMLGLGL and Cyc-SyLMLGGGL, in addition to the HRMS spectra of Cyc-SyLMLGGGL.
Figure S6. SEC plots of copolymers, Week 2 of hydrolysis.

Figure S7. SEC plots of copolymers, Week 3 of hydrolysis.
Figure S8. SEC plots of copolymers, Week 4 of hydrolysis.

Figure S9. SEC plots of copolymers, Week 5 of hydrolysis.
Figure S10. SEC plots of copolymers, Week 6 of hydrolysis.

Figure S11. SEC plots of copolymers, Week 7 of hydrolysis.
Figure S12. SEC plots of copolymers, Week 8 of hydrolysis.

Figure S13. SEC plots of copolymers, Week 9 of hydrolysis.
Figure S14. SEC plots of copolymers, Week 10 of hydrolysis.

References