Electronic Supplementary Material (ESI) for Polymer Chemistry
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Supplemental Materials

Synthesis of low-temperature benzocyclobutene cross-linker and utilization

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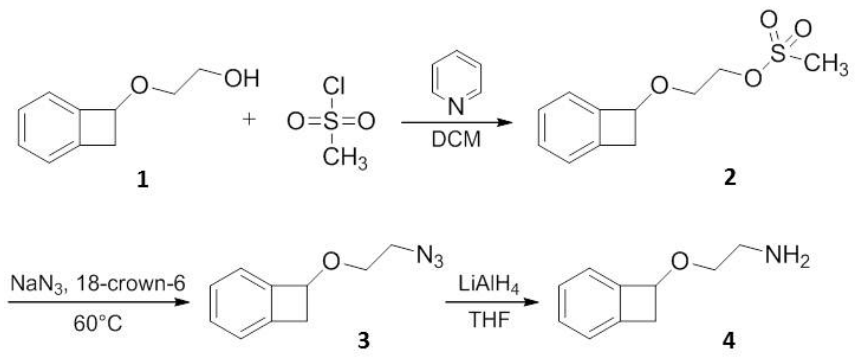
Experimental Section

General Methods. Reagent chemicals were purchased from Aldrich and Acros and used as received. Analytical TLC was performed on commercial Merck plates coated with silica gel GF254 (0.24 mm thick). Silica gel for flash chromatography was Merck Kieselgel 60 (230-400 mesh, ASTM). Nuclear magnetic resonance was run on a Bruker AC300 Fourier Transform Spectrometer and a Bruker AC 400 Fourier Transform Spectrometer, using deuterated solvents and the solvent peak as a reference. To obtain the TEM micrographs of the polymeric nanoparticles, a Philips CM20T transmission electron microscope (TEM) was employed, operating at 200 kV in bright-field mode. Ultrathin Carbon Type-A, 400 Mesh Copper Grids were purchased from Ted Pella to use with the TEM. Dynamic light scattering (DLS) was performed using a Zetasizer Nano Series instrument with a CGS-3 compact goniometer system by Malvern instruments. The average of three measurements was recorded at a fixed angle of 90° at 25 °C.

Cross-linker Synthesis:



2-(1,2-dihydrocyclobutabenzen-1-yloxy)ethanol, 1. To a 100-mL flask containing sodium hydride (3.15 g, 131.1 mmol) was added ethylene glycol (12.2 g, 196 mmol) slowly at 0 °C. The reaction mixture was removed from ice and 4-bromo-benzocyclobutene was added at once (4.00 g, 21.9 mmol). The flask was heated for 3 h at 90 °C. The mixture was quenched with water (10 mL), and the reaction mixture was extracted three times with ether (75 mL). The organic phases were combined, and the crude

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product was dried over Na_2SO_4 and concentrated. The product was purified by column chromatography using ethyl acetate/hexane (2:1) as the eluting solvents to yield the bromobenzocyclobutene alcohol derivative, **1**, (2.62 g, 73.1%) as a light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.33-7.14 (m, 4H, ArH), 5.10 (d, 1H, CH), 3.78-3.66 (m, 4H, CH_2), 3.48 (dd, 1H, CH_2), 3.14 (d, 1H, CH_2), 2.26 (br s, 1H, OH); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 145.91, 142.47, 129.46, 127.08, 123.54, 122.83, 76.91, 70.07, 61.46, and 38.48.

2-(1,2-dihydrocyclobutabenzen-1-yloxy)ethyl methanesulfonate, 2. Anhydrous dichloromethane and anhydrous pyridine (3:1) were added to a dry, 100-mL flask and then purged with argon. 2-(1,2-dihydrocyclobutabenzen-1-yloxy)ethanol, **1**, (0.53 g, 3.22 mmol) was added to the flask, cooled to 0^o C, and stirred 10 min. Mesyl chloride (16.14 mmol, 1.85 g) was diluted in anhydrous dichloromethane (19 mL) and added drop-wise to the stirring, cooled solution. The contents of the flask were allowed to warm to room temperature and stirred overnight. The reaction was concentrated and then diluted in dichloromethane and washed once with saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography using ethyl acetate/hexane (1:1) to give the pure mesylated derivative, (**2**), (0.55 g, 78.2%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34-7.15 (m, 4H, ArH), 5.13 (dd, 1H, CH), 4.45-4.42 (m, 2H, CH_2), 3.95-3.84 (m, 2H, CH_2), 3.50 (dd, 1H, CH_2), 3.15 (d, 1H, CH_2), 3.04 (s, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 145.07, 142.22, 129.63, 127.17, 123.54, 122.65, 76.93, 69.07, 66.22, 38.34, and 37.63.

1-(2-azidoethoxy)-1,2-dihydrocyclobutabenzene, 3. To a 25-mL flask was added 2-(1,2-dihydrocyclobutabenzen-1-yloxy)ethyl methanesulfonate, **2**, (0.55 g, 3.03 mmol), sodium azide (0.57 mg, 8.75 mmol), 18-crown-6 (10 mg) and DMSO (5 mL). The reaction mixture was heated to 60 ^{o}C overnight and allowed to stir overnight. It was cooled to room temperature, quenched with water (10 mL), and extracted three times with dichloromethane (40 mL). The organics were combined, dried over sodium sulfate, filtered and concentrated. The crude product was purified via column chromatography using dichloromethane to yield the pure azide derivative, **3**, (0.41 g, 71.6%) as a yellow oil; ^{1}H NMR

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(300 MHz, $CDCl_3$) δ ppm 7.33-7.14 (m, 4H, ArH), 5.12 (dd, 1H, CH), 3.86-3.73 (m, 2H, CH_2), 3.52 (d, 1H, CH_2), 3.48-3.44 (m, 2H, CH_2), 3.17 (d, 1H, CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 145.40, 142.34, 129.52, 127.11, 123.51, 122.74, 76.93, 67.12, 50.76, and 38.42.

2-(1,2-dihydrocyclobutabenzen-1-yloxy)ethanamine, 4. Lithium aluminum hydride (2.0 M in THF, 4.43 mmol) was slowly added to a 250-mL flask containing 1-(2-azidoethoxy)-1,2-dihydrocyclobutabenzene, **3**, (0.70 g, 3.69 mmol) and anhydrous THF (13 mL). The reaction flask was cooled to 0 ^oC and allowed to stir two hours. Deionized water (0.5 mL) was slowly added to quench the reaction followed by concentration via the rotary evaporator. The crude product was purified by filtration through a short pad of Celite using dichloromethane. The organic was dried over Na_2SO_4, filtered, and concentrated to yield the pure amine derivative, **4**, (0.50 g, 82.6%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.33-7.143 (m, 4H, ArH), 5.08 (d, 1H, CH), 3.73-3.59 (m, 2H, CH_2), 3.49 (dd, 1H, CH_2), 3.15 (d, 1H, CH_2), 2.92 (t, 2H, CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 145.90, 142.46, 129.33, 127.01, 123.49, 122.67, 76.99, 70.98, 42.03, and 38.58.

Model Reactions of 2-(1,2-dihydrocyclobutabenzen-1-yloxy)ethanol to Investigate Isomerization Temperature.

2-(1,2-dihydrocyclobutabenzen-1-yloxy)ethanol, **1**, (50.0 mg, 0.305 mmol) was dissolved in xylenes (3 mL) in a vial and allowed to stir for 1 h at 90 ^oC. The reaction mixture was concentrated. The same procedure was performed at 100 ^oC, 110^oC, 120^oC, and 130^oC.

For a 150 ^oC reaction, 2-(1,2-dihydrocyclobutabenzen-1-yloxy)ethanol (50.0 mg, 0.305 mmol) was dissolved in the higher-boiling solvent, DMF (3 mL), and stirred for 1 h. The reaction mixture was diluted in DCM (5 mL) and washed with water (5 mL) once. The organic phase was dried over Na_2SO_4 and concentrated.

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Polymer Synthesis:

Polymerization of Acrylic Acid via RAFT

Acrylic acid (7.21 g, 100 mmol) was weighed into an ampule equipped with a stirbar. AIBN (4.69 mg, 0.03 mmol) and the COOH initiator, 4-cyanopentanoic acid dithiobenzoate (0.14 g, 0.59 mmol), were each weighed out separately and quantitatively transferred using DMF. The contents of the sample endured three freeze-pump-thaw cycles, and then the ampule was flame sealed under argon. The ampule was heated at 70 ^{o}C for 7 h. The polymer solution was purified via precipitation in ethyl acetate to yield a pink, sticky polymer, M_W = 75 300; PDI = 1.21. ^{1}H NMR (400 MHz, MeOD): δ ppm 2.46-2.40 (br m, CH), 1.96 (br s, CH, CH_2), 1.74-1.55 (br m, CH, CH_2).

Grafting of Amine-LTCL, 4, onto PAA

Poly(acrylic acid) (0. 19 g, M_w = 35 300, PDI = 1.21) was dissolved in DMF (20 mL) and transferred to a dry 100-mL flask and cooled to 0 ^{o}C. 4-Methylmorpholine (13.4 mg, 0.00013 mmol) and isobutyl chloroformate (19.9 mg, 0.00015 mmol) were each weighed out separately and quantitatively transferred using DMF. The reaction mixture activated for 1 h at 0 ^{o}C. 2-(1,2-dihydrocyclobutabenzen-1-yloxy)ethanamine (21.6 mg, 0.00013 mmol) was weighed out and transferred to the flask using DMF. The mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched with water (20 mL) and stirred for 1 h before adding THF (20 mL) and allowing to stir 8 h. The crude product was purified by dialysis, initially using THF:H_2O and transitioning to 100% methanol, with Spectra/Por® dialysis membrane (MWCO = 25 000) for 12 h and then concentrated to yield the final product, (0.15 g), with 5% LTCL attached. ^{1}H NMR (300 MHz, MeOD) δ ppm 7.29-7.14 (m, ArH), 5.11 (s, CH), 3.56 (br t, CH_2), 3.47 (br d, CH_2), 3.12 (br d, CH_2), 2.94 (br s, CH_2), 2.70 (br s, CH), 2.44 (br s, CH, CH_2), 2.03-1.52 (br m, CH, CH_2).

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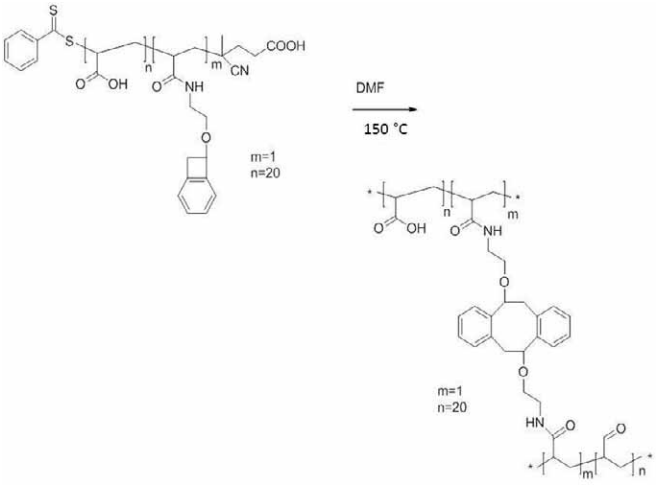

Nanoparticle Formation via intramolecular Chain Collapse:

A 250-mL three-neck round bottom flask was equipped with a condenser, an internal thermometer, and a rubber septum. DMF (125 mL) was added to the flask and heated to 150 °C. The linear RAFT copolymer (0.145 g, M_W = 35 500, 4.98 % LTCL) was dissolved in DMSO (5.5 mL) and added drop wise into the vigorously stirring flask via a peristaltic pump at ca. 12 mL/h. Once all of the polymer solution had been added to the stirring DMF, the contents were allowed to stir an additional 30 min before being removed from heat. The reaction mixture was concentrated to yield the crude product, which was purified via dialysis against varying mixtures of THF, methanol, and water with Spectra/Por® dialysis membrane (MWCO = 15 000) for 48 h to lend the pure product (0.137 g). While the peaks in the NMR of the product do not shift, there is a broadening observed of the cross-linking protons.

DLS of Nanoparticles. Samples of the nanoparticles were diluted to a concentration with methanol to give the optimal number of counts to yield a good signal-to-noise ratio.

TEM of Nanoparticles. Samples were prepared by dissolving nanoparticles (17.0 mg) in deionized water (0.75 mL). The samples were stained with 8 drops each of ruthenium tetroxide solution (0.2 g ruthenium(III) chloride hydrate, 100 mL water, 5 mL of a 5% sodium chlorite solution in water),

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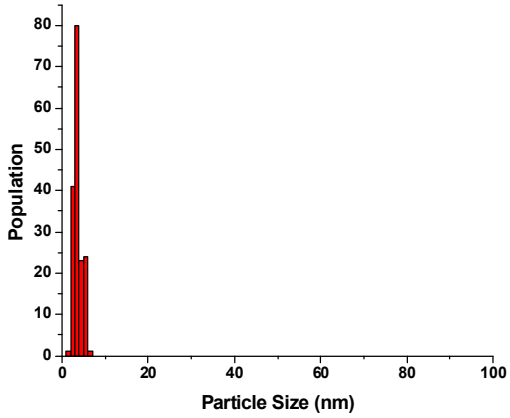
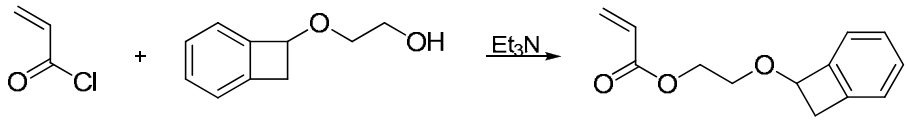
sonicated 20 min, allowed to sit overnight, and sonicated another 20 min. The carbon grids were prepared by dipping an Ultrathin Carbon Type-A 400 Mesh Copper Grid into the nanoparticle solutions three times and allowing to dry. Images of the particles were taken at varying magnification levels.



Other products:



2
LTCL 1

2-(1,2-dihydrocyclobutabenzen-1-yloxy)ethyl acrylate, 1a 2-(1,2-dihydrocyclobutabenzen-1-yloxy)ethanol, **1**, (1.38 g, 8.38 mmol) was added to a 250-mL round bottom flask and dissolved in dichloromethane (69 mL). Triethylamine was added (3.39 g, 33.5 mmol) at once to the derivative, and the contents of the flask were cooled to 0 ^{o}C. Acryloyl chloride (2.28 g, 25.2 mmol) was added slowly to the flask which turned the solution yellow. The reaction mixture was stirred at room temperature for 2 h. It was quenched with water (10 mL) and washed once with water (100 mL) and once with sodium bicarbonate (100 mL). The organic phase was dried over Na_2SO_4 and concentrated to yield a red-brown crude product. A short filtration column was performed using hexanes/ethyl acetate (3:1) as the eluting

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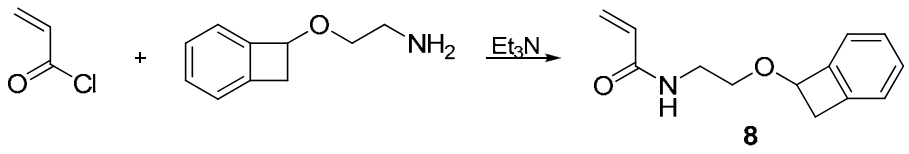
solvents, yielding the acrylate benzocyclobutene derivative, (**1a**), (1.48 g, 81 %) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.22-7.08 (m, 4H, ArH), 6.35 (dd, 1H, CH), 6.13-6.03 (m, 1H, CH_2), 5.68 (dd, 1H, CH_2), 4.98 (s, 1H, CH), 4.27 (dd, 2H, CH_2), 3.80-3.65 (m, 2H, CH_2), 3.35 (dd, 1H, CH_2), 3.05 (d, 1H, CH_2).

This monomer unit was prepared but the copolymerization did not lead to controlled polymers for further use.



8

LTCL 2

N-(2-(1,2-dihydrocyclobutabenzen-1-yloxy)ethyl)acrylamine, 2a. 2-(1,2-dihydrocyclobuta-benzen-1-yloxy)ethanamine, **4**, (0.49 g, 3.00 mmol) was added to a 100-mL round bottom flask and dissolved in dichloromethane (24.5 mL). Triethylamine was added (0.61 g, 6.01 mmol) at once to the derivative and the contents of the flask were cooled to 0 ^{o}C. Acryloyl chloride (0.33 g, 3.60 mmol) was added slowly to the flask which turned the solution yellow. The reaction mixture was stirred at room temperature for 3 h. It was quenched with water (10 mL) and washed once with water (50 mL) and once with saturated sodium bicarbonate (50 mL). The organic phase was dried over Na_2SO_4 and concentrated to yield an orange-yellow crude product. A short column was performed using hexane/ethyl acetate (1:1). The monomer was concentrated to yield the acrylamide benzocyclobutene derivative, (**2a**), (0.51 g, 78 %) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.31-7.11 (m, 4H, ArH), 6.26 (m, 1H, CH), 6.06 (m, 1H, CH_2), 5.67 (m, 1H, CH_2), 5.10 (m, 1H, CH), 3.63 (m, 4H, CH_2), 3.54 (m, 1H, CH_2), 3.40 (m, 1H, CH_2), 3.06 (d, 1H, CH_2).

This monomer unit was prepared but the copolymerization did not lead to controlled polymers for further use.