

## Supplemental Material

for

### Fluorination Increases Hydrophobicity at the Macroscopic Level but not at the Microscopic Level

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### I Synthesis Procedure

**C1→C2:** NaNO<sub>2</sub> (1.08 g, 15.66 mmol) in water (7.2 mL) and methyl-2-aminotetrphate (3.00 g, 15.37 mmol, **C1**) were slowly added to a round flask bottle dispersed in ice-cold concentrated HCl (30 mL) with vigorous stirring for 5 min to exclude the evolved gas. Then, the mixture was allowed to stir for 0.5 h, followed by filtering through a sintered filter funnel. The filtrate was directly added to a stirring solution of KI (25.80 g, 155.10 mmol) for 1 h to substitute the diazonium salt. Then, 96 mL dichloromethane (DCM) was added. The organic phase was washed with 24 mL saturated Na<sub>2</sub>SO<sub>3</sub> solution, filtered through a polypropylene membrane, recrystallized from methanol (MeOH) and dried under vacuum to yield methyl-2-iodoterephthalate (1.80 g, 5.88 mmol, Yield = 38%, **C2**).

**C2 → C3:** The obtained methyl-2-iodoterephthalate (3.00 g, 9.80 mmol, **C2**), Pd(Ac)<sub>2</sub> (22.4 mg, 0.10 mmol), 24 mL anhydrous acetonitrile (ACN) and 3.0 mL N,N-Diisopropylethylamine (DIPEA) (2.10 g, 16.24 mmol) were loaded in a flame-dried Schlenk tube and degassed through three freeze-pump-thaw cycles. Finally,

diphenylphosphine (1824.6 mg, 9.80 mmol) was injected through a rubber septum by a syringe under argon gas. The reaction mixture was allowed to reflux overnight, cooled to room temperature, diluted with DCM, washed by 1 M HCl, recrystallized from cold MeOH to obtain the desired **C3** (2.40 g, 6.56 mmol, Yield = 67%).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>), δ (ppm) = 8.06--8.10 (m, 2H), 7.66--7.67 (d, 1H, *J* = 3.5 Hz), 7.27--7.39 (m, 10H), 3.75 (s, 3H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>), δ (ppm) = 170.54, 166.71, 141.62, 141.39, 139.03, 138.88, 136.96, 136.87, 135.59, 133.94, 133.78, 131.84, 130.60, 129.73, 129.06, 128.71, 128.65, 52.38.

**ESI-MS (-)**, 364.1, [M]<sup>-</sup>, cald for C<sub>21</sub>H<sub>7</sub>O<sub>4</sub>P: 364.0864.

**C3 → C4:** **C3** (1.00 g, 2.74 mmol), O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluorophosphate (HBTU) (1.24 g, 3.28 mmol), DIPEA (1020 μL, 5.48 mmol) and N-Boc-ethylenediamine (0.52 g, 3.28 mmol) were dissolved well in anhydrous DCM/ACN and stirred for 4 h at room temperature. The obtained mixture was subsequently washed with 1 M HCl, saturated NaHCO<sub>3</sub> solution and brine, dried by anhydrous MgSO<sub>4</sub> overnight. The crude product was purified by a flash chromatography purification (DCM : MeOH = 98 : 2, v/v) to obtain **C4** (1.18 g, 2.32 mmol, Yield = 85%).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>), δ (ppm) = 8.04--8.07 (dd, 1H, *J* = 8.0, 3.9 Hz), 7.73--7.77 (dd, 1H, *J* = 8.2, 1.2 Hz), 7.27--7.41 (m, 11H), 6.91--6.97 (br, 1H), 4.82--4.92 (br, 1H), 3.74 (s, 3H), 3.40--3.45 (m, 2H), 3.26--3.31 (m, 2H), 1.40 (s, 9H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>), δ (ppm) = 166.67, 157.34, 141.61, 141.38, 137.22, 137.14, 136.94, 136.76, 136.61, 133.99, 133.83, 133.05, 130.78, 128.97, 128.67, 128.61, 126.37, 80.10, 53.44, 52.23, 41.94, 39.92, 28.33.

**ESI-MS (+)**, 545.3, [M+K]<sup>+</sup>, cald for C<sub>28</sub>H<sub>31</sub>N<sub>2</sub>O<sub>5</sub>P: 506.1971.

**C4 → C5:** The obtained **C4** was deprotected by DCM/Trifluoroacetic acid (5mL, v/v = 3:1) at room temperature for 3 h until completely conversion as monitored by thin layer chromatography. After removing solvent under vacuum, the residue was dissolved in saturated NaHCO<sub>3</sub> solution in MeOH, filtered, and concentrated to yield **C5** precursor. To an anhydrous DCM (20 mL) solution of 4-cyano-4-(thiobenzoylthio) pentanoic acid (0.50 g, 1.79 mmol), HBTU (0.82 g, 2.15 mmol) and DIPEA (664 μL, 3.57 mmol) were added and dissolved well by stepwise addition of anhydrous ACN. Then **C5** precursor (0.87 g, 2.15 mmol) was added under argon flow. The reaction was conducted in an ice-water bath for 4 h to minimize the aminolysis of the dithiobenzoate group in alkaline

environment. Then, the organic phase was extracted with 1 M HCl, saturated NaHCO<sub>3</sub> solution, brine and dried by anhydrous MgSO<sub>4</sub>. After removal of the solvent, the crude product was loaded on a silica column eluting with DCM/MeOH (v/v = 99:1) to give **C5** as a red solid (0.50 g, 0.75 mmol, Yield = 42%).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>), δ (ppm) = 8.05--8.08 (dd, 1H, *J* = 8.0, 3.6 Hz), 7.86--7.89 (dd, 2H, *J* = 8.5, 1.0 Hz), 7.71--7.74 (dd, 1H, *J* = 8.0, 1.8 Hz), 7.54--7.58 (m, 1H), 7.27--7.40 (m, 13H), 6.75 (br, 1H), 6.16 (br, 1H), 3.73 (s, 3H), 3.48 (m, 2H), 3.42 (m, 2H), 3.35--3.60 (m, 6H), 1.91 (s, 3H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>), δ (ppm) = 222.39, 171.75, 167.13, 166.68, 144.43, 141.83, 141.51, 137.15, 137.07, 136.63, 134.00, 133.83, 133.10, 132.98, 130.87, 129.00, 128.69, 128.60, 126.66, 126.44, 118.66, 99.99, 53.43, 52.26, 45.95, 40.88, 40.14, 33.95, 31.76, 24.32.

**ESI-MS (+)**, 706.3, [M+K]<sup>+</sup>, calcd for C<sub>36</sub>H<sub>34</sub>N<sub>3</sub>O<sub>4</sub>PS<sub>2</sub> : 667.1728.

**C5** → **C6**: **C5** is a Staudinger installed reversible addition-fragmentation chain transfer (RAFT) reagent controlling polymerizing monomers to form a bifunctional polymer chain with a Staudinger handle, which can selectively react with an azide group on the substrate, and a ditiobenzoate group on the other end, which can be furtherly transformed to thiol group to react with the maleimide on the AFM tip. Briefly, azodiisobutyronitrile (AIBN) (0.4 mg, 2.5 μmol) and **C5** (8.3 mg, 12.5 μmol) and freshly distilled styrene (1.30 g, 12.5 mmol, or other monomers with the same moles) were placed in a flame-dried Schlenk tube. Oxygen was removed by three freeze-pump-thaw cycles. The argon protected Schlenk tube was immersed in a 80 °C oil bath for 72 h to conduct the polymerization with a moderate conversion rate. After cooling to room temperature, Tetrahydrofuran was added to the tube to dissolve polymer. The diluted solution was dropwise added to a stirring cold MeOH solution to precipitate polymer for 3 times. The precipitate was collected and dried by vacuum.

The NMR characterization of six polymers (PS, FPS1~4, and PPF5) is as following (Fig. S1~S6):

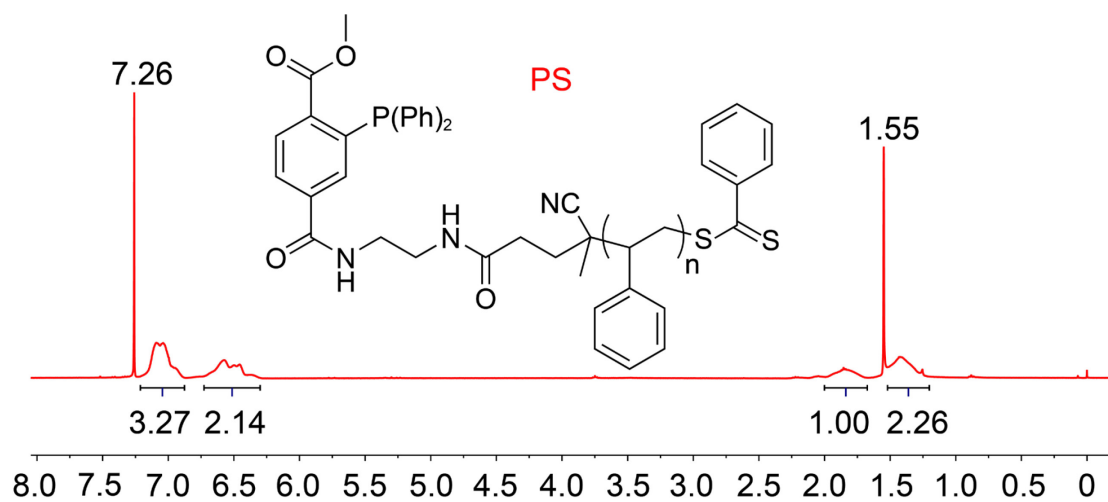


Fig. S1 The <sup>1</sup>H NMR spectrum of PS.

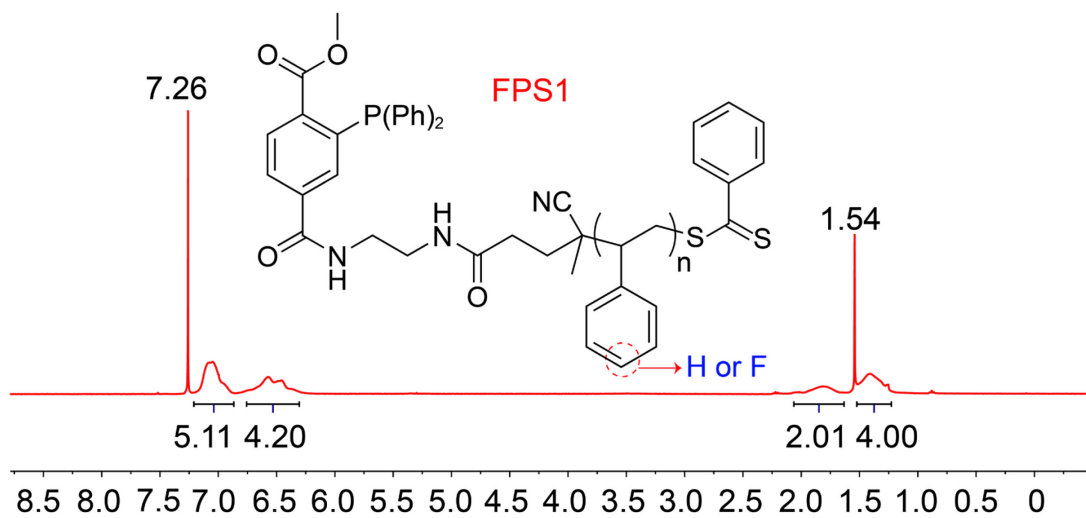


Fig. S2 The <sup>1</sup>H NMR spectrum of FPS1.

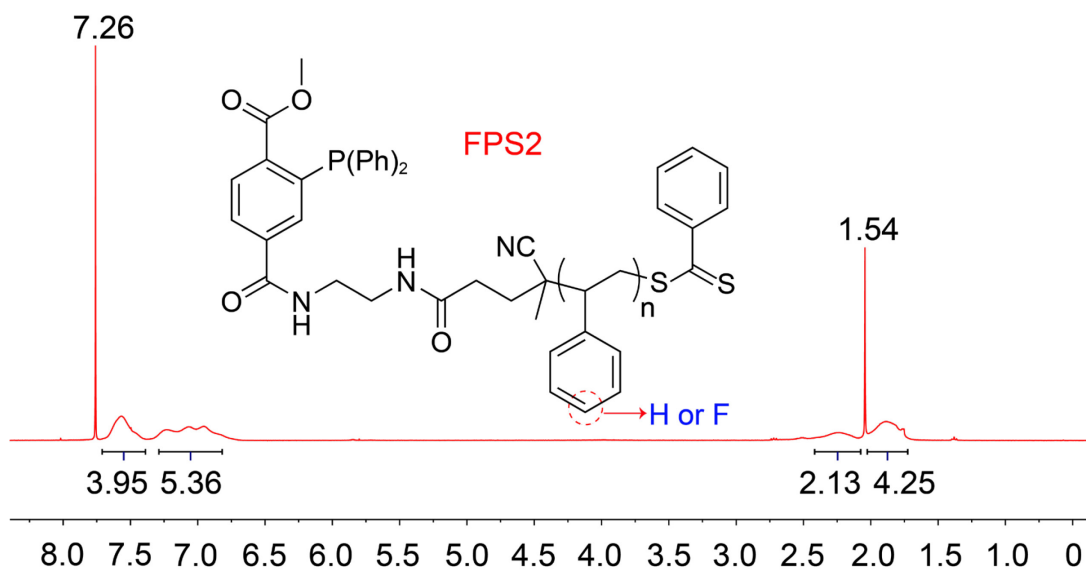


Fig. S3 The <sup>1</sup>H NMR spectrum of FPS2.

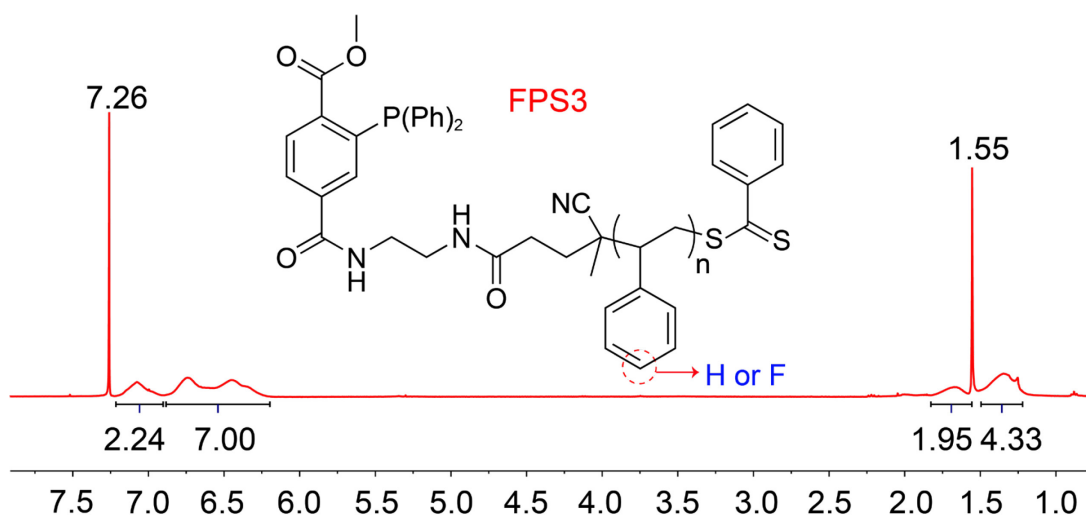


Fig. S4 The <sup>1</sup>H NMR spectrum of FPS3.

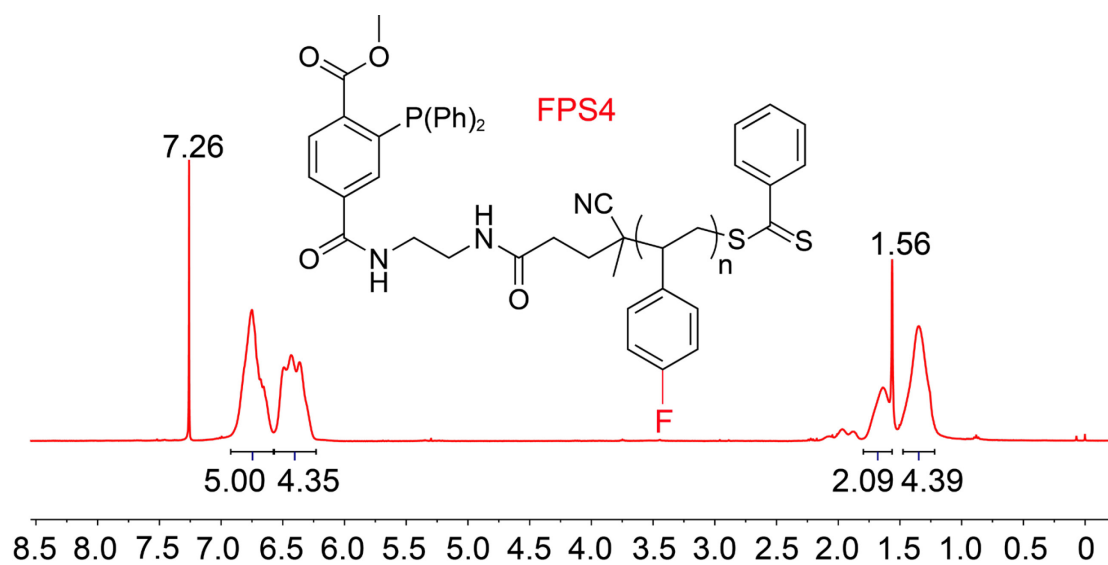


Fig. S5 The  $^1\text{H}$  NMR spectrum of FPS4.

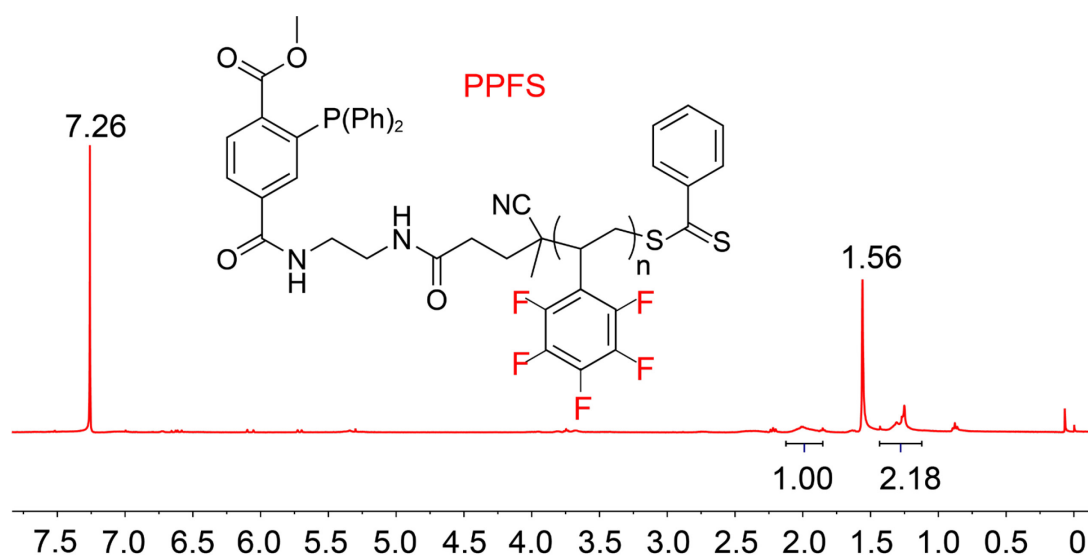


Fig. S6 The  $^1\text{H}$  NMR spectrum of PPFS.

## II Force-extension Curves of Unfolding the Polymer Nnanosphere

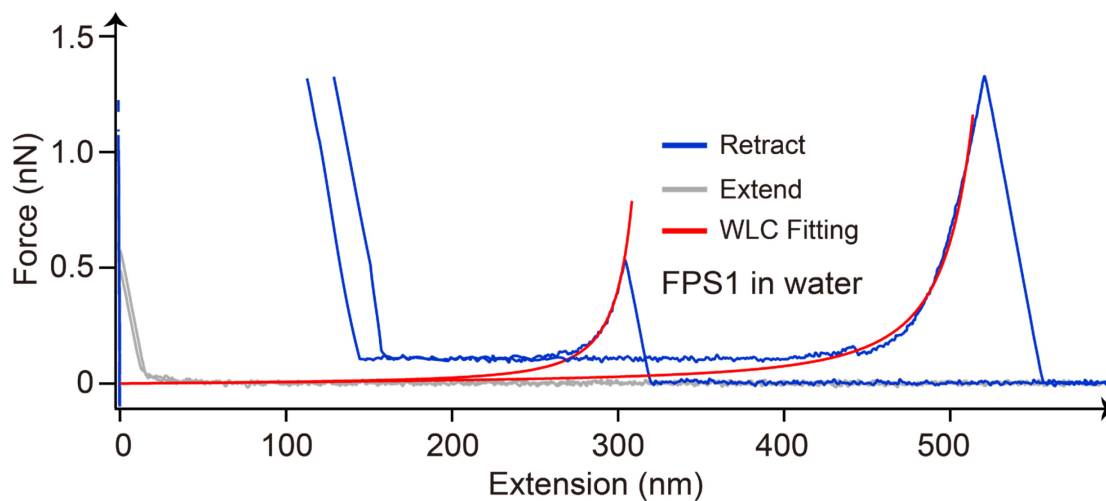


Fig. S7 The force-extension curves of unfolding FPS1 nanosphere in water. The grey line is extending curve, the blue line is retracting line, and the red line is WLC fitting to the elastic stretching of force-extension curves.

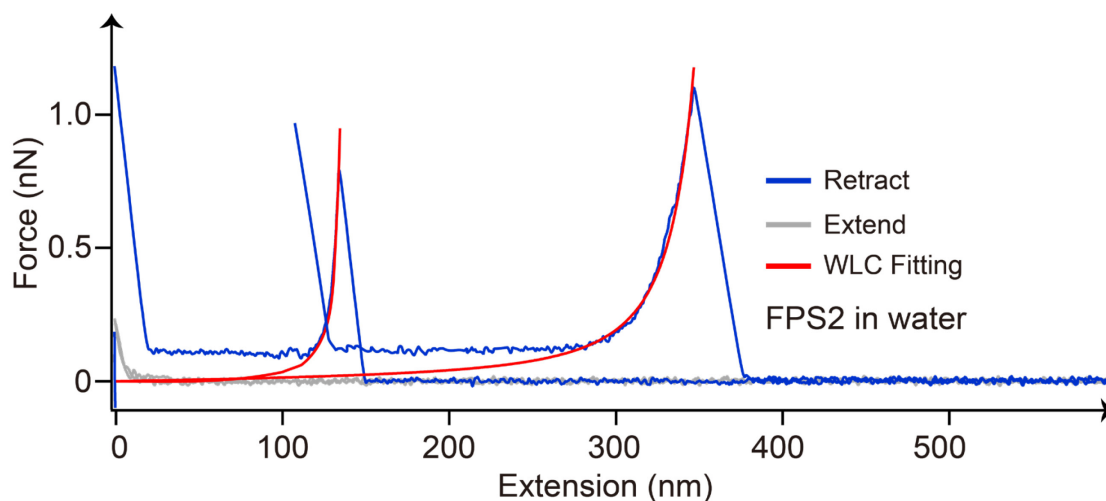


Fig. S8 The force-extension curves of unfolding FPS2 nanosphere in water. The grey line is extending curve, the blue line is retracting line, and the red line is WLC fitting to the elastic stretching of force-extension curves.

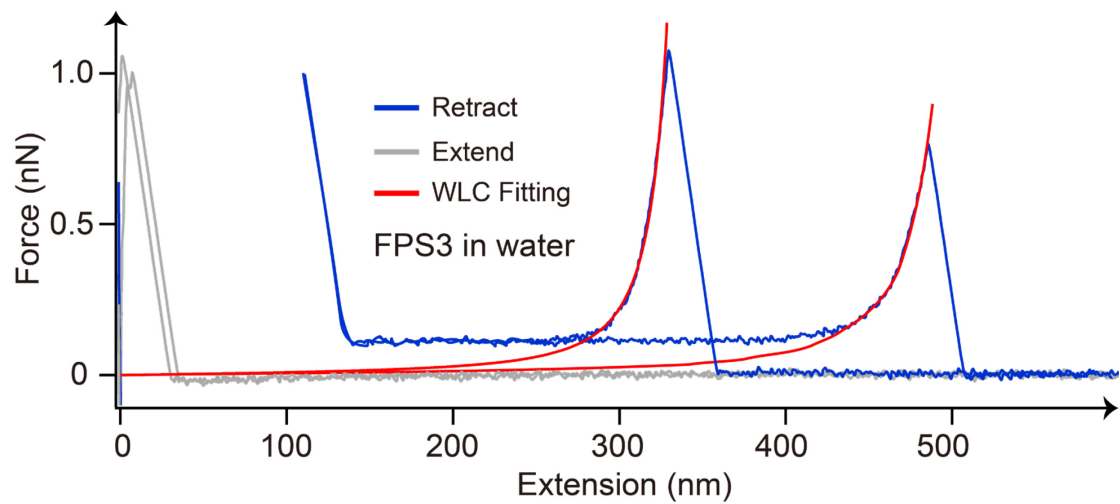


Fig. S9 The force-extension curves of unfolding FPS3 nanosphere in water. The grey line is extending curve, the blue line is retracting line, and the red line is WLC fitting to the elastic stretching of force-extension curves.

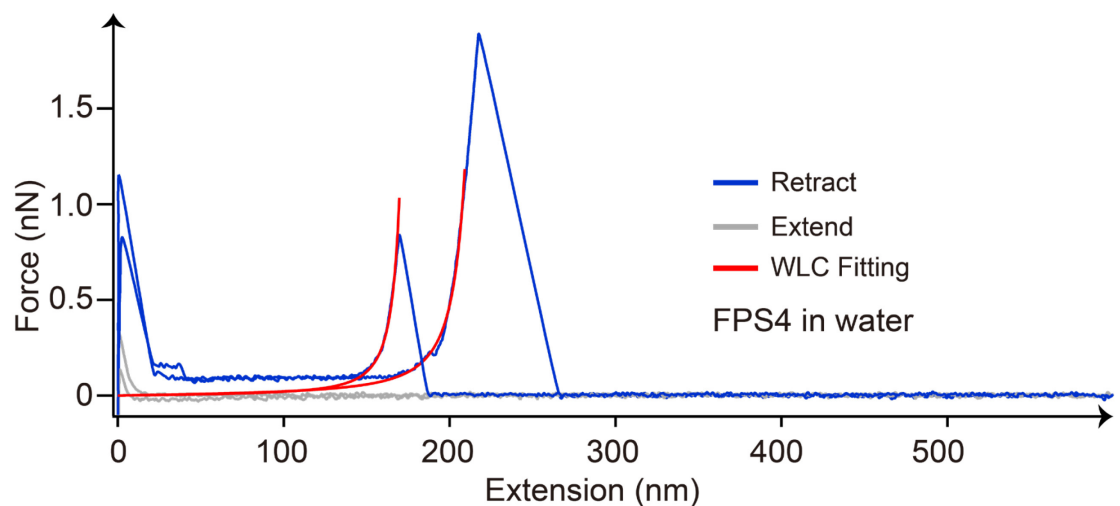


Fig. S10 The force-extension curves of unfolding FPS4 nanosphere in water. The grey line is extending curve, the blue line is retracting line, and the red line is WLC fitting to the elastic stretching of force-extension curves.



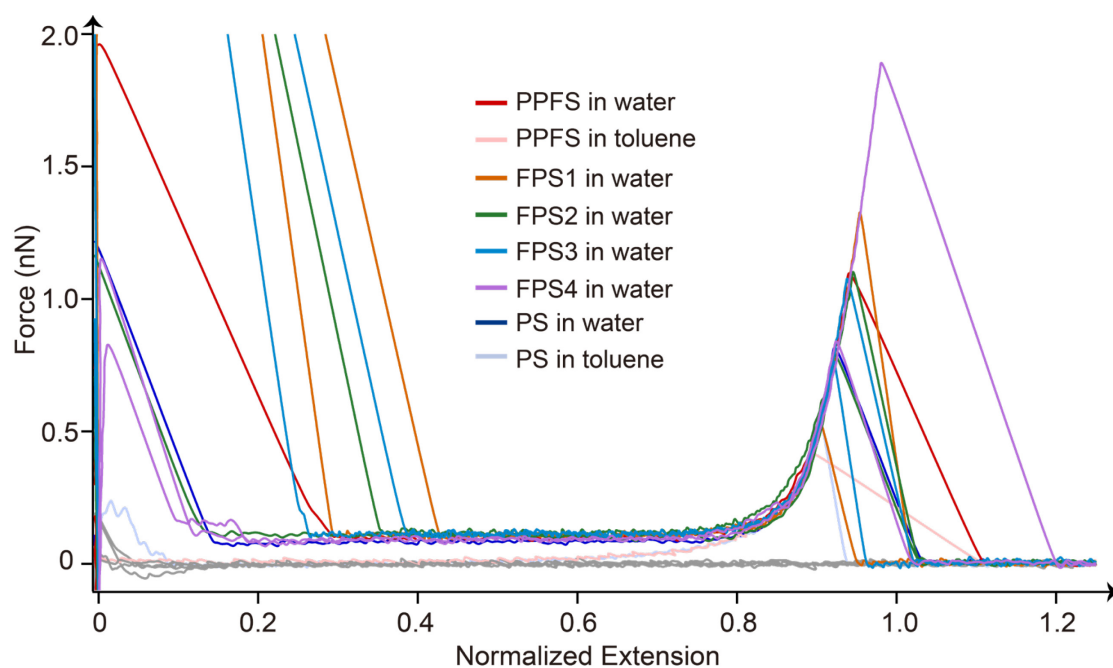


Fig. S11 The normalized force-extension curves of unfolding PS, FPS1, FPS2, FPS3, FPS4, and PPFS nanosphere in water and pulling PS and PPFS polymer chain in organic solvent toluene by their contour length. The elastic stretching parts of all curves are all overlapped. Note that these curves are from Fig. S7~S10 and Fig. 2 in main text.