Supporting Information For

Programmable Microcapsules from Self-Immolative Polymers

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I. General Experimental Details

Unless otherwise stated, all starting materials and chemicals were obtained from Sigma-Aldrich commercial suppliers and used without purification. Anhydrous dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were obtained from Aldrich (Aldrich sure seal, 99.9%). Dry dichloromethane was obtained from an Anhydrous Engineering Solvent Delivery System (SDS) equipped with activated alumina columns. The commercial polyurethane (PU) prepolymer, Desmodur® L 75, was purchased from Bayer Material Science and used as received. Desmodur® L 75 is a prepolymer solution in ethyl acetate with a reported equivalent weight of 315 g and an isocyanate content of 13.3 ± 0.4 wt%

Analytical gel permeation chromatography (GPC) analyses were performed with a Waters 515 HPLC pump, a Viscotek TDA Model 300 triple detector array, a Thermoseparations Trace series AS100 autosampler, and a series of 3 Waters HR Styragel columns (7.8 × 300mm, HR3, HR4, and HR5) in THF at 30 °C. The GPC was calibrated using monodisperse polystyrene standards. DELETED PREPARATORY GPC SECTION.

Flash column chromatography was conducted with silica gel 60 (230-400 mesh) from Silicycle. Melting points were obtained using an electrothermal melting temperature apparatus (Mel-Temp, Model 1001). ^{1}H and ^{13}C NMR spectra were obtained using a Varian 400 MHz spectrometer in the VOICE NMR laboratory at the University of Illinois; the residual solvent protons were used to reference the chemical shift. Coupling constants (*J*) are reported in Hertz (Hz), and splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad).

UV-vis absorption spectra were recorded using a Shimadzu UV-2401PC. Quartz cells with a path length of 1 cm were used. UV irradiation of samples dissolved in THF was performed with a Model UVG-11 Mineralight lamp (short wave UV – 254 nm). Mass spectra were obtained through the Mass Spectrometry Facility, SCS, University of

Illinois and elemental analyses were performed by the University of Illinois Micro-Analytical services.

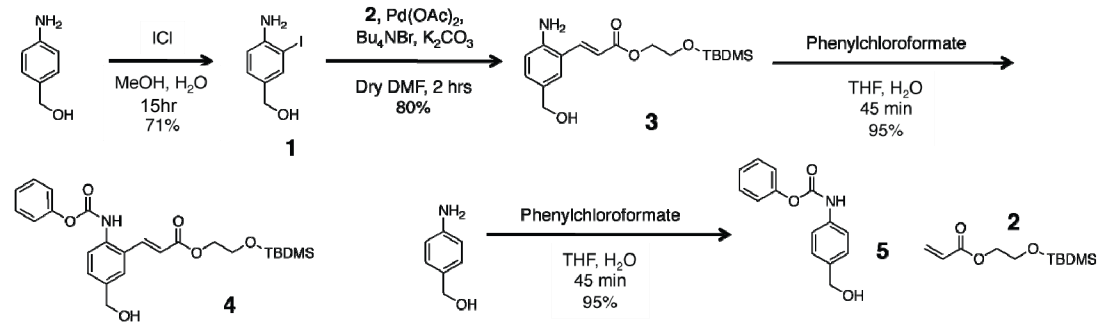
Microcapsules were imaged using a Leica DMR Optical Microscope at various magnifications, and ImageJ software was used to measure capsule diameters from acquired images for each batch of capsules produced. Scanning electron microscopy (SEM, Philips XL30 ESEM-FEG) was used to image microcapsules mounted on carbon-tape covered stages. SEM images were acquired after sputter-coating the samples with gold-palladium.

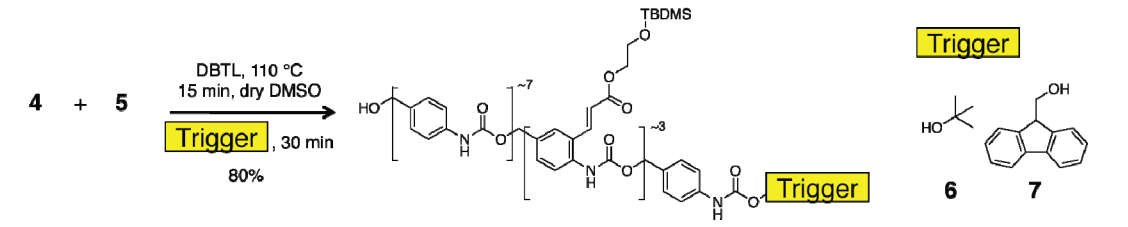
Thermogravimetric analysis was performed on a Mettler-Toledo TGA851^{e}, calibrated with indium, aluminum, and zinc standards. Unless otherwise indicated, a heating rate of 10 °C·min^{-1} was used in an atmosphere of nitrogen. For each experiment, the sample (ca. 5 mg) was accurately weighed (± 0.02 mg) into an alumina crucible. The mass loss was recorded during a heating cycle over the temperature range of 25 °C to 650 °C for a dynamic experiment.

A Hewlett-Packard 5890 Series II gas chromatograph (**GC**, GMI, Inc.) with a 530 μm internal diameter capillary column and flame ionization detector was used to quantify the core materials in microcapsules. The temperature was linearly ramped at a heating rate of 7 °C/min. GC samples were prepared as described in below. Control tests of pure ethyl phenylacetate, ethanol, THF and piperidine were performed for comparison.

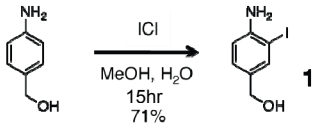
Abbreviations. DCM – dichloromethane, DMF – dimethylformamide, EtOAc – ethyl acetate, Hex – n-hexanes, THF – tetrahydrofuran, ACN – acetonitrile, MeOH – methanol, HCl – hydrochloric acid, Pip – piperidine, EPA – ethyl phenylacetate, NaOH – sodium hydroxide, AcOH – acetic acid, DMSO – dimethylsulfoxide, DBTL – dibutyltin dilaurate, TFA – trifluoroacetic acid, RT – room temperature – ca. 25 °C.

II. Synthetic Details



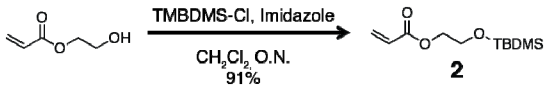


(4-amino-3-iodophenyl) methanol (1)



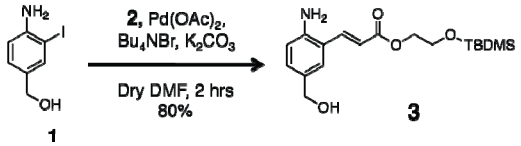
Compound **1** was synthesized using a modified literature procedure [i]. A solution of $CaCO_3$ (6.01 g, 60 mmol) in water (128 mL) was added to a solution of 4-amino-benzyl-alcohol (4.93 g, 40 mmol) in methanol (120 mL), followed by a solution of ICl (6.65 g, 41.0 mmol) in methanol (64 mL). The mixture was stirred at room temperature for 15 h, and then diluted with ether and quenched with water. The aqueous layer was extracted with ether and the combined organic phases were dried with Na_2SO_4. After filtration and removal of the Na_2SO_4, the product was purified by column chromatography (1:4 EtOAc, Hex, R_f 0.2). This product ((4-amino-3-iodophenyl)methanol) was identified by spectral comparison with literature data[ii]. ICl is extremely caustic and has a low viscosity. It should be handled with caution.

2-9[tert-Butyl(dimethyl)silyl]oxy)ethyl acrylate (2)



Compound **2** was synthesized using an unmodified literature procedure[iii]. Into a three-neck-flask under a stream of nitrogen, a stirring bar, 2-hydroxyethyl acrylate (23.2 g 0.20 mol) in THF (800 mL) was placed, and two equivalents of imidazole (27.2 g, 0.40 mol) were added. After cooling to 0 °C by immersing the reaction flask in an ice-water bath, *t*-butyldimethylchlorosilane (30.12 g, 0.20 mol) in CH_2Cl_2 (600 mL) was added slowly under stirring. After 12 h the resultant white salt precipitate was removed by filtration, and the solvent was evaporated by rotary evaporation. The residue was further purified by flash chromatography (EtOAc /Hex 1:3 (v/v), R_f = 0.76) to give the desired product (91.0%, 40.8 g). The product was identified by spectral comparison with literature data.[iii]

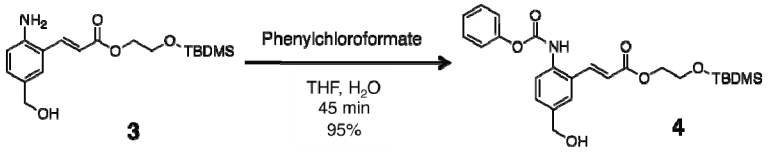
2-((tert-butyldimethylsilyl)oxy)ethyl 3-(2-amino-5-(hydroxymethyl)phenyl)acrylate (3)



Compound **3** was synthesized using a modified literature procedure[ii]. Compound **1** (10.0 g, 400 mmol) was dissolved in 75 mL dry DMF under N_2 atmosphere. $Pd(OAc)_2$ (450 mg, 2.00 mmol), K_2CO_3 (27.5 g, 200 mmol), *n*Bu_4NBr (16 g, 50 mmol), and compound **2** (14 g, 60 mmol) were added. The reaction mixture was then heated to 60 °C and stirred for 1.5 hours and was monitored by TLC (EtOAc:Hex 40:60). Allowing the reaction to proceed any longer than the minimum time required for completion leads to multiple products and was thus avoided. After cooling to RT, the reaction mixture was diluted with EtOAc, washed twice with brine, and the organic layer dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude product was purified by column chromatography on silica gel (EtOAc:Hex 30:70, R_f = 0.45) to yield the desired product as a yellow/green oil (11.3 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.1 (s, 6H), 0.91 (s, 9H), 3.88 (q, 2H, *J* = 2.5 Hz), 4.27 (q, 2H, *J* = 2.5 Hz), 4.51 (s, 2H), 6.41 (d, *J* = 16 Hz,

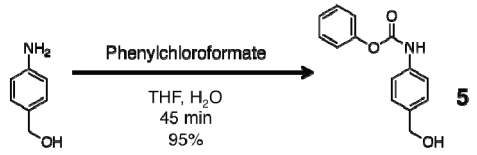
1H), 6.71 (m, 1H), 7.25 (m, 3H), 7.401 (m, 3H) 7.51 (d, J = 2 Hz, 1H) 7.90 ppm (d, J = 16 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ –5.3, 25.8, 61.3, 64.8, 65.8, 116.9, 117.8, 119.5, 127.0, 130.7, 131.3, 140.0, 145.1, 167.2. HRMS-EI (*m/z*): calcd for $C_{18}H_{30}NO_4Si$ [M+], 352.1944; found, 352.1932.

2-((tert-butyldimethylsilyl)oxy)ethyl 3-(5-(hydroxymethyl)-2 ((phenoxycarbonyl)amino)phenyl)acrylate (4)



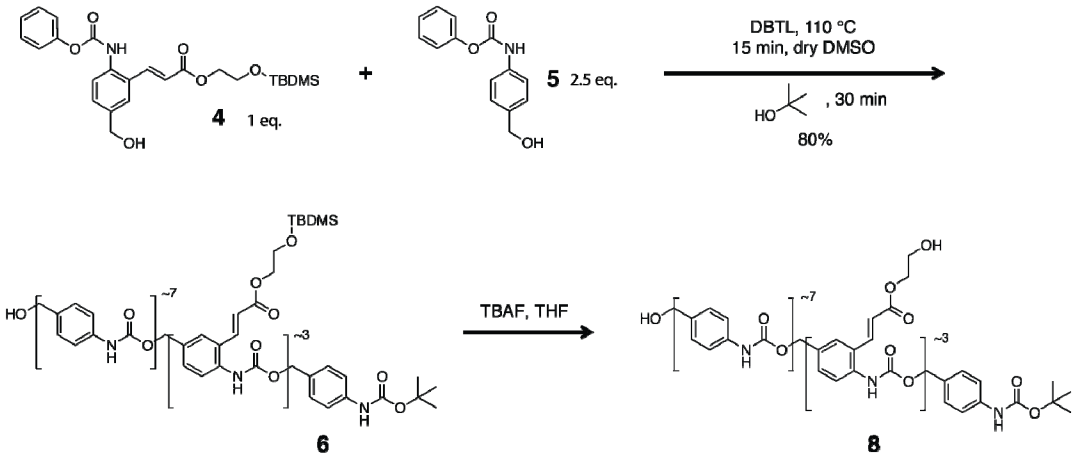
Compound **4** was synthesized using a modified literature procedure[ii]. Compound **3** (6.0 g, 17 mmol) was suspended in a 90 mL mixture of THF : sat. $NaHCO_3$: water (ratio 2:2:1) after which phenylchloroformate (2.2 mL, 19 mmol) was added dropwise over 5 min. The reaction was monitored to completion by TLC (EtOAc:Hex 30:70). EtOAc was then added, and the organic phase washed twice with saturated NH_4Cl solution. The solvents were removed by rotary evaporation, and the crude product was crystallized using 50:50 EtOAc:Hex. The product was placed in Hex and the suspension was heated and EtOAc was added, while continuting heating, until the product dissolved. The desired product was filtered, yielding a light yellow crystalline solid (7.9 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.1 (s, 6H), 0.91 (s, 9H), 3.90 (q, 2H, J = 2.5 Hz), 4.31 (q, 2H, J = 2.5 Hz), 4.7 (s, 2H), 6.47 (m, 1H), 7.15 (m, 1H) 7.65 (d, J = 2 Hz, 1H) 7.84 ppm (d, J = 16 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ -5.3, 25.8, 61.3, 64.3, 66.1, 120.6, 121.50, 125.57, 125.7, 129.4, 129.5, 134.9, 139.2, 150.4, 152.2, 166.71, HRMS-EI (*m/z*): calcd for $C_{25}H_{34}NO_6Si$ [M+], 472.2155; found, 472.2147.

Phenyl (4-(hydroxymethyl)phenyl)carbamate (5)



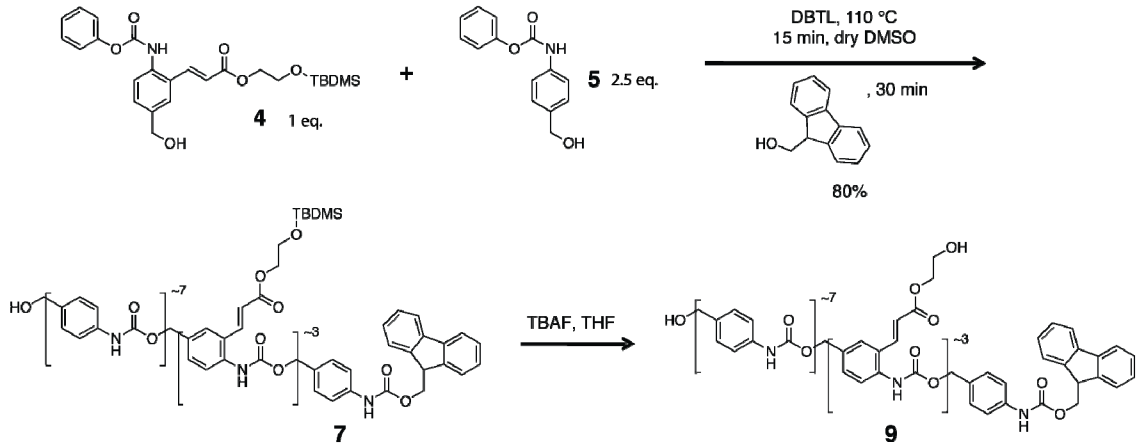
Compound **5** was synthesized using a modified literature procedure[ii]. Commercially available 4-aminobenzyl alcohol (1.0 g, 8.1 mmol) was suspended in a 15 mL mixture of THF : sat. $NaHCO_3$: water (ratio 2:2:1) and Phenylchloroformate (1.04 mL, 8.29 mmol) was added dropwise over 5 min. The reaction was monitored to completion by TLC (EtOAc:Hex 1:1). EtOAc was then added, and the organic phase washed twice with saturated NH_4Cl solution. The solvents were removed by rotary evaporation, and the crude product was purified by crystallization in 30:70 EtOAc:Hex, yielding the desired product as a white solid (1.87 g, 95%). The product was placed in Hex and the suspension was heated and EtOAc was added, while continuting heating, until the product dissolved. This product was identified by spectral comparison with literature data.[2]

III. Polymer Synthesis



Polymer 6. Compound **4** (2.00 g, 4.25 mmol), compound **5** (2.41 g, 9.92 mmol), and DBTL (420 ⌈L, 0.71 mmol) were added via syringe to dry DMSO (8 μL), which was preheated to 110 °C under N_2 atmosphere. The reaction mixture was stirred for 15 min after which *t*-butanol (6.8 mL, 70 mmol) in dry DMSO (6 mL) was then added. The reaction mixture was stirred for additional 30 min and was then allowed to cool to RT. The polymer was precipitated from methanol, filtered, and was dried under reduced pressure (300 mtorr) at RT for 3 h. Polymer **6** was obtained as a greenish-yellow powder (2.5 g). ^{1}H NMR (400 MHz, DMSO) δ 0.034 (s, 33H), 0.77 (s, 49H), 1.05 (s, 9H) 3.74 (m, 9 H,), 4.15 (m, 9H), 5.01 (s, 22H), 5.09 (s, 9H), 6.52 (d, *J* = 16 Hz, 7H), 6.71 (m, 7H), 7.12 (m, 20H), 7.22 (m, 19H), 7.28 (d, 26, H, *J* = 6 Hz), 7.48(d, 26H, *J* = 6 Hz) 7.55

(m, 7H) 7.90 (m, 7H).



Polymer 7. Compound **4** (3.5 g, 7.4 mmol), compound **5** (4.225 g, 17.37 mmol), and DBTL (742.1 ⌈L, 0.71 mmol) were added via syringe to dry DMSO (12 mL), which was preheated to 110 °C under N_2 atmosphere. The reaction was stirred for 15 min after which 9-fluorenemethanol (9.74 g, 490 mmol) in dry DMSO (6 mL) was then added. The reaction mixture was stirred for additional 30 min and was then allowed to cool to RT. The polymer was precipitated from methanol, filtered, and dried under reduced pressure (300 mtorr) for 3 h at RT. Polymer **7** was obtained as a dark green powder (5.2 g). ^{1}H NMR (400 MHz, DMSO) δ 0.01 (s, 34H), 0.79 (s, 52H), 3.74 (m, 9 H), 3.9 (m, 2H), 4.15 (m, 9H), 4.37 (d, 2H, J = 2.5 Hz), 5.01 (s, 22H), 5.05 (s, 8H), 6.49 (d, *J* = 16 Hz, 6H), 6.69 (m, 7H), 6.92(m, 2H), 6.98 (m, 2H) 7.10 (m, 20H), 7.18 (m, 19H), 7.25 (d, 24H, *J* = 6 Hz), 7.38 (d, 24H, *J* = 6 Hz) 7.52 (m, 8H) 7.72 (m, 2H), 7.88 (m, 7H).

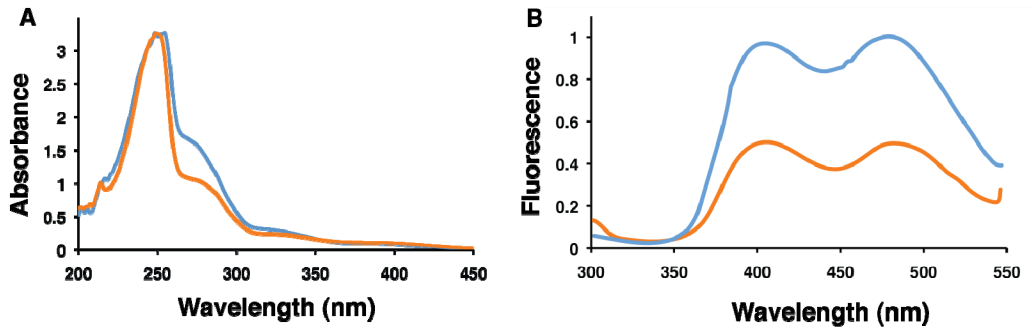


Figure S-4. UV-vis absorption and emission spectra of polymers **6** and **7**. (a) Absorption spectra in THF of **6** (Boc, blue) and **7** (Fmoc, orange). (b) Emission spectrum (λ_{ex} = 290 nm) of **6** and **7** in THF.

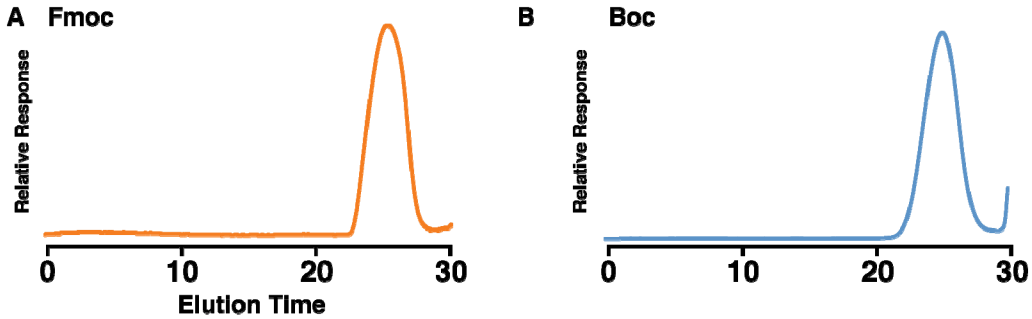


Figure S-3. GPC traces of synthesized polymers. Chromatograms of polymers **6** & **7**. a) the RI signal of Fmoc capped polymer (**7**), M_n = 13,300, M_w = 19,100, PDI = 1.44. b) the RI signal of Boc capped polymer (**7**), M_n = 12,900 M_w = 21,800, PDI = 1.68.

General Procedure for Removal of TBDMS

Polymer (4 g) was dissolved in THF (100 mL), and the solution was cooled to 0 °C by immersing the reaction flask in an ice-water bath. Afterward TBAF (40 mL, 1 M solution in THF) was dropwise. The stirred reaction was allowed to warm to RT and continued stir for 1 h. Occasionally, polymer precipitation was observe; in these cases MeOH was added dropwise until polymer redissolved. The reaction volume was reduced to 50 mL by rotary evaporation, and the polymer was precipitated by addition of excess MeOH, filtered and dried under reduced pressure (300 mtorr) for 3 h at RT. Deprotected polymer was obtained as a dark green powder. Removal of the TBDMS group was verified by ^{1}H-NMR.

Polymer 8: ^{1}H NMR (400 MHz, DMSO) δ 0.051 (s, 1H), 0.77 (s, 1H), 1.05 (s, 9H) 3.62 (m, 9 H,), 4.17 (m, 9H), 5.02 (s, 23H), 5.12 (s, 9H), 6.45 (d, *J* = 16 Hz, 8H), 6.67 (m, 8H), 7.20 (m, 22H), 7.21 (m, 21H), 7.23 (d, 26H, *J* = 6 Hz), 7.49 (d, 26H, *J* = 6 Hz) 7.57 (m, 8H) 7.87 (m, 8H).

Polymer 9: ^{1}H NMR (400 MHz, DMSO) δ 0.02 (s, .05H), 0.81 (s, 1H), 3.61 (m, 9 H), 3.9 (m, 2H), 4.12 (m, 9H), 4.38 (d, 2H, J = 2.5 Hz), 5.01 (s, 22H), 5.05 (s, 8H), 6.49 (m, 6H), 6.69 (m, 7H), 6.92 (m, 2H), 6.98 (m, 2H) 7.13 (m, 21H), 7.19 (m, 20H), 7.25 (d, 24H, *J* = 6 Hz), 7.38 (d, 24H, *J* = 6 Hz) 7.49 (m, 8H) 7.75 (m, 2H), 7.89 (m, 7H).

III. Pre-Polymer Synthesis

This procedure is modified from a previously published method[iv]. Deprotected polymer (1.2 g) was added to cyclohexanone (20 mL) from a freshly opened bottle of cyclohexanone. The solution was sonicated for 2 h to allow for dissolution of the polymer. If required, MeOH (0.05 mL) was added to assist in dissolving. [Note: We have found that cyclohexanone's hygroscopicity leads to foaming of the reaction product. We used a freshly opened bottle to avoid this problem; alternatively one could distill the cyclohexanone prior to use.] The solution of polymer in cyclohexanone was added to a flame-dried 3-neck round-bottomed flask containing cyclohexanone (480 mL) under N_2. The solution was cooled to 0 °C by immersion in an ice-water bath, and 2,4-TDI (30 mL, 36.4 g, 209 mmol) was added dropwise to the rapidly stirred solution. The reaction was allowed to proceed overnight and was then heated to 80 °C for 4 h. The remaining TDI and cyclohexanone were removed by distillation under vacuum (2 torr at 100 °C). The distillation typically took 3-4 h to reach completion. The distillation was halted at the moment the solution viscosity arrested the stir-bars rotation. Further distillation resulted in a solid product that could not be redissolved.

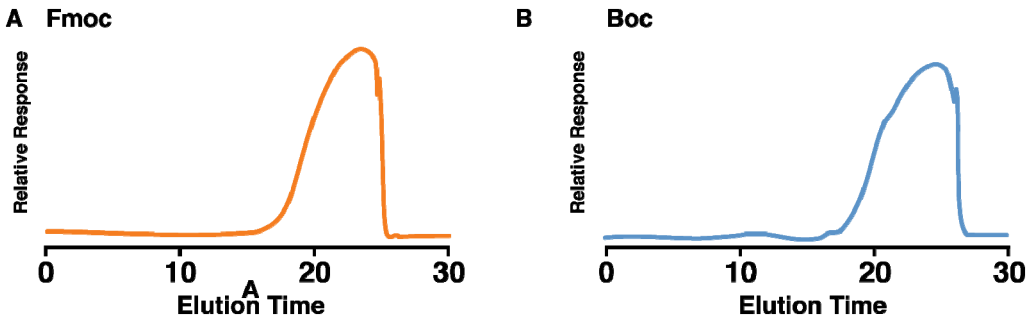


Figure S-5. GPC trace of 2,4-TDI reacted polymers. Chromatograms of polymers **8** & **9**. a) the RI signal of Fmoc capped polymer, M_n = 15,600, M_w = 47,400, PDI = 3.01 (**9**), b) the RI signal of Boc capped polymer (**8**). M_n = 17,300, M_w = 42,900, PDI = 2.48.

V. Microcapsule Synthesis

As depicted in Figure S-6, deionized water (15 mL) and gum arabic (2.25 g) surfactant were mixed at RT in a 60 mL beaker. The beaker was suspended in a temperature-controlled water bath on a programmable hot plate with an external temperature probe. The solution was agitated with a digital mixer (Eurostar, IKA Labortechnik), driving a three-bladed propeller for 3 h before beginning encapsulation to allow dissolution of the gum arabic. To facilitate ease, this step was typically performed several hours prior to encapsulation.

To prepare the microencapsulation solution, the pre-polymer (2.0 g) was dissolved into EPA (8 mL) via vigorous stirring and application of a heat gun. This step typically required 1 h for complete dissolution. This mixture was then slowly poured into the gum arabic solution agitated at a rate of 400 rpm. The agitation rate was then accelerated to 1200 rpm, and the water bath was heated to 70 °C at a rate of 7 °C/min. At 50 °C, 1,4-butanediol (1.8 g) was added dropwise, to the emulsion as a chain extender. After 1.5 h of agitation, the mixer and hot plate were switched off. In this process, a polyurethane shell formed at the interface between the aqueous and oil phases. Once cooled to ambient temperature, the suspension of microcapsules was rinsed with deionized water and was filtered using a Buchner funnel and the house vaccum line. Microcapsules were air-dried for 48 h before further analysis. The average yield of microcapsules was about 60 wt %. The microcapsules were found to be composed of 70% core solvent by TGA analysis.

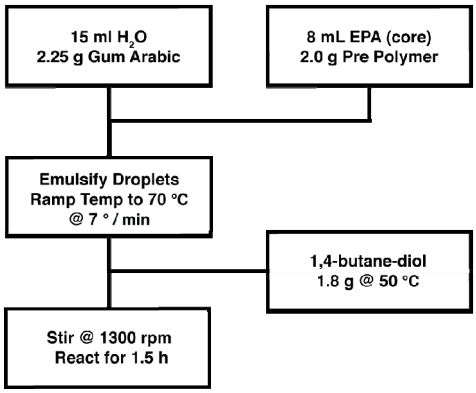


Figure S-6. Flow chart depicting microcapsule synthesis.

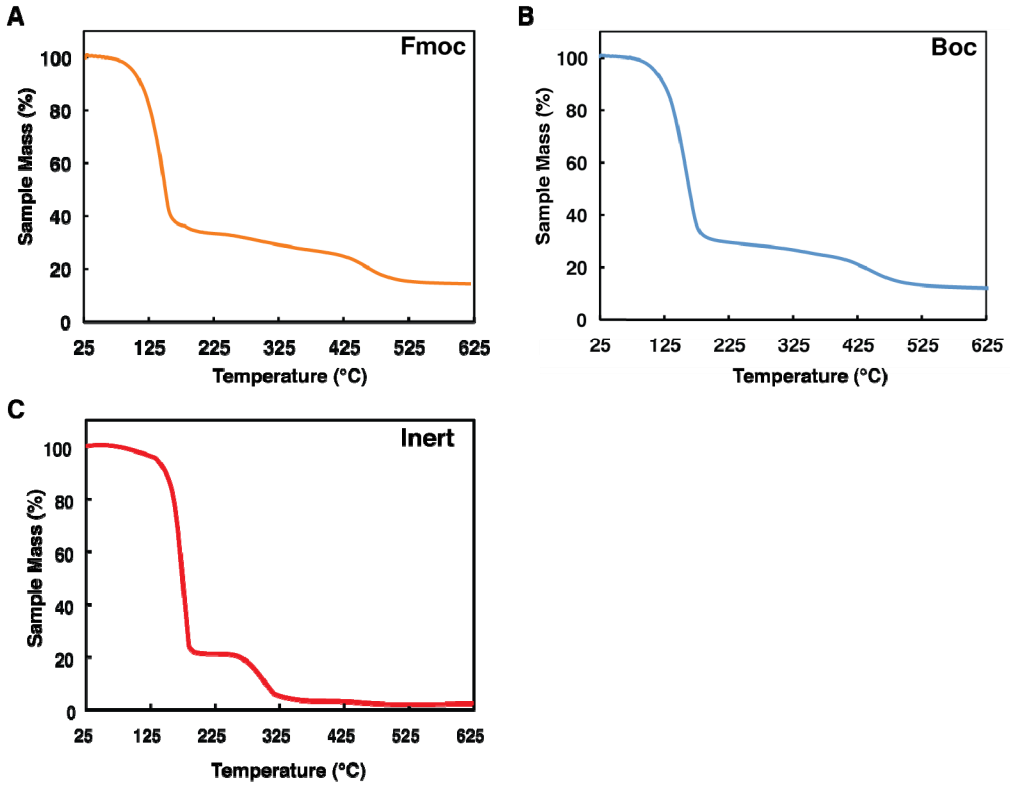


Figure S-7. Dynamic TGA traces of Fmoc microcapsules (orange), Boc microcapsules (blue line), and EPA capsules (red, average diameter size = 30 microns, 2 months after preparation).

General Procedure for GC Analysis of Microcapsule Release

Triplicate samples of 0.5 g of microcapsules were each placed in separate vials containing 5 mL of triggering solution. Solutions were either 4 M HCl w/ 10% EtOH or

in THF w/ 5% piperidine. The microcapsule shell-wall was composed of TDI-reacted polymer **8** (Boc), TDI-reacted polymer **9** (Fmoc), or Desmodur L75 (Control). Aliquots (0.1 mL) were extracted at designated times with minimum agitation of the microcapsules that typically rested at the bottom of the vial. A small Kimwipe ball was placed in the aliquot and 5 µL was extracted slowly via syringe in order to filter out any remaining microcapsules without manually rupturing them. The 5 µL was then analyzed by GC using a 25-250 °C temperature sweep with a ramp rate of 7 °C/ min. Typical GC traces are shown below. Identical samples were made where the capsules were manually ruptured by repeated compression of a solution of capsules through a 0.45 µm syringe filter, and their GC values were used as the 100% value in all graphs.

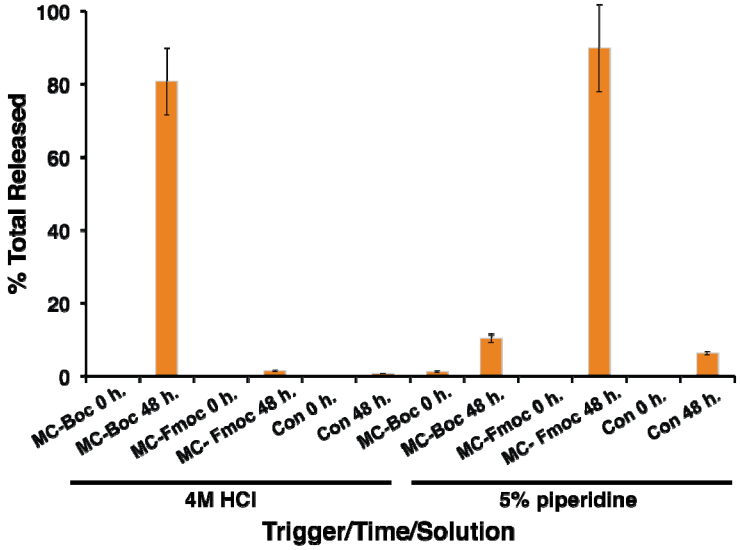


Figure S-8. Complete Data Set from Figure 5a. All capsules were measured for rupture upon immediate exposure to triggering solution and again after 48 h.

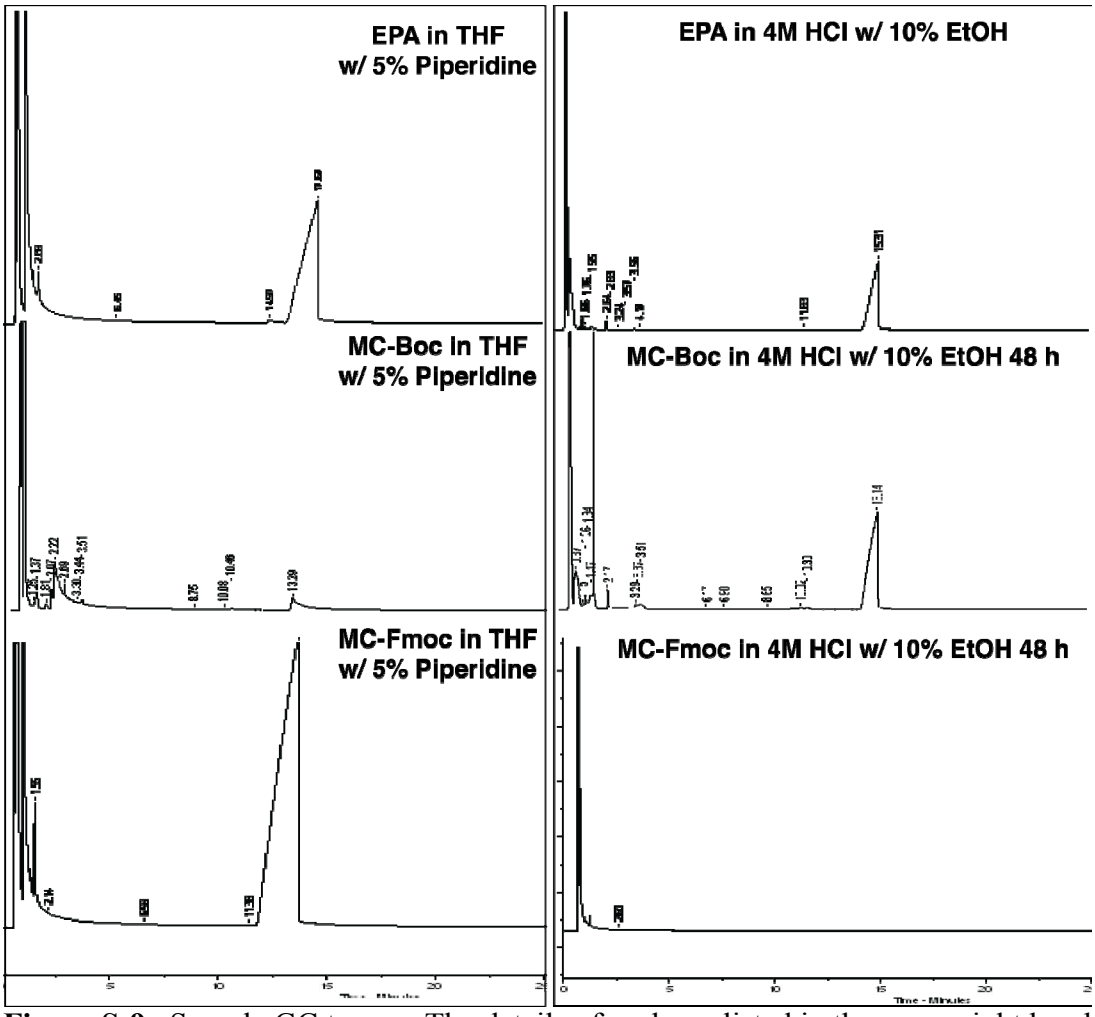


Figure S-9. Sample GC traces. The details of each are listed in the upper right hand corner of each trace.

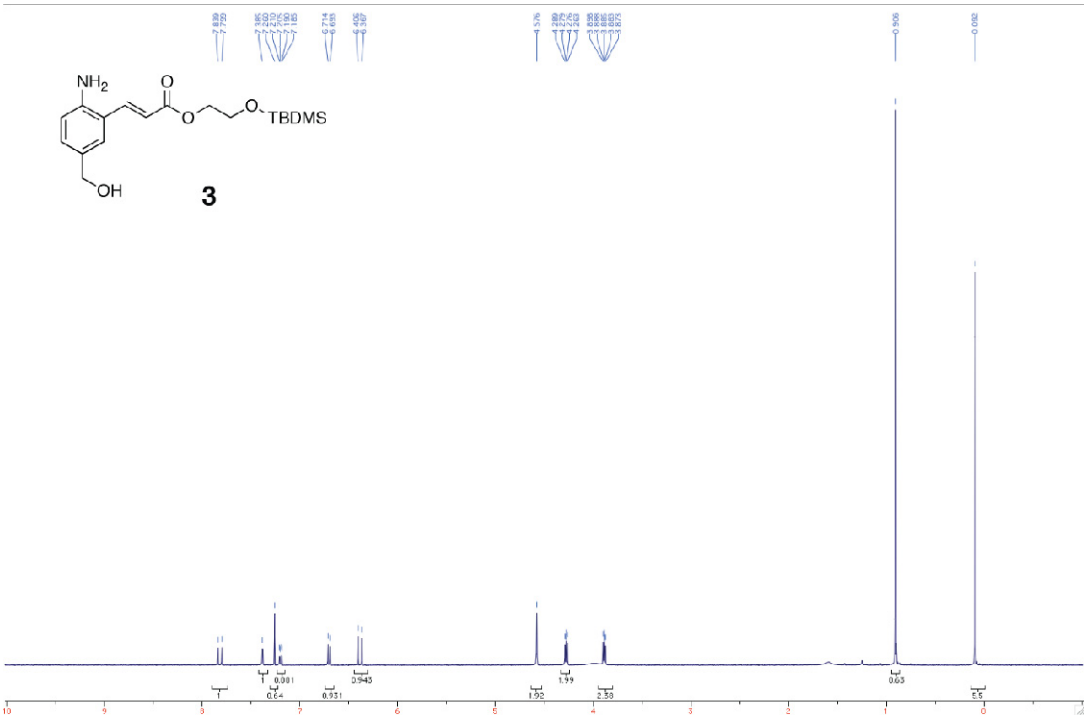


Figure S-10. ^{1}H-NMR of Product **3**.

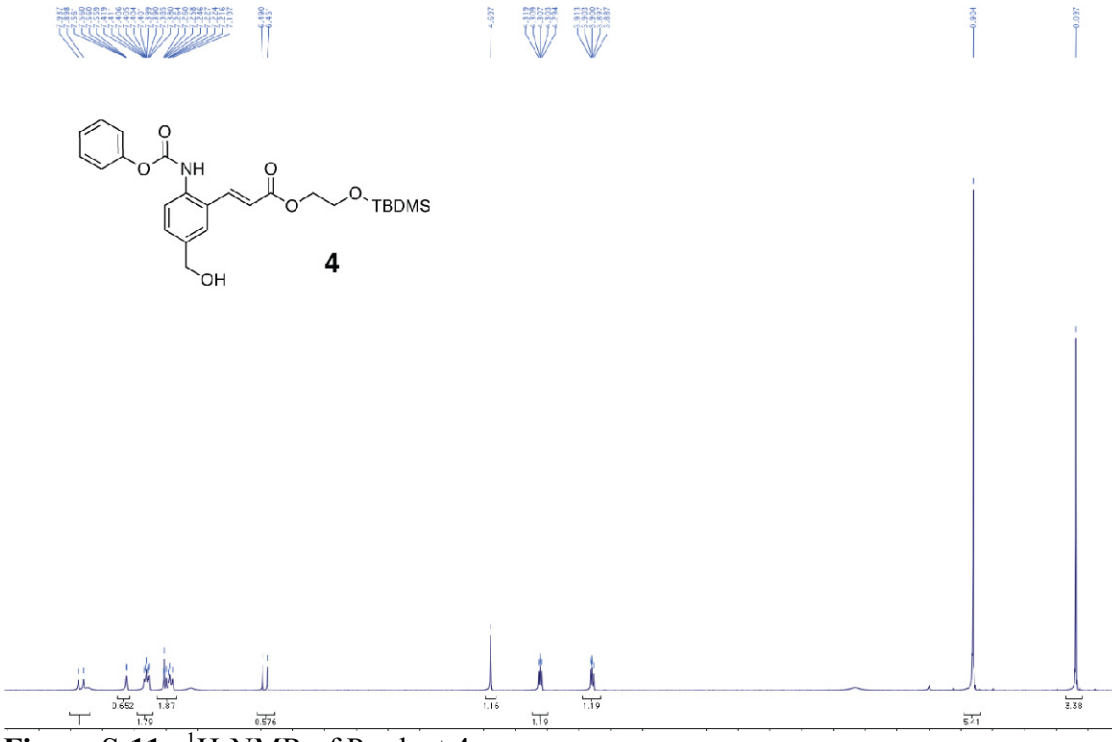


Figure S-11. ^{1}H-NMR of Product **4**.

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[iii] Yin, M.; Habicher, W. D.; Voit, B. *Polymer* **2005**, *46*, 3215-3222.

[iv] Yang, J.; Keller, M. W.; Moore, J. S.; White, S. R.; Sottos, N. R. *Macromolecules* **2008**, *41*, 9650-9655.