

# Metastable Supramolecular Polymer Nanoparticles Via Intramolecular Collapse of Single Polymer Chains

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## Supporting Information

General Considerations	S2
Synthesis	S3-S5
Synthetic Scheme for UPy Urethane	S3
Synthetic Scheme for UPy Urea	S4
Polymerizations	S6
Deprotection	S6
Example of Monitoring Deprotection Via NMR	S7
Acidification	S7
Film Experiments	S7
GPC Data	S8
GPC Monitoring of Collapse	S9-S10
Particle Analysis of AFM	S11
Example Calculation of Volume of Half an Ellipsoid/Radius in solution	S13

## General Considerations

All the solvents purchased from Acros Chimica, Aldrich or Fluka were of p.a. quality. All synthetic steps were conducted under an argon atmosphere, in flame dried glassware. Reaction solvents dichloromethane (DCM) and chloroform (CHCl<sub>3</sub>) were distilled and dried over molecular sieves. Dimethylformamide (DMF) was dried over molecular sieves. Solvents for column chromatography were used as provided. 2-Nitro-benzyl chloride, dibutyltin dilaurate, 2-amino-dodecan-1-ol, norborn-5-ene-2-carboxylic acid, dicyclohexylcarbodiimide, norborn-5-en-2-yl-methanol, 4-dimethylaminopyridine were purchased from Sigma-Aldrich and used without further purification. 1-(6-Isocyanato-hexyl)-3-(6-methyl-4-oxo-1,4-dihydro-pyrimidin-2-yl)-urea<sup>1</sup> and decyl bicyclo[2.2.1]hept-5-ene-2-carboxylate<sup>2</sup> were prepared according to previously reported methods. Thin layer chromatography was performed using 60-F254 (250 nm) silica gel precoated plates. Flash chromatography was performed using 200–425 mesh silica gel (Type 60A Grade 633) available from Fisher Scientific. Electrospray mass-spectra were recorded with a Perkin-Elmer SCIEX API 165 single quadrupole LC/MS instrument.

Deuterated solvents were obtained from Cambridge Isotope Laboratories. <sup>1</sup>H NMR were recorded at room temperature on a Varian Mercury 400. Chemical shifts are given in ppm ( $\delta$ ) relative to tetramethylsilane. Abbreviations used are s = singlet, d = doublet, dd = double doublet, t = triplet and m = multiplet.

GPC was performed on 300 x 7.5 mm Polymer Laboratories Resipore (for UPy Urethane) and Polypore (UPy Urea) columns with a Shimadzu SPD-M20A diode array detector. HPLC grade chloroform was used, with a constant flow rate of 1 mL/min. Molecular weights were obtained relative to polystyrene standards. Polymer solutions were prepared in HPLC grade chloroform. Separations of polymers from deprotection byproduct o-nitrosobenzaldehyde were performed on S-X8 Bio-Beads from Bio-Rad Laboratories.

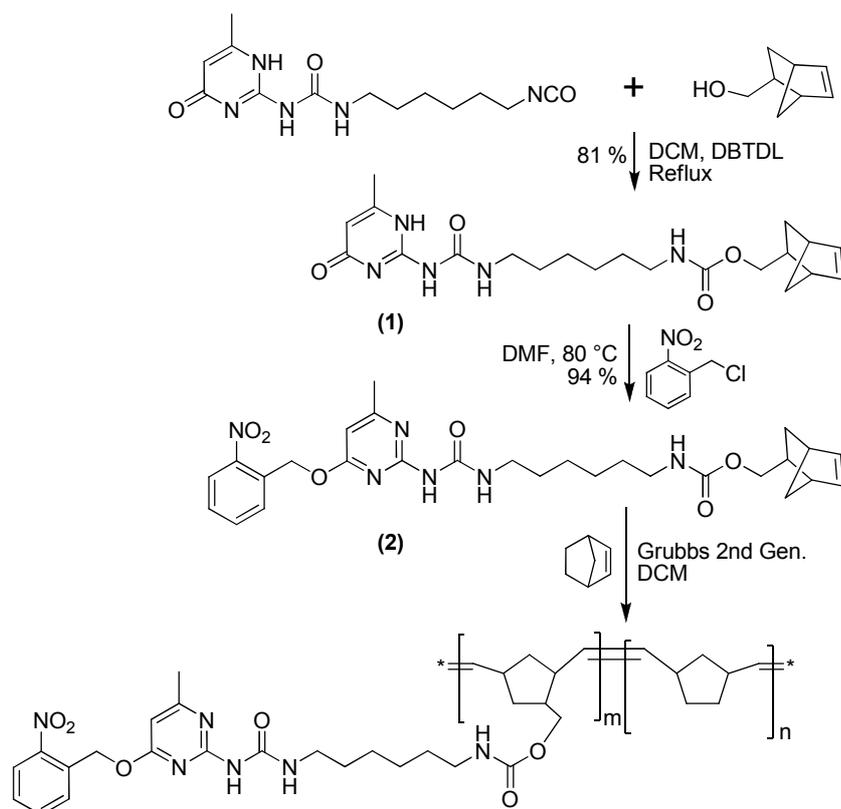
Atomic force micrographs were recorded under ambient conditions with silicon cantilever tips (PPP-NCH, 300-330 kHz, 42 N/m from Nanosensors) using an Asylum Research MFP-3D-Bio in non-contact mode. For the atomic force microscopy, 2  $\mu$ l of the solution at ambient temperature was dropcast on freshly cleaved mica and allowed to dry in air.

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<sup>1</sup> Yamauchi, K. ; Kanomata, A. ; Inoue, T. ; Long, T. *Macromolecules* **2004**, 37(10), 3519-3522.

<sup>2</sup> Pollino, Joel M.; Weck, Marcus; *Synthesis* **2002**, 9, 127 -1285.

## Synthesis



**Figure S1:** Synthetic Scheme for UPy Urethane functionalized polymer

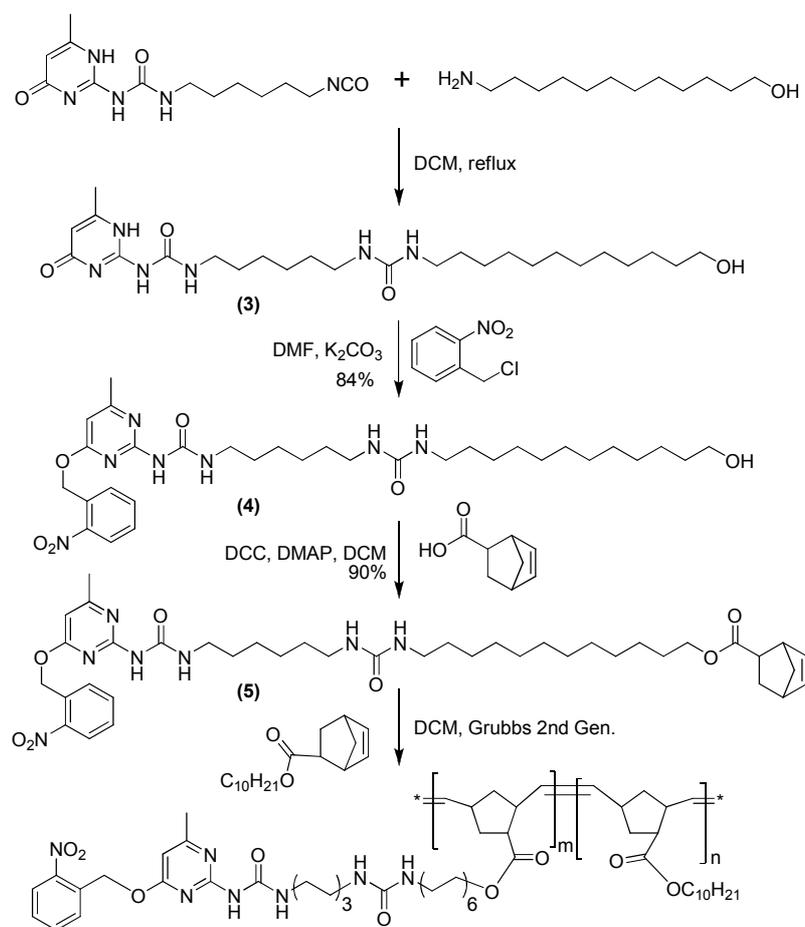
### (2S)-bicyclo[2.2.1]hept-5-en-2-ylmethyl 6-(3-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)ureido)hexylcarbamate (1)

To a stirring solution of 1-(6-isocyanato-hexyl)-3-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)-urea (1.838 g, 6.26 mmol) and norborn-5-en-2-yl-methanol (0.778 g, 6.27 mmol) in dry dichloromethane (70 mL) was added dibutyltin dilaurate (one drop). The reaction was heated to reflux for 8 hours then cooled to room temperature. Solvent was evaporated under reduced pressure and the resultant white solid recrystallized from hot DMF to yield (2S)-bicyclo[2.2.1]hept-5-en-2-ylmethyl 6-(3-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)ureido)hexylcarbamate (1) (2.121 g, 81 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>, TFA) Relative Protons. δ 0.58-0.52 (m, 1.00 H), 1.18-1.12 (m, 0.58 H), 1.40-1.23 (m, 12.1 H), 1.62-1.44 (m, 9.41 H), 1.77-1.68 (m, 0.72 H), 1.88-1.80 (m, 1.20 H), 2.01-1.95 (m, 0.61 H), 2.48-2.34 (m, 7.48 H), 2.70-2.66 (m, 0.59 H), 2.89-2.80 (m, 2.89 H), 3.22-3.13 (m, 3.88 H), 3.34-3.24 (m, 3.94 H), 3.76-3.66 (m, 1.05 H), 3.96-3.87 (m, 1.69 H), 4.07-3.97 (m, 0.49 H), 4.24-4.15 (m, 0.47 H), 5.95-5.88 (m, 0.96 H), 6.12-6.05 (m, 1.09 H), 6.20-6.15 (m, 1.03 H), 6.24-6.20 (m, 1.63 H), 6.75-6.67 (m, 0.40 H). ESI-MS 419 (M+1)

### (2S)-bicyclo[2.2.1]hept-5-en-2-ylmethyl 6-(3-(4-methyl-6-(2-nitrobenzyloxy)pyrimidin-2-yl)ureido)hexylcarbamate (2)

To a stirring solution of (1) (1.217 g, 2.943 mmol) and 2-nitro-benzyl chloride (0.555 g, 3.237 mmol) in DMF (50 mL) was added K<sub>2</sub>CO<sub>3</sub> (0.653 g, 4.709 mmol). The

reaction was stirred at 80 °C overnight, cooled and the solvent removed under reduced pressure. The resultant brown solid was taken up in CHCl<sub>3</sub>, washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Silica gel chromatography (gradient from 20 to 40% EtOAc in heptanes) yielded a light brown liquid, (2), (1.529 g, 94%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) Relative Protons. δ 0.57-0.52 (m, 1.00 H), 1.18-1.12 (m, 0.52 H), 1.41-1.21 (m, 13.0 H), 1.63-1.43 (m, 9.03 H), 1.76-1.67 (m, 0.63 H), 1.88-1.80 (m, 1.40 H), 2.04-1.93 (s, 2.98 H), 2.48-2.34 (m, 6.68 H), 2.70-2.64 (m, 0.59 H), 3.22-3.13 (m, 3.88 H), 3.31-3.24 (m, 3.72 H), 3.76-3.63 (m, 1.05 H), 3.96-3.81 (m, 1.69 H), 4.07-3.97 (m, 0.49 H), 4.23-4.11 (m, 0.58 H), 5.73 (s, 2.39 H), 6.14-5.92 (m, 2 H), 6.28 (s, 1.02 H), 7.13 (s, 0.96 H), 7.51 – 7.48 (m, 1.05 H), 7.65-7.63 (m, 2.53 H), 8.13 – 8.11 (m, 1.03), 9.12 (broad s, 1.45 H). ESI-MS 552 (M<sup>+</sup>)



**Figure S2:** Synthetic Scheme for UPy Urea functionalized polymer

### Compound 3

To a stirring solution of 1-(6-isocyanato-hexyl)-3-(6-methyl-4-oxo-1,4-dihydro-pyrimidin-2-yl)-urea (2.058 g, 7.02 mmol) in dichloromethane (50 mL) was added 2-amino-dodecan-1-ol (1.413 g, 7.02 mmol). The reaction was stirred under reflux overnight, and the solvent removed under reduced pressure. The resultant white solid, Compound 3, was used without purification.

### Compound 4

Compound 3 (1.465 g, 2.96 mmol) was reacted with 2-nitro-benzyl chloride (0.508 g, 2.96 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.450 g, 3.26 mmol) in DMF (50 mL) as in the synthesis of (2), to yield a yellow solid, Compound 4 (1.566 g, 84%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, TFA) Relative Protons. δ 1.81-1.14 (m, 31 H), 2.66-2.54 (s, 3 H), 3.39-2.94 (m, 8 H), 3.85-3.71 (m, 2 H), 5.89-5.79 (s, 2 H), 6.55-6.49 (s, 1 H), 7.35-7.25 (broad s, 1 H), 7.65-7.55 (m, 1 H), 7.74-7.65 (m, 2 H), 8.19-8.10 (d, J = 8.1 Hz) 1 H, 9.88-9.29 (broad s, 4 H), 10.44-10.42 (s, 1 H), 10.80-10.66 (broad s, 1 H). ESI-MS 630 (M+1)

### 12-(3-(6-(3-(4-methyl-6-(2-nitrobenzyloxy)pyrimidin-2-yl)ureido)hexyl)ureido)dodecyl bicyclo[2.2.1]hept-5-ene-2-carboxylate (5)

To a stirring solution of Compound 4 (0.219 g, 0.348 mmol), norborn-5-ene-2-carboxylic acid (0.048 g, 0.358 mmol) and dicyclohexylcarbodiimide (0.072 g, 0.348 mmol) in dry dichloromethane (30 mL) was added 4-dimethylaminopyridine (0.010 g, 0.082 mmol). The reaction was heated to reflux for 3 hours and the solvent removed under reduced pressure. The solid was recrystallized from dichloromethane and subsequently passed through silica gel (30 % EtOAc in heptane) to yield 12-(3-(6-(3-(4-methyl-6-(2-nitrobenzyloxy)pyrimidin-2-yl)ureido)hexyl)ureido)dodecyl bicyclo[2.2.1]hept-5-ene-2-carboxylate (5) (0.235 g, 90%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 10.13 (bs), 9.16 (bs), 8.16 (m, 2H), 7.65 (d, 1H), 7.55 (m, 1H), 7.08 (s, 1H), 6.70 (s, 1H), 6.65 (s, 1H), 6.29 (bs, 1H), 6.19 (s, 1H), 6.00 (m, 1H), 5.92 (m, 1H), 5.73 (s, 3H), 5.14 (s, 2H), 4.53 (m, 1H), 4.43 (m, 1H), 4.09 (m, 1H), 4.01 (m, 1H), 3.66 (m, 1H), 3.50 (m, 2H), 3.34 (m, 4H), 3.16 (m 9H), 2.89 (s, 2H), 2.37 (s, 3H), 1.95-1.23 (m, 32H). δ ESI-MS 750 (M+1)

## *Polymerizations*

### **UPy-Urea polymer (protected)**

Compound 5 (0.121 g, 0.161 mmol) and decyl bicyclo[2.2.1]hept-5-ene-2-carboxylate (0.224 g, 0.803 mmol) was dissolved in dry, degassed CH<sub>2</sub>Cl<sub>2</sub> (100 mL). To the stirring solution of the monomers was added quickly Grubbs 2<sup>nd</sup> Generation catalyst (0.14 mg, 0.0002 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). The reaction was allowed to stir vigorously for 2 hours under an atmosphere of argon. Upon completion, the reaction was quenched with excess ethyl vinyl ether and allowed to stir for a further 30 minutes. The polymer was precipitated by dropping slowly into hexanes and dried under reduced pressure.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.14, 8.22, 8.13, 7.64, 7.50, 7.03, 6.52, 6.28, 6.20, 6.00, 5.91, 5.73, 5.34, 5.20, 4.41, 4.32, 3.68, 3.48, 3.35, 3.14, 3.02, 2.78, 2.43, 2.37, 1.87, 1.78, 1.57, 1.34, 1.25, 1.04, 1.01.

### **UPy-Urethane polymer (protected)**

Reaction as above. Compound 2 (0.355 g, 0.850 mmol) and bicyclo[2.2.1]hept-2-ene (0.400 g, 4.25 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (125 mL). The polymer was precipitated by dropping slowly into hexanes and dried under reduced pressure.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.12, 8.13, 7.63, 7.48, 7.09, 6.27, 5.74, 5.35, 5.20, 4.61, 4.02, 3.84, 3.33, 3.15, 2.78, 2.43, 1.86, 1.76, 1.54, 1.35, 1.04.

## *Deprotection*

A 2 x 10<sup>-3</sup> mg/mL solution of polymer was stirred in dry CHCl<sub>3</sub> with 350 nm UV light (broad band) in a Rayonet reactor for 2 hours. If removal of the deprotection side product was needed, the polymer was passed through S-X8 Bio-Beads from Bio-Rad Laboratories using CHCl<sub>3</sub> as an eluent.

### **UPy-Urethane polymer (deprotected)**

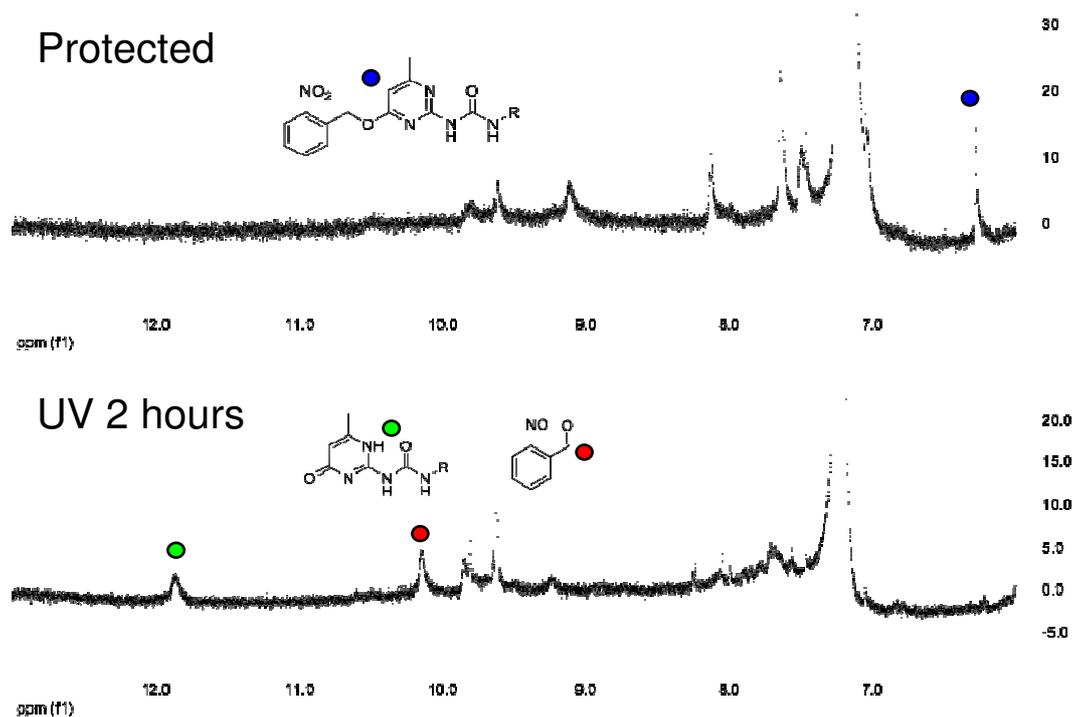
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.91, 10.19, 7.71, 5.89, 5.35, 5.22, 4.07, 3.89, 3.28, 3.15, 2.80, 2.44, 2.23, 1.88, 1.87, 1.80, 1.36, 1.05, 1.03, 1.00.

### **UPy-Urethane polymer (deprotected, acid)**

<sup>1</sup>H NMR (CDCl<sub>3</sub>, TFA) δ 9.75, 9.59, 8.85, 8.26, 8.18, 7.90, 7.78, 7.65, 7.06, 6.57, 6.30, 5.83, 5.38, 5.29, 5.14, 4.78, 4.48, 4.16, 4.01, 3.29, 3.22, 1.87, 1.58, 1.37, 1.06, 0.90

### **UPy-Urea polymer (deprotected)**

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.86, 10.06, 8.21, 7.79, 7.60, 6.69, 6.17, 5.99, 5.34, 5.19, 3.98, 3.63, 3.46, 3.21, 3.13, 2.78, 2.43, 2.23, 1.78-1.01.



**Figure S3:** Example of Monitoring Deprotection Via NMR

### *Acidification*

To 10 mL of  $2 \times 10^{-3}$  g/mL solution of polymer was sequentially added formic acid (in 1  $\mu$ L aliquots). After 24 hours of stirring, GPC was used to monitor the expansion of the polymers.

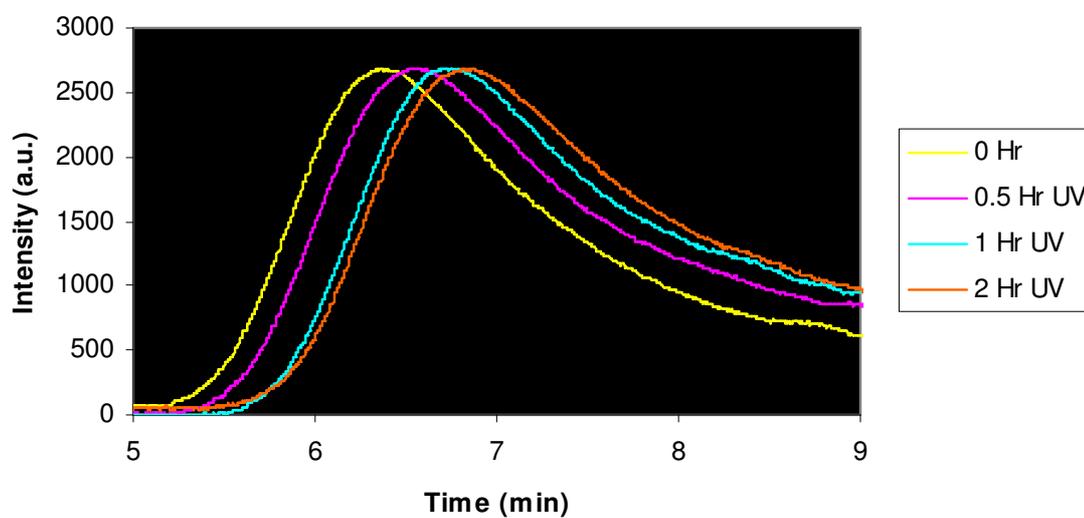
### *Film Experiments*

A 0.1 mg/mL solution of nanoparticles in  $\text{CHCl}_3$  was coated on a glass slide and the solvent evaporated. Solubility was tested by scraping polymer from the surface and re-dissolving in  $\text{CHCl}_3$ . Initially, the film easily redissolved within minutes. Upon heating the slide to 80  $^\circ\text{C}$  for 20 minutes and subsequent cooling the film remained essentially insoluble (partial swelling) after repeated attempts, consistent with supramolecular network formation.

**GPC Data Table**

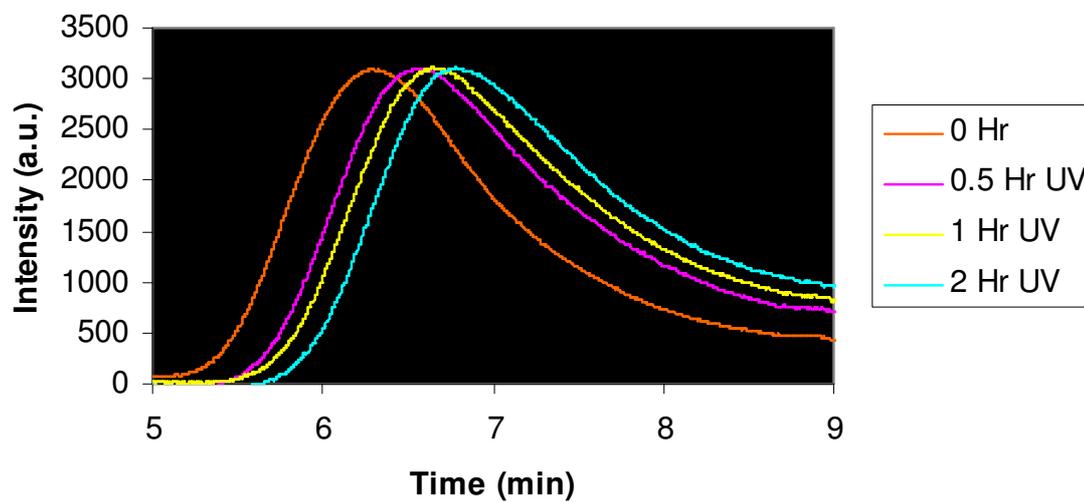
	<b>0 Hr</b>	<b>1 Hr UV</b>	<b>2 Hr UV</b>	<b>2 Hr UV + H+</b>	<b>% Change</b>
					<b>After 2 Hr</b>
<b>20% UPy-Urea</b>	207000	175000	153000	193000	26
$M_w/M_n$	1.55	1.53	1.54	1.64	
<b>10% UPy-Urea</b>	195000	160000	155000	199000	21
$M_w/M_n$	1.49	1.47	1.47	1.52	
	<b>0 Hr</b>	<b>1 Hr UV</b>	<b>2 Hr UV</b>	<b>2 Hr UV + H+</b>	<b>% Change</b>
					<b>After 2 Hr</b>
<b>20% UPy-Urethane</b>	174000	126000	115000	105000	34
$M_w/M_n$	1.78	1.67	1.67	1.65	
<b>10% UPy-Urethane</b>	162000	129000	129000	100000	20
$M_w/M_n$	1.81	1.8	1.75	1.76	

### 10 % UPy Urethane



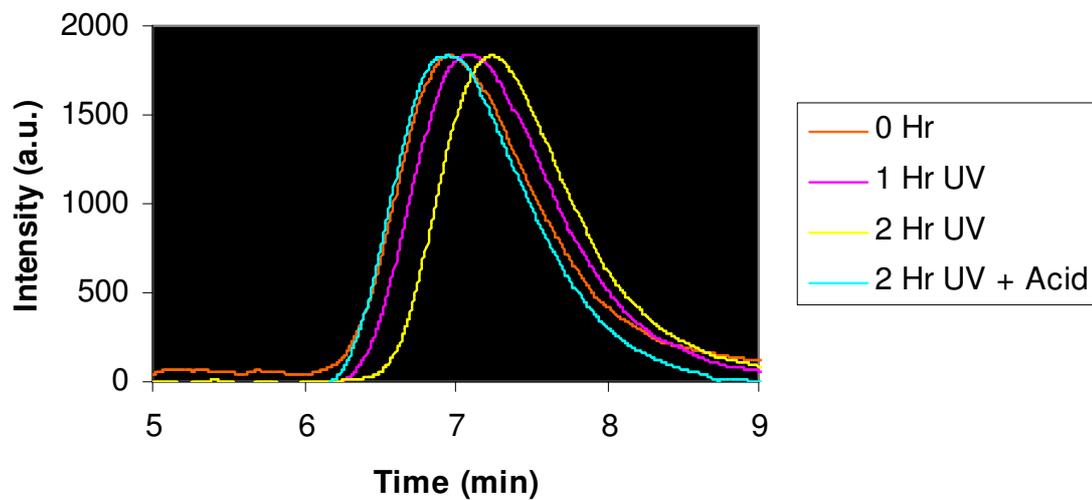
**Figure S4:** Collapse of the random coil polymer, 10 % UPy Urethane, with 350 nm light.

### 20% UPy Urethane



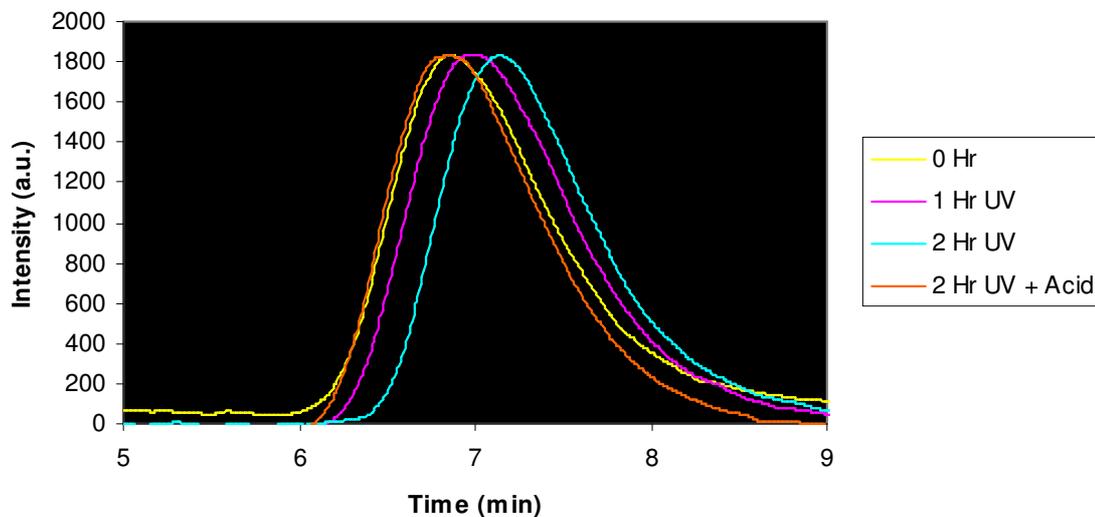
**Figure S5:** Collapse of the random coil polymer, 20% UPy Urethane, with 350 nm light.

### 10 % UPy Urea

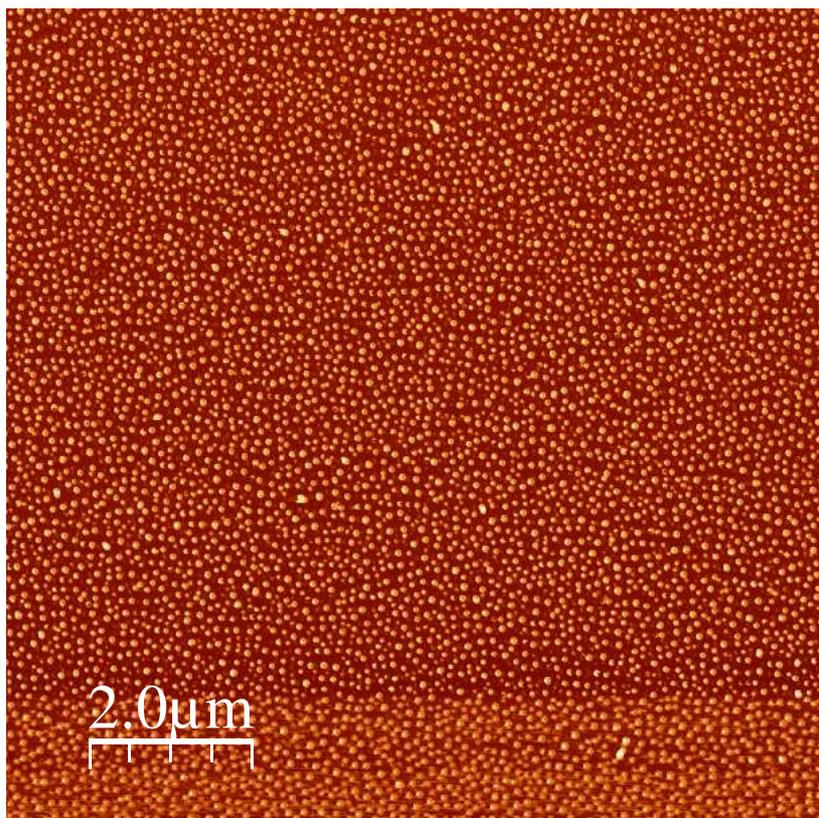


**Figure S6:** Collapse of the random coil polymer, 10% UPy Urea, with 350 nm light.

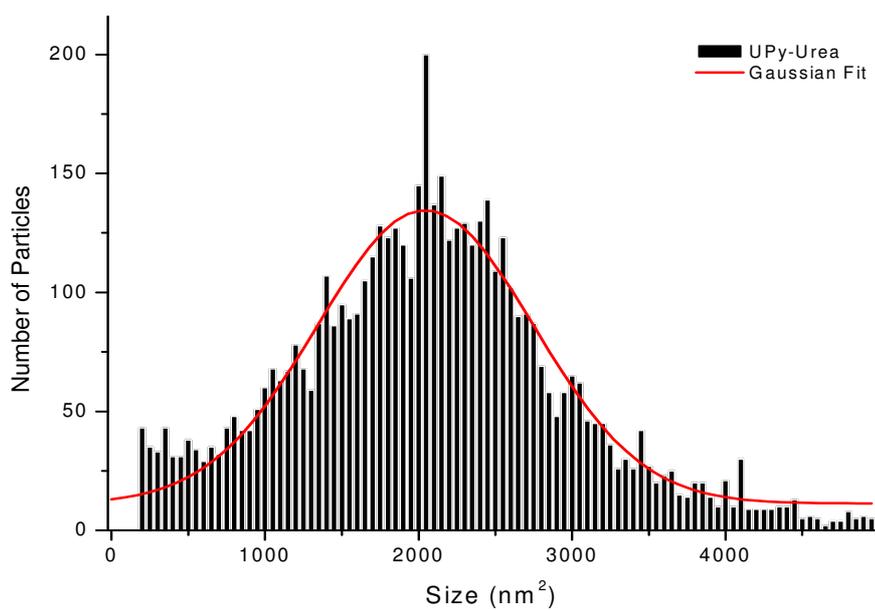
### 20 % UPy Urea



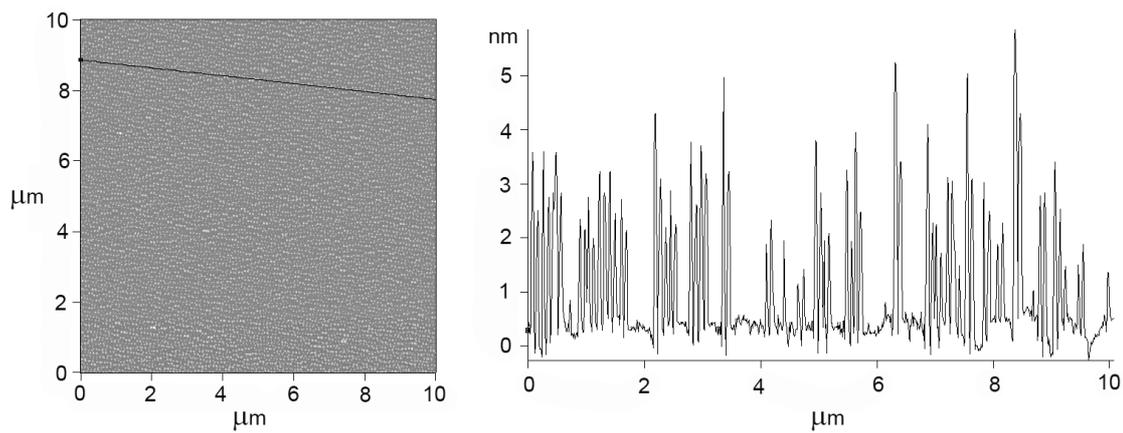
**Figure S7:** Collapse of the random coil polymer, 20% UPy Urea, with 350 nm light.



**Figure S8:** AFM of 20% UPy Urea Polymer, 2  $\mu\text{L}$  of a  $2\text{e-}6$  g/mL solution on mica. Particles present: 9853.



**Figure S9:** Histogram of AFM Image in Figure 8. PDI = 1.44,  $M_n = 2254 \text{ nm}^2$ ,  $M_w = 3245 \text{ nm}^2$ .  $M_n$  and  $M_w$  were calculated using standard equations. In this case, particle size was substituted for mass.



**Figure S10:** Height profile of AFM image from figure S8.

***Example Calculation of Volume of half an Ellipsoid/ Radius in solution***

$$V = 1/2 * 4/3 * \pi * r^2 * h$$

Where r = radius from the AFM, h = height from AFM (in nm)

$$r = 30 \text{ nm}, h = 0.4 \text{ nm}$$

$$V = 0.5 * 1.333 * \pi * (30*30) * 0.4$$

$$V = 1508 \text{ nm}^3$$

$$\text{Volume of a sphere} = 4/3 * \pi * r^3$$

$$1508 = 4/3 * \pi * r^3$$

$$r = 7.1 \text{ nm (Radius of un-flattened sphere)}$$