Electronic supplementary information (ESI):

Synthesis of Stimuli-Responsive Nanosized Ring-Like Colloids and Cyclic Polymers via A Dual-Template Approach

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1. Experimental Details

Materials. Ferrocene carboxylic acid (Fc-COOH) and β-cyclodextrin (β-CD, >99%) were purchased from Aladdin. Triethylamine (TEA) was purchased from TCI. 2-bromoisobutyryl bromide, copper (I) bromide (CuBr, 99%), stannous (II) octanoate ($Sn(Oct)_2$), *N*, *N*, *N*', *N*'', *N*''-pentamethyldiethylenetriamide (PMDETA, 99%) and 2-(hydroxymethyl) propane 1, 3-diol were purchased from Sigma-Aldrich and used without further purification. Oligo (ethylene glycol) monomethyl ether methacrylate (OEGMA300, M_n= 300 g/mol with 4~5 pendent EO units) purchased from Aldrich was purified by passing through a column filled with basic alumina to remove the inhibitor. Oxalyl chloride，*N*, *N*'-dimethylformamide (DMF) and tetrahydrofuran (THF) were purchased from Tianjin Chemical Reagent Factory (China) and used without further purification. Dialysis tube (MWCO= 3.5 kDa and 10 kDa) were purchased from Mym Biological Technology Company.

Instrumentation.^{1}H NMR spectra of all the synthesized polymers were recorded on a JEOL-ECS 400M nuclear magnetic resonance instrument by using $CDCl_3$ or d_6-DMSO as the solvents. And the size exclusion chromatography and multi-angle laser light scattering (SEC-MALLS) analyses were carried out to determine the molecular weight (MW) and molecular weight distribution (*Đ*) of all the synthesized polymers. SEC using HPLC-grade DMF with 0.1 wt% LiBr at 60 °C as the eluent at a flow rate of 1 mL/min, Tosoh TSK-GEL R-3000 and R-4000 columns (Tosoh Bioscience) were connected in series to an Agilent 1260 series (Agilent Technologies), an interferometric refractometer (Optilab-rEX, Wyatt Technology) and a MALLS device (DAWN EOS, Wyatt Technology). And the MALLS detector was operated at a laser wavelength of 690.0 nm. The average hydrodynamic size of the micelles was measured by using dynamic light scattering (DLS) on a Zetasizer (Nano ZS, Malvern, Worcestershire, UK) at a fixed detection angle of 173^o at 25 or 37 °C. AFM observation was performed on the Atomic Force Microscope of Agilent 5500 in tapping mode in air at room temperature. The samples were prepared by spin casting a

diluted polymer solution (0.01 mg/ mL) onto a silicon wafer. The TEM images were acquired on a JNM-2010 instrument operating at an acceleration voltage of 200 keV.

Synthesis of β-CD-based macroinitiator (4Br-β-CD)

Briefly, to 40 mL of anhydrous DMF, β-CD (5.11 g, 4.5 mmol) was added with stirring, then the solution was cooled to 0 °C. Under N_2 atmosphere, a solution of 2-bromo-isobutyric bromide (4.14 g, 18.0 mmol) was added dropwise to the mixture of β-CD for 1 h at 0 °C. After the addition, the mixture was maintained in an ice bath for 2 h and warmed to room temperature for further 24 h. Then the final mixture was precipitated in 900 mL of anhydrous diethyl ether. After centrifugation, the white powder was collected and then washed with 30 mL of acetone twice to purify the macroinitiator. Subsequently, the crude product was suspended in 100 mL of DI water, and the mixture was stirred overnight at room temperature.[1] After centrifugation, the resulting white powder was collected and washed with 30 mL of acetone twice, then dried under vacuum. (4.58 g, yield: 64.37%)

Synthesis of β-CD-initiated poly[(oligo ethylene glycol) methyl ether methacrylate] (4Br-β-CD-POEGMA$_{37}$)

Typically, 4-bromo-β-cyclodextrin (51.93 mg, 0.03 mmol) was dissolved in 350 μL of anhydrous DMF and 700 μL of anisole, followed by addition of PMDETA (25 μL, 0.12 mmol) and OEGMA300 (300 μL, 1.05 mmol). After three freeze–pump–thaw cycles, CuBr (17.22 mg, 0.12 mmol) was introduced under the protection of nitrogen flow. After another three freeze–pump–thaw cycles, the reaction started and the polymerization proceeded for 0.5 h in an oil bath thermostated at 60 °C. After precipitation in an excess of ice-cold diethyl ether, the crude product was collected by centrifugation. Then the product was further purified by extensive dialysis against distill water for 36 h to remove any unreacted monomer and the copper catalyst. The purified 4Br-β-CD-POEGMA$_{37}$ was harvested by freeze-drying. (Yield: 85.34 %)

Synthesis of 4Br-β-CD-POEGMA$_{37}$-LA$_8$ conjugates

In a typical procedure, 4Br-β-CD-POEGMA$_{37}$ (130 mg, 0.01 mmol), DCC (25.09 mg, 0.12 mmol) and DMAP (12.38 mg, 0.10 mmol) were dissolved in anhydrous DCM (3 mL), and the solution was cooled to 0 °C. Then a solution of lipoic acid (20.91 mg, 0.1mmol) in DCM (2.0 mL) was added dropwise to the reaction mixture in an ice bath. After the addition, the mixture was maintained at 0 °C for 0.5 h and then warmed to room temperature for approximately 48 h further. After vacuum filtration, the mixture was precipitated three times in an excess of ice-cold diethyl ether to get the purified 4Br-β-CD-POEGMA$_{37}$-LA$_8$ (Yield, 82.7 %). The DP of LA was determined to be 8 by comparing the integral ratio of peak *o* assigned to LA to that of peak *d* attributed to OEGMA in the typical ^{1}H NMR spectrum of 4Br-β-CD-POEGMA$_{37}$-LA$_8$.

Synthesis of 4Br-β-CD-POEGMA$_{37}$-LA$_{13}$ conjugates

In a typical procedure, lipoic acid (152.3 mg, 0.74 mmol) was dissolved in anhydrous DCM (5 mL), and the solution was cooled to 0 °C. Then a solution of DCC (95.24 mg, 0.46 mmol) in DCM (3.0 mL) was added dropwise to the reaction mixture in an ice bath. After the addition, the mixture was maintained at 0 °C for 0.5 h and warmed to room temperature for approximately 12 h further. After vacuum filtration, the precipitates generated during the reaction were removed, then 4Br-β-CD-POEGMA$_{37}$ (130 mg, 0.01 mmol) was added to the filtrate. And the reaction proceeded for approximately 48 h at room temperature, which was purified three times by redissolving/reprecipitating with DCM/ice-cold diethyl ether and further dried under vacuum. (Yield: 51.3%)

Synthesis of 3-arm hydroxyl-terminated poly(ε-caprolactone) (3-PCL$_7$-OH)

3-PCL$_7$-OH was synthesized by Sn(Oct)$_2$-catalyzed ROP of ε-CL using 2-(hydroxymethyl) propane 1, 3-diol as the initiator. Briefly, 2-(hydroxymethyl) propane 1, 3-diol (53.06 mg, 0.5 mmol) and ε-CL (1.16 g, 10.5 mmol) were added into a thoroughly dried tube. After three freeze–pump–thaw cycles, the tube was put into an oil bath preheated at 125°C, then stirred to obtain a homogeneous solution for

5 min. Thereafter, $Sn(Oct)_2$ (8.52 mg, 0.021 mmol) in 50 μL of anhydrous toluene was introduced under the protection of nitrogen flow. After another three freeze–pump–thaw cycles, the reaction mixture was sealed and placed in an oil bath thermostated at 125 °C to start the polymerization. After 40 min, the reaction was cooled to room temperature, diluted with 2 mL of THF, and precipitated in ice-cold methanol to yield the crude white powder, which was purified three times by precipitation in excess ice-cold methanol and further dried under vacuum. A white powder was isolated. (1.05 g, yield: 86.79 %).

Synthesis of 3-arm hydroxyl-terminated poly(ε-caprolactone) (3-PCL_{14}-OH)

3-PCL_{14}-OH was synthesized by $Sn(Oct)_2$-catalyzed ROP of ε-CL using 2-(hydroxymethyl) propane 1, 3-diol as the initiator. Briefly, 2-(hydroxymethyl) propane 1, 3-diol (109.40 mg, 1.0 mmol) and ε-CL (3.46 g, 30 mmol) were added into a thoroughly dried tube. After three freeze–pump–thaw cycles, the tube was put into an oil bath at 125°C, then stirred to obtain a homogeneous solution for 5 min. Thereafter, $Sn(Oct)_2$ (24.60 mg, 0.06 mmol) in 50 μL of anhydrous toluene was introduced under the protection of nitrogen flow. After another three freeze–pump–thaw cycles, the reaction mixture was sealed and placed in an oil bath thermostated at 125 °C to start the polymerization. After 3 h, the reaction was cooled to room temperature, diluted with 4 mL of THF, and precipitated in ice-cold methanol to yield the crude white powder, which was purified three times by precipitation in excess ice-cold methanol and further dried under vacuum. A white powder was isolated (2.89 g, yield: 90.52 %).

Synthesis of ferrocene-decorated 3-arm PCL (3-PCL_7-Fc)

Taking the synthesis of 3-PCL_7-Fc as an example, ferrocenecarboxylic acid (138.02 mg, 0.6 mmol) was suspended in 10 mL of DCM in a dry flask. DMF (15 μL) was added to the flask, followed by dropwise addition of oxalyl chloride (137.10 μL, 1.62 mmol), then the mixture was stirred for 6 h at room temperature. After evaporating the excess amount of oxalyl chloride and solvent thoroughly, hydroxyl-terminated 3-

arm PCL (0.25 g, 0.1 mmol) was dissolved in 15 mL of DCM and added to the flask. After stirring overnight (20 h) at room temperature, the solution was concentrated via rotary evaporation and precipitated in an excess of ice-cold methanol to yield the crude yellow powder, which was purified three times by precipitation in excess ice-cold methanol and further dried under vacuum. A yellow powder was harvested (0.21 g, yield: 63.89 %).

3-PCL_{14}-Fc was prepared following the same procedures mentioned above.

Preparation of supramolecular micelles based on 12-arm star-shaped amphiphilic copolymers (3-PCL-Fc/4-CD-POEGMA-LA)

In a typical procedure, 22.37 mg of 4Br-β-CD-$(POEGMA)_{37}$-LA_8 and 1/3-fold equivalent molar amount of 3-PCL_7-Fc (1.63 mg) were mixed in 1 mL of DMF, and then the mixture was sonicated for 1 h to ensure the formation of 3-PCL_7-Fc/4-CD-$POEGMA_{37}$-LA_8 supramolecular inclusion complex. Subsequently, the solution (1 mL) was added to the 20 mL of deionized water *via* a syringe pump at a flow rate of 0.1 mL/h in 1 h, and stirred for another 3 h to ensure the formation of supramolecular micelles at room temperature. Then the product was further subjected to extensive dialysis against distill water for 24 h to remove DMF. The supramolecular micelles were harvested by freeze-drying.

3-PCL_{14}-Fc/4-CD-$POEGMA_{37}$-LA_8 and 3-PCL_7-Fc/4-CD-$POEGMA_{37}$-LA_{13} were prepared following the same procedures mentioned above.

Preparation of cross-linked micelles

In a typical procedure, the crosslinking of 3-PCL-Fc/4-CD-POEGMA-LA micelles was carried out in the presence of 10 mol% DTT relative to the lipoyl units under nitrogen atmosphere in the dark.[2] Taking the preparation of 3-PCL_7-Fc/4-CD-$POEGMA_{37}$-LA_8 as an example, 10 mol% DTT (0.19 mg) relative to the amount of lipoyl units was added to the 80 mL of the above-prepared micelle solution (0.3 mg/mL) under nitrogen at room temperature. After stirring for 27 h in the dark, the nanoparticle solution was further dialyzed against distilled water for 24 h. The cross-

linked micelles were harvested by freeze-drying. (23.0 mg, yield: 95.9 %)

Preparation of cyclic polymer via a sacrificing core-template approach

Taking the cross-linked 3-PCL_7-Fc/4-CD-$POEGMA_{37}$-LA_8 as an example, 20 mg of the crosslinked 3-PCL_7-Fc/4-CD-$POEGMA_{37}$-LA_8 was dissolved in 2 mL of DMF, and the mixture was thereafter transferred to a dialysis tube (MWCO= 10kDa), then dialyzed against DMF thermostated at 50 $^oC^3$ to remove the sacrificing core template of 3-PCL_7-Fc. Note that DMF was refreshed every 24 h. After 48 h, the solution in the dialysis tube was further dialyzed against distilled water for 24 h to remove DMF. Finally, the cyclic polymers were harvested by freeze-drying. (12.9 mg, yield: 69.6 %)

***In vitro* drug loading and drug release study**

For the preparation of DOX@Cyclic P1, 1 mg of DOX·HCl was firstly stirred with 300 μL of triethylamine in 1 mL of DMF overnight in the dark to get the free DOX base. Then 1 mL of DMF solution containing 10 mg of Cyclic P1 was added to the free DOX base. Thereafter, the mixture solution (2 mL) was added to 10 mL of DI water *via* a syringe pump at a flow rate of 0.2 mL/h and stirred for another 3 h in the dark. The resulting solution was further subjected to dialysis for 24 h in the dark. And the DOX@Cyclic P1 was collected by lyophilization.

The *in vitro* drug release profiles of the DOX@Cyclic P1were investigated in the phosphate buffer (pH 7.4, 150 mM) and PBS (pH 7.4) with 10 mM DTT. Briefly, 1 mL of suspension containing DOX@Cyclic P1 (1 mg/mL) was transferred to a dialysis tube (MWCO= 3.5 kDa), and immersed in 25 mL of fresh PBS solution with or without DTT at 37^{o}C. In the dark, a 3 mL of release medium was taken out and replaced by a 3 mL of fresh medium at predetermined time intervals. And the amount of DOX released from the DOX@Cyclic P1 was determined by quantifying the absorbance of DOX at 485 nm.

2. Theoretical calculation regarding the range of the contour

length of the etching template comprising three-arm star-shaped PCL

Two respective formulas for calculating the mean square end-to-end distance (h^2) of a freely jointed chain under two different kinds of extreme conditions[4] were adopted to estimate the range of end-to-end distance (h) for a single PCL arm of a three-arm star shaped PCL (3-PCL).

In the case of an extremely flexible chain,

$$h^2 = nl^2 \qquad (1)$$

And in the case of an extremely rigid chain,

$$h^2 = n^2l^2 \qquad (2)$$

where n is the number of bond in the main chain, and l is the bond length. In the case of 3-PCL_7, n is 49 for a single PCL arm, and l is 0.154 nm for C-C bond length. Note that the same value was used for the C-O bond with actually slightly smaller bond length to simplify the calculation. On the basis of formulas (1) and (2), the h is 7.5 nm for an extremely rigid chain, and 1.1 nm for an extremely flexible chain. Given the round plane constructed by the three polymer termini of a three-arm star-shaped PCL, the diameter of the round structure is estimated to be twice the h value. Thus the actual contour length of 3-PCL_7 and 3-PCL_{14} should be between the two extreme values, *i.e.*, 2.2 nm < h <15 nm, 3.0 nm < h <30.2 nm, respectively. Note that the above calculation was based on the pure 3-PCL moiety without the consideration of contribution from the large hydrophilic stabilizing corona consisting of three hydrophilic 4-arm star-shaped POEGMA moieties, LA, as well as β-CD. Therefore it is reasonable to obtain a ring with 30 nm in diameter from three cross-linked 4Br-β-CD-POEGMA-LA segments.

References

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2. A. Sadownik, J. Stefely and S. L. Regen, *J. Am. Chem. Soc.*, 1986, **108**, 7789-7791.

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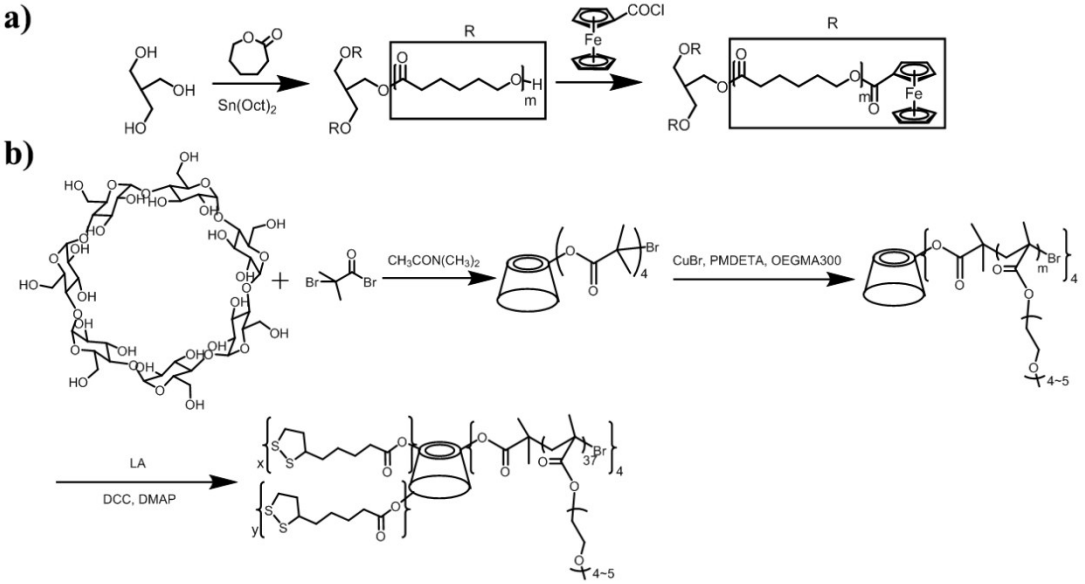
4. H. Wei, C. Yu, C. Chang, C. Quan, S. Mo, S. Cheng, X. Zhang and R. Zhuo, *Chem. Commun.*, 2008, 4598-4600.

3. Scheme S1

4. Table S1

5. Figure S1-S17



Scheme S1. Synthesis of 3-PCL-Fc, 4Br-β-CD-POEGMA, and 4Br-β-CD-POEGMA-LA.

Table S1. Molecular parameters of all the synthesized polymers.

Sample	M_n[a] (kDa)	M_n[b] (kDa)	$Đ$[c]	Yield (%)
3-PCL_7-OH	2.5	2.9	1.27	86.8
3-PCL_7-Fc	3.1	3.7	1.31	63.9
3-PCL_{14}-OH	4.9	6.1	1.12	90.5
3-PCL_{14}-Fc	5.5	7.4	1.23	73.9
4Br-β-CD-$POEGMA_{37}$	12.8	20.8	1.30	85.3
4Br-β-CD-$POEGMA_{37}$-LA_8	14.3	29.5	1.21	82.7
4Br-β-CD-$POEGMA_{37}$-LA_{13}	15.3	31.1	1.23	51.3
Cyclic P1	NA	96.8	1.32	69.6
Cyclic P2	NA	103.9	1.27	74.1
Cyclic P3	NA	100.9	1.38	61.4

[a]Determined by ^{1}H NMR

[b,c]Determined by SEC-MALLS

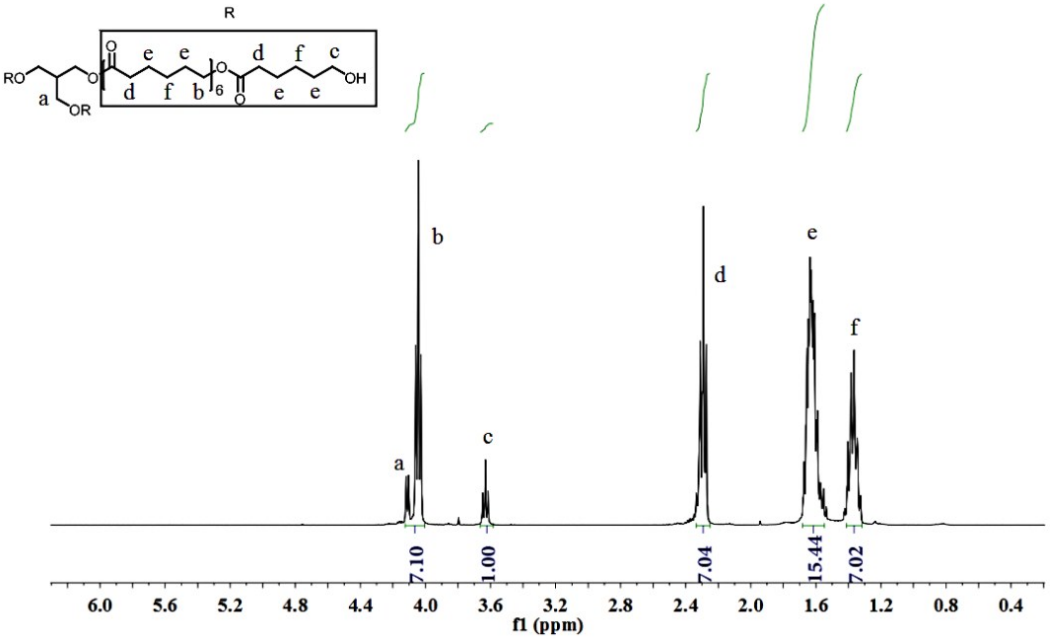


Figure S1.[1]H NMR spectrum of 3-PCL_7-OH in $CDCl_3$.

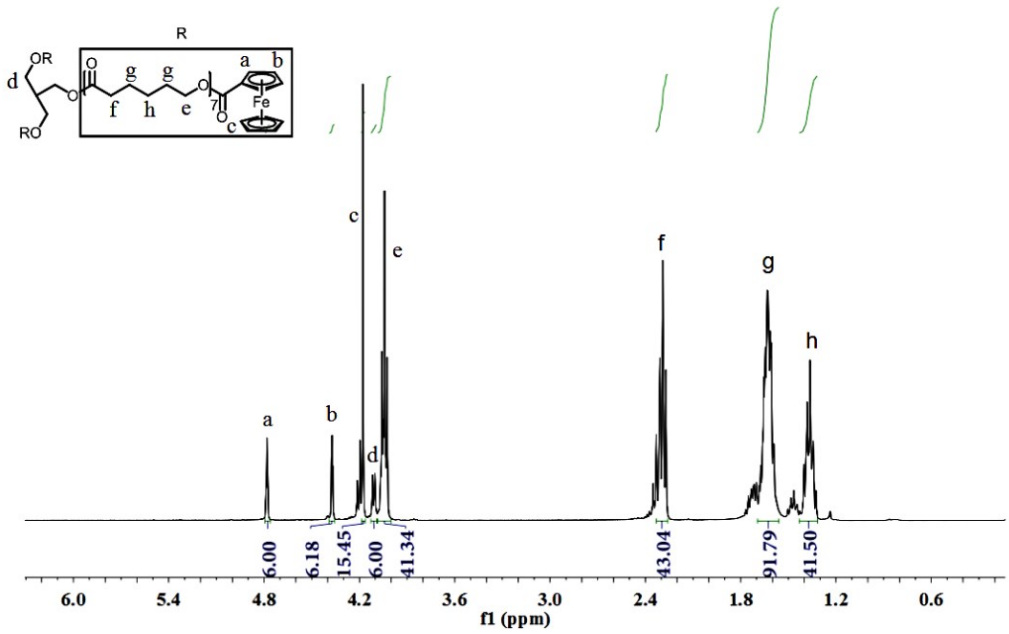


Figure S2.[1]H NMR spectrum of 3-PCL_7-Fc in $CDCl_3$.

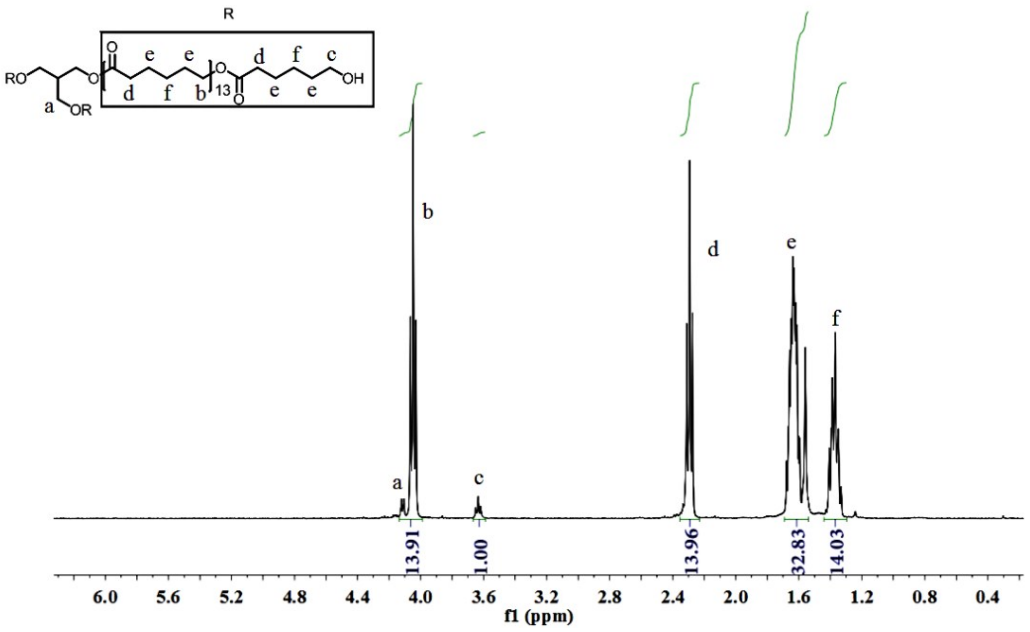


Figure S3.[1]H NMR spectrum of 3-PCL_{14}-OH in $CDCl_3$.

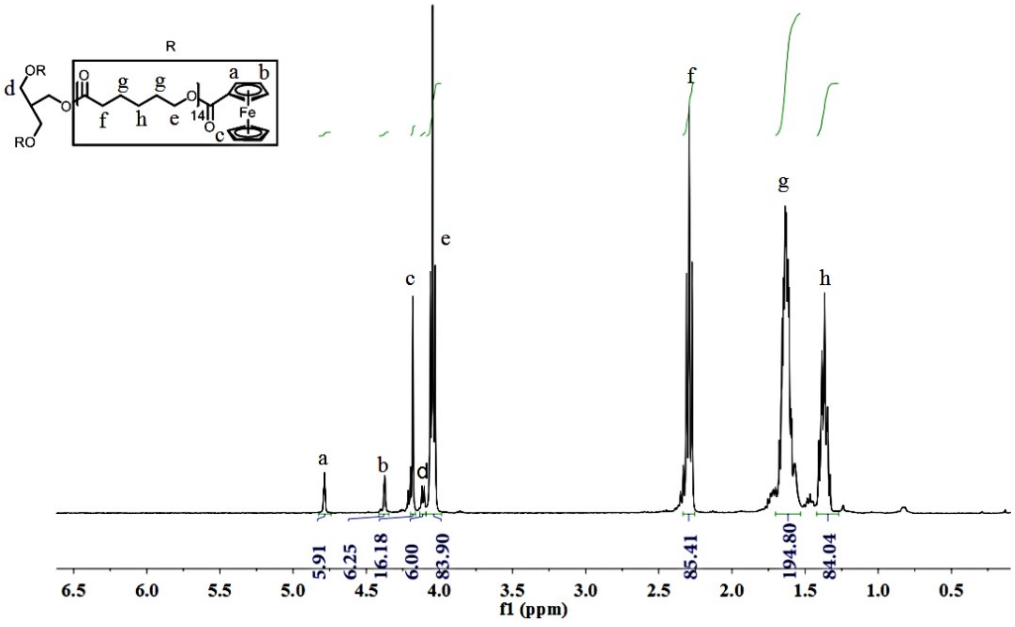


Figure S4.[1]H NMR spectrum of 3-PCL_{14}-Fc in $CDCl_3$.

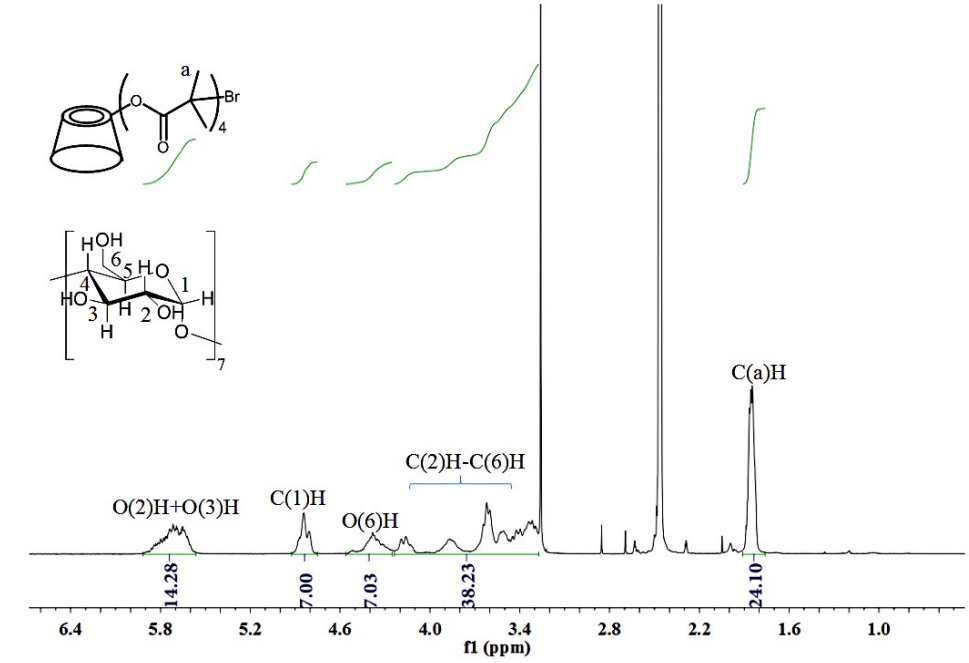


Figure S5.[1]H NMR spectrum of 4Br-β-CD in DMSO-d_6.

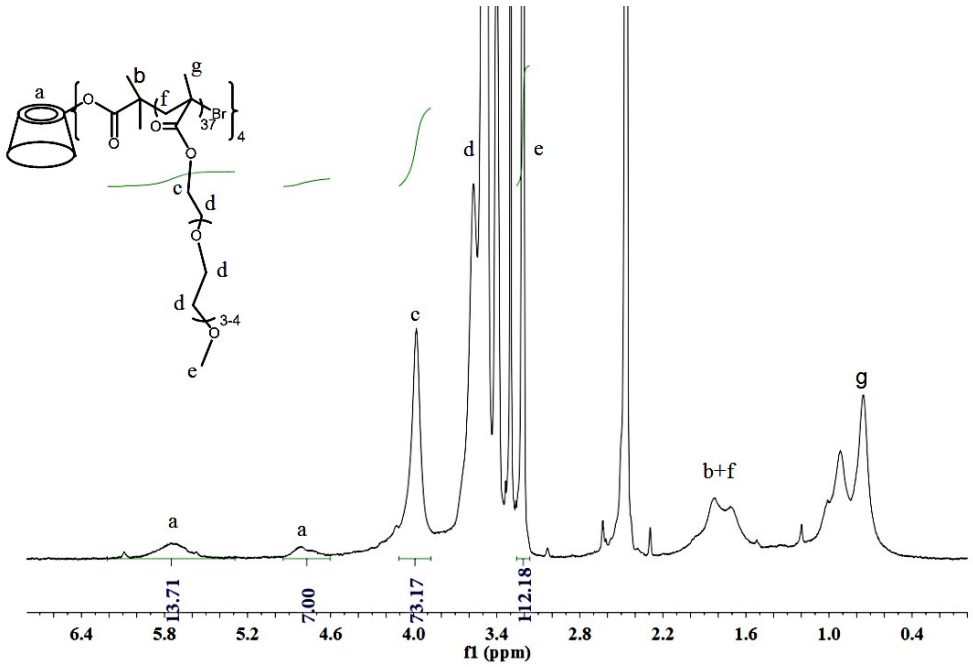


Figure S6.[1]H NMR spectrum of 4Br-β-CD-POEGMA$_{37}$ in DMSO-d_6.

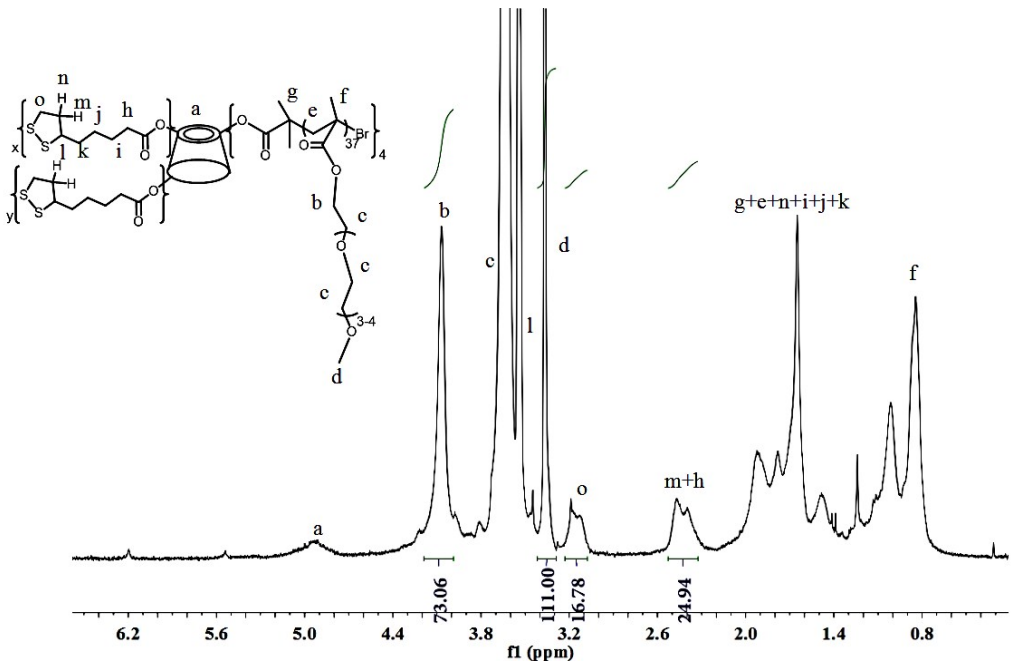


Figure S7.[1]H NMR spectrum of 4Br-β-CD-POEGMA$_{37}$-LA$_8$ in $CDCl_3$.

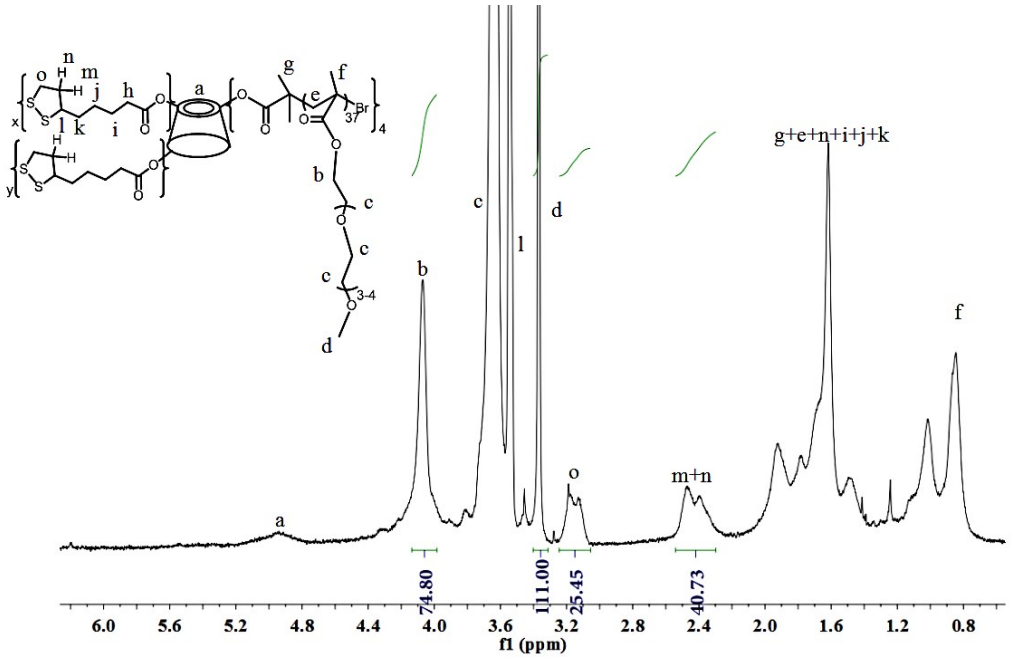


Figure S8.[1]H NMR spectrum of 4Br-β-CD-POEGMA$_{37}$-LA$_{13}$ in $CDCl_3$.

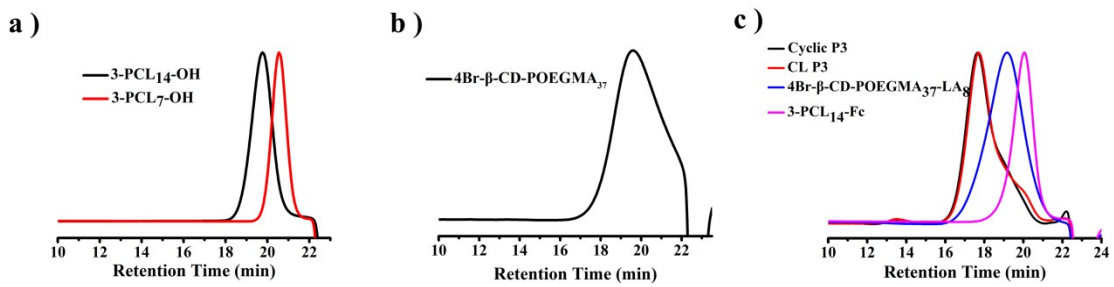


Figure S9. SEC elution traces of a) 3-PCL_7-OH, 3-PCL_{14}-OH, b) 4Br-β-CD-$POEGMA_{37}$, and c) 3-PCL_{14}-Fc, 4Br-β-CD-$POEGMA_{37}$-LA_8, CL P3, Cyclic P3.

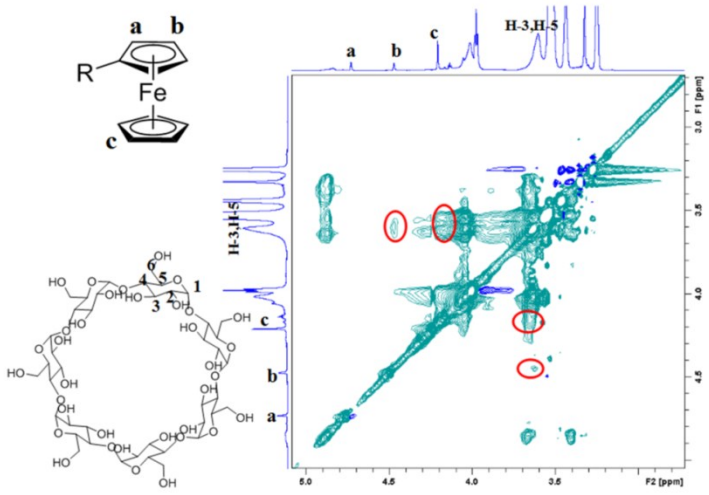


Figure S10. 2D NOESY NMR spectra of 3-PCL-Fc and 4Br-β-CD-POEGMA in DMSO-d_6.

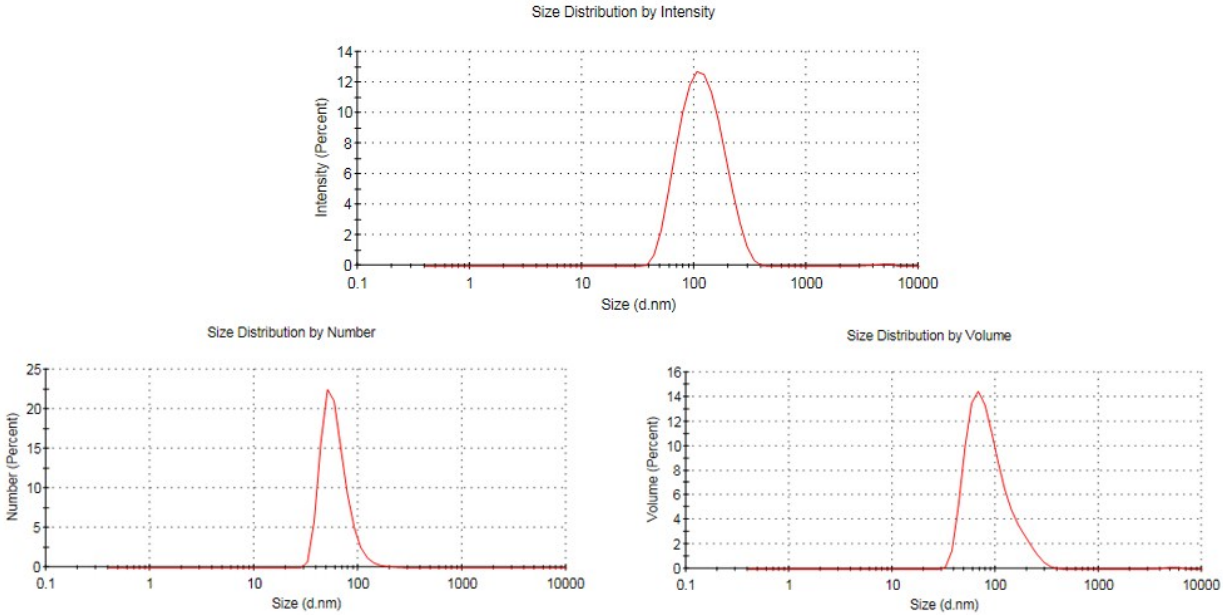


Figure S11. Intensity, number and volume-average size distributions of P1determined by DLS at a polymer concentration of 0.30 mg/mL.

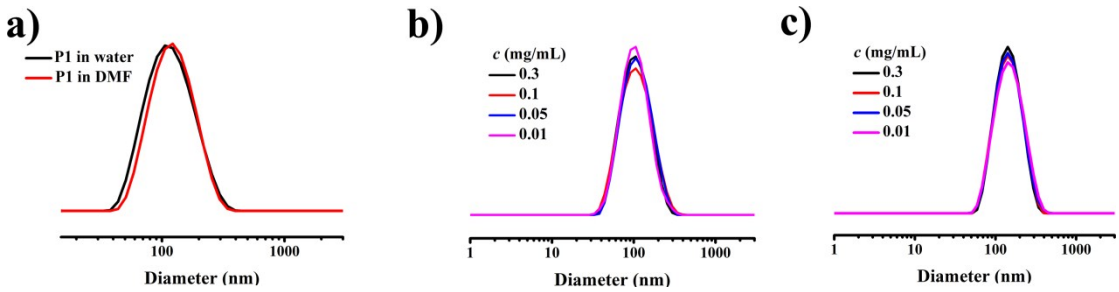


Figure S12. Intensity-average size distributions from DLS of a) P1 in DMF and water, b) P2 and c) P3 at various polymer concentrations from 0.01 to 0.30 mg/mL.

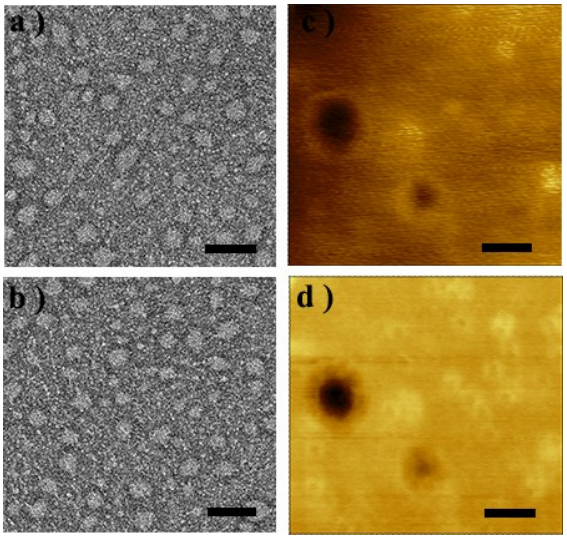


Figure S13. TEM images of a) P3, b) CL P3. AFM height c) and phase d) images of Cyclic P3 on a silicon wafer (scale bar=100 nm).

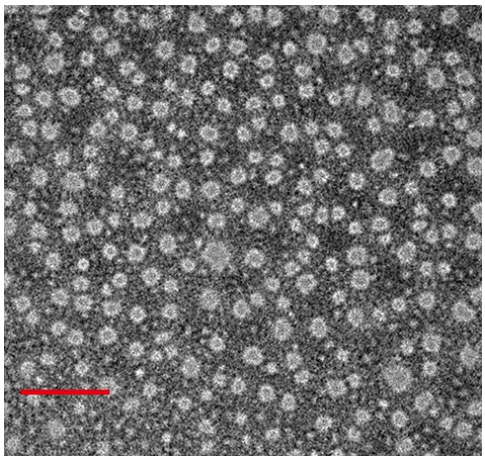


Figure S14. A typical high resolution TEM image of Cyclic P2 (scale bar=200 nm).

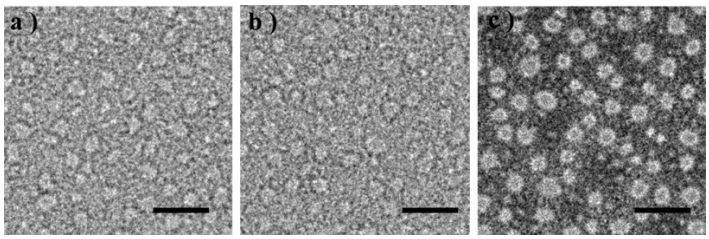


Figure S15.TEM images of a) P2, b) CL P2 and c) Cyclic P2 (scale bar=100 nm).

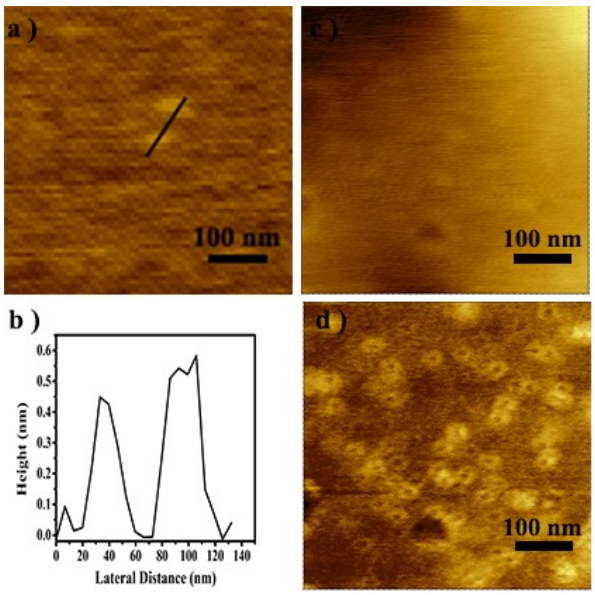


Figure S16. a) AFM height image of CL P1and b) profile analysis of CL P1 indicated by the blackline in a). AFM height c) and phase d) images of Cyclic P1 (scale bar=100 nm).

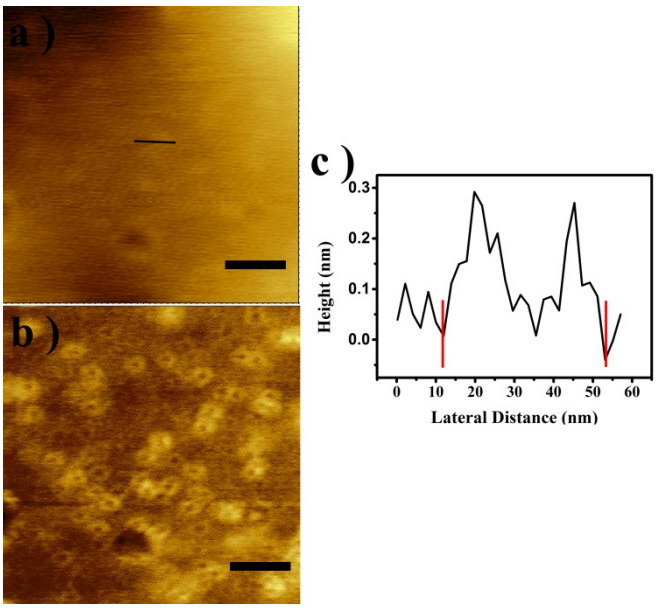


Figure S17. AFM height a) and phase b) images of Cyclic P1and c) profile analysis of CL P1 indicated by the blackline in a) (scale bar=100 nm).