## Supporting information for:

## Triggered degradation of poly(ester amide)s via cyclization of pendant functional groups of amino acid monomers

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**Figure S1**. <sup>1</sup>H NMR spectra in 0.1 M, pH 7.4 phosphate buffered  $D_2O$  of compound 11: a) Immediately following dissolution in the buffer; b) After 5 hr in the same buffer; c) After 10 hr in the same buffer. Assignments for the lactam are based on V. A. Gorpinchenko, D. V. Petrov, S. S. Lozhkin, E. G. Galkin, and V. A. Dokichev, *Chem. Heterocycl. Compd.* 2009, **45**, 1202. Though the chemical shift of the  $\alpha$ -H can vary with solvent and pH, particularly characteristic of the cyclic lactam are the peaks at ~3.35 ppm assigned to G, as well as the large chemical shift between the diastereotopic protons labeled H above. The % ester remaining was quantified based on the relative integrations of peaks A and F, while the composition of the lactam (**12a**) versus acid (**12b**) was quantified based on the relative integrations of peaks C and J.



**Figure S2**. <sup>1</sup>H NMR spectra in 0.1 M, pH 7.4 phosphate buffered  $D_2O$  of compound 1: a) Immediately following dissolution in the buffer; b) After 34.5 hr in the same buffer; c) After 70 hr in the same buffer.



**Figure S3.** <sup>1</sup>H NMR spectra in 0.1 M, pH 7.4 phosphate buffered D<sub>2</sub>O of compound **2** in the presence of DTT: a) Immediately following DTT addition; b) After 2.5 hr in the same buffer; c) After 5 hr in the same buffer. Peak assignments are based on the AIST:RIO-DB Spectral Database for Organic Compounds (Databased No: thiolactone 13282HSP-49-019; amino acid 3739HSP-49-643; pyridinethione: 4059HSP-44-765; DTT: 20440HSP-564; oxidized DTT: 23793HSP-45-331). The  $\alpha$ -H can vary with solvent and pH, but particularly characteristic are the cyclic thiolactone peaks at ~3.5 ppm assigned to L. The % ester remaining was quantified based on the relative integrations of peaks B and G.



**Figure S4.** <sup>1</sup>H NMR spectra in 0.1 M, pH 7.4 phosphate buffered  $D_2O$  of compound **2** in the absence of DTT: a) Immediately following dissolution; b) After 16 hr in the same buffer; c) After 75 hr in the same buffer. Note that the appearance of a new methyl peak at ~1.25 ppm, downfield of the peak in the original compound (not in the presence of DTT addition) and also a

new set of aromatic peaks, upfield from the original peaks is suggestive of a side reaction. This side reaction is proposed to involve the formation of a 5-membered cyclic sulfenamide via displacement of the thiopyridyl group by the  $\alpha$ -amine (structures shown in the figure). This would not have occurred in the case of DTT addition because the disulfide was rapidly reduced and cyclization occurred rapidly. This compound can also undergo background ester hydrolysis. In this case, ethanol evolution was quantified based on the integration of peak p compared to w + a + q.



**Figure S5**. ln(% ethyl ester remaining) versus time for compound **11** upon incubation in pH 7.4 phosphate buffer. Rate constant  $k = 0.16 \pm 0.02 \text{ h}^{-1}$  (± represents the 95% confidence interval).



**Figure S6**. ln(% ethyl ester remaining) versus time for compound **1** upon incubation in pH 7.4 phosphate buffer. Rate constant  $k = 0.017 \pm 0.003 \text{ h}^{-1}$  (± represents the 95% confidence interval).



**Figure S7**. ln(% ethyl ester remaining) versus time for compound **2** upon incubation in pH 7.4 phosphate buffer in the presence of DTT. Rate constant  $k = 0.038 \pm 0.04 \text{ h}^{-1}$  (± represents the 95% confidence interval).



**Figure S8**. ln(% ethyl ester remaining) versus time for compound **2** upon incubation in pH 7.4 phosphate buffer in the absence of DTT. Rate constant  $k = 0.011 \pm 0.001 \text{ h}^{-1}$  (± represents the 95% confidence interval).



**Figure S9.** <sup>1</sup>H NMR spectrum of a) polymer **3** (600 MHz, DMSO-d<sub>6</sub>); b) polymer **21** (400 MHz; DMSO-d<sub>6</sub>).



Figure S10. <sup>1</sup>H NMR spectrum of polymer 4 (600 MHz; DMSO-d<sub>6</sub>).



**Figure S11**. <sup>1</sup>H NMR spectra (400 MHz) in 7/2/1 ratio of DMSO-d<sub>6</sub>/acetone–d<sub>6</sub>/0.1 M pH 7.4 phosphate buffered D<sub>2</sub>O showing gradual degradation of the disulfide linkage in polymer **4** even in the absence of DTT. For this reason, it was not included as a control. a) Immediately following dissolution; b) After 2 days in the same buffer at 70 °C; c) After 7 days in the same buffer at 70 °C (refer to Figure S10 for peak assignments of starting polymer).



**Figure S12**. <sup>1</sup>H NMR spectra (400 MHz) in 7/2/1 ratio of DMSO-d<sub>6</sub>/acetone–d<sub>6</sub>/0.1 M pH 7.4 phosphate buffered D<sub>2</sub>O of a) Polymer **3** immediately following dissolution. b) After 12 days in the same solution at 70 °C. Evidence of degradation is present, particularly in the region of 3.75-4 ppm, but overlap of peaks makes it impossible to accurately quantify the degree of degradation accurately. Refer to Figure S9 for peak assignments.



**Figure S13**. <sup>1</sup>H NMR spectra (400 MHz) in 7/2/1 ratio of DMSO-d<sub>6</sub>/acetone–d<sub>6</sub>/0.1 M pH 7.4 phosphate buffered D<sub>2</sub>O of a) Polymer **21** immediately following dissolution. b) After 12 days in the same solution at 70 °C. Evidence of lactam formation is indicated in the figure at ~ 3.3 ppm, but overlap of peaks makes it impossible to accurately quantify the degree of degradation. Refer to Figure S9 for peak assignments.



**Figure S14**. <sup>1</sup>H NMR spectra (400 MHz) in 7/2/1 ratio of DMSO-d<sub>6</sub>/acetone–d<sub>6</sub>/0.1 M pH 7.4 phosphate buffered D<sub>2</sub>O of a) Polymer **4** immediately following dissolution. b) After adding DTT and then incubating for 12 days in the same solution at 70 °C. Overlap of peaks makes it impossible to accurately quantify the degree of degradation. Refer to Figure S10 for peak assignments.



**Figure S15**. a) Evolution of  $M_w$  over time for polymers **3**, **4**, and **21**, as measured by SEC in DMF, following incubation in a 7/2/1 ratio of DMSO/acetone–D<sub>6</sub>/0.1 M pH 7.4 phosphate buffered D<sub>2</sub>O at 70 °C.



**Figure S16**. Representative evolution of SEC traces for polymer **21** following incubation in a 7/2/1 ratio of DMSO/acetone–D<sub>6</sub>/0.1 M pH 7.4 phosphate buffered D<sub>2</sub>O at 70 °C.



**Figure S17.** Scanning electron microscopy images ( $500 \times \text{magnification}$ ) of melt pressed films of polymers following incubation in 0.1 M, pH 7.4 phosphate buffer at 70 °C: a-d) for 1 week; e-h) for 5 weeks: a,e) polymer **20**; b,f) polymer **1**; c,g) polymer **21**; d,h) polymer **2** in the presence of DTT.



**Figure S18**. <sup>1</sup>H NMR spectra (400 MHz) of: a) polymer **24** prior to photodegradation in DMSO- $d_6$ ; b) following 2 h irradiation (in 7:2:1 DMSO- $d_6$ :acetone- $d_6$ :0.1 M pH 7.4 D<sub>2</sub>O), showing disappearance of the benzylic peak (labaled S in a)) characteristic of the nitrobenzyl carbamate.



**Figure S19.** <sup>1</sup>H NMR spectrum of compound **6** (400 MHz; CDCl<sub>3</sub>; ' indicates diastereotopic peaks).



**Figure S20.** <sup>1</sup>H NMR spectrum of compound **1** (400 MHz; D<sub>2</sub>O).



Figure S21. <sup>1</sup>H NMR spectrum of compound 8 (400 MHz; CD<sub>3</sub>OD).



**Figure S22.** <sup>1</sup>H NMR spectrum of compound **9** (400 MHz; CDCl<sub>3</sub>; ' indicates diastereotopic peaks).



Figure S23. <sup>1</sup>H NMR spectrum of compound 10 (400 MHz; CDCl<sub>3</sub>; ' indicates diastereotopic peaks).





**Figure S25.** <sup>1</sup>H NMR spectrum of compound **15** (400 MHz; CDCl<sub>3</sub>; 'indicates diastereotopic peaks).



**Figure S26.** <sup>1</sup>H NMR spectrum of compound **16** (400 MHz; CDCl<sub>3</sub>; ' indicates diastereotopic peaks).



**Figure S27.** <sup>1</sup>H NMR spectrum of compound **17** (400 MHz; CDCl<sub>3</sub>; 'indicates diastereotopic peaks).



Figure S28. <sup>1</sup>H NMR spectrum of compound 18 (400 MHz; CDCl<sub>3</sub>).



Figure S29. <sup>1</sup>H NMR spectrum of compound 23 (400 MHz; CDCl<sub>3</sub>).