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Supporting Information

Covalent Attachment and Release of Small Molecules from Functional Polyphenylene Dendrimers

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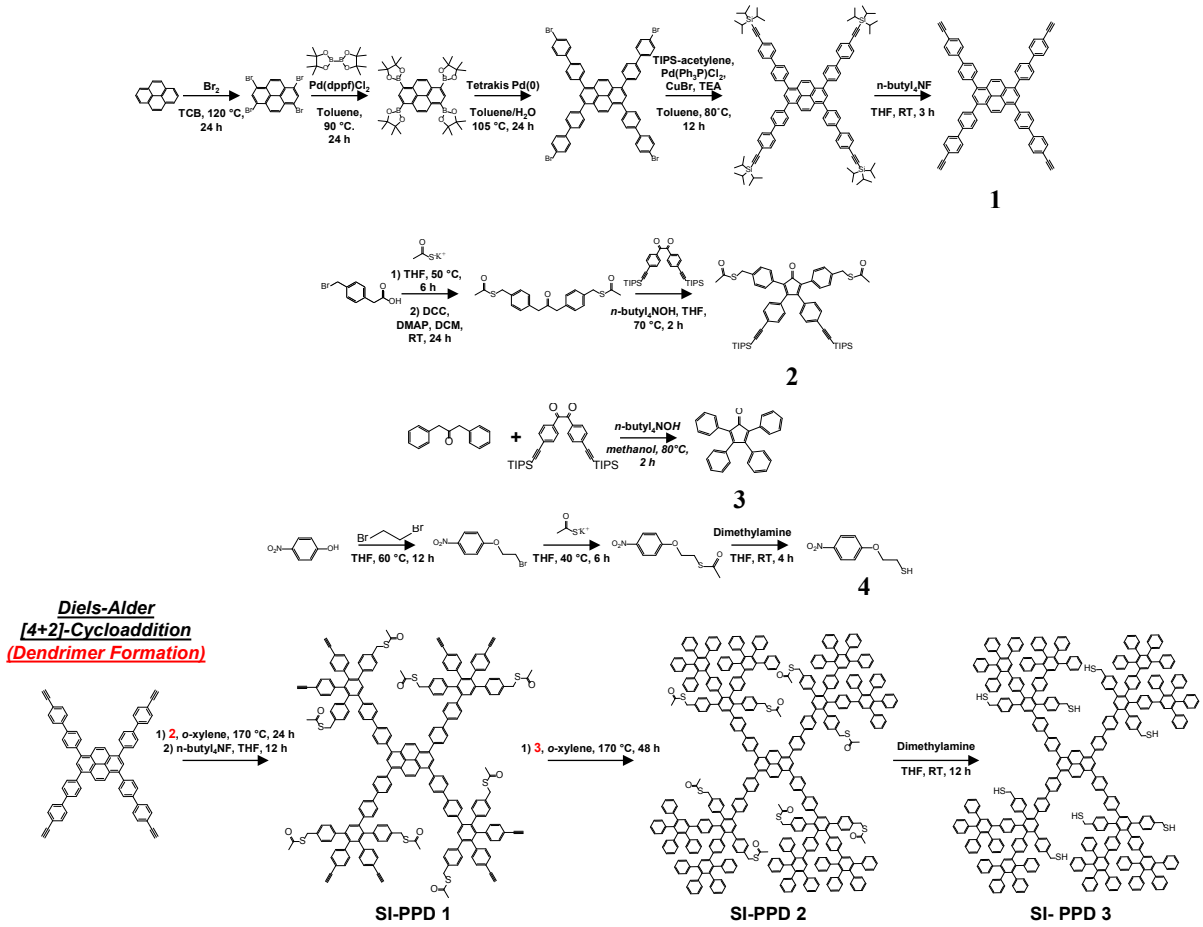
Experimental Section

Scheme 1: Synthesis of pyrene-based core, functional cyclopentadienones, and polyphenylene dendrimers.

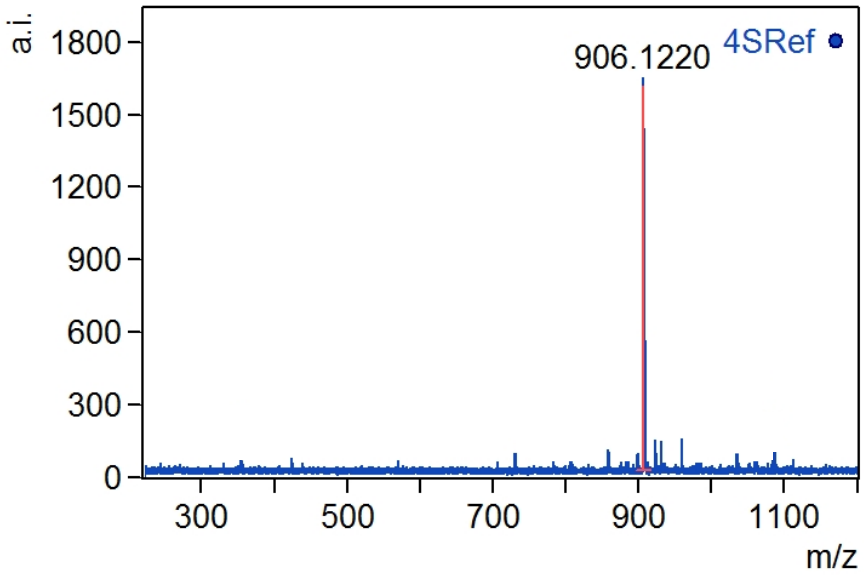


Techniques: ^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX250, AC300, AMX500, and AMX700 NMR spectrometers using the residual proton of the solvent or the carbon signal of the deuterated solvent as an internal standard. MALDI-TOF mass spectra were measured using a Bruker Reflex II, which was calibrated against poly(ethylene glycol) (3000 g/mol). Samples for MALDI-TOF MS were prepared by mixing the analyte with the matrix (dithranol) in THF in a ratio of 1:50. In some cases, cationization by mixing the matrix with potassium trifluoroacetate (K) or silver trifluoroacetate (Ag) was performed. All reported MALDI-TOF MS measurements were within the experimental error, characteristic for the applied technique. UV-Vis absorbance spectra were recorded on a Perkin-Elmer Lambda 25 spectrophotometer.

Materials: *n*-Butylammonium hydroxide (1 M sol. in methanol), methyl bromide (1 M sol. in THF), and dimethyl amine (1 M sol. in THF) were purchased from Sigma Aldrich. Dialysis tubing (benzoylated dialysis tubing, average flat width 9 mm, molecular weight cut-off of 2,000 g/mol) was purchased from Sigma Aldrich. All other chemicals were purchased from Sigma Aldrich and used as received unless otherwise stated.

***Synthesis of 1,3,6,8-tetrakis(4'-ethynyl-[1,1'-biphenyl]-4-yl)pyrene core (1)*:**

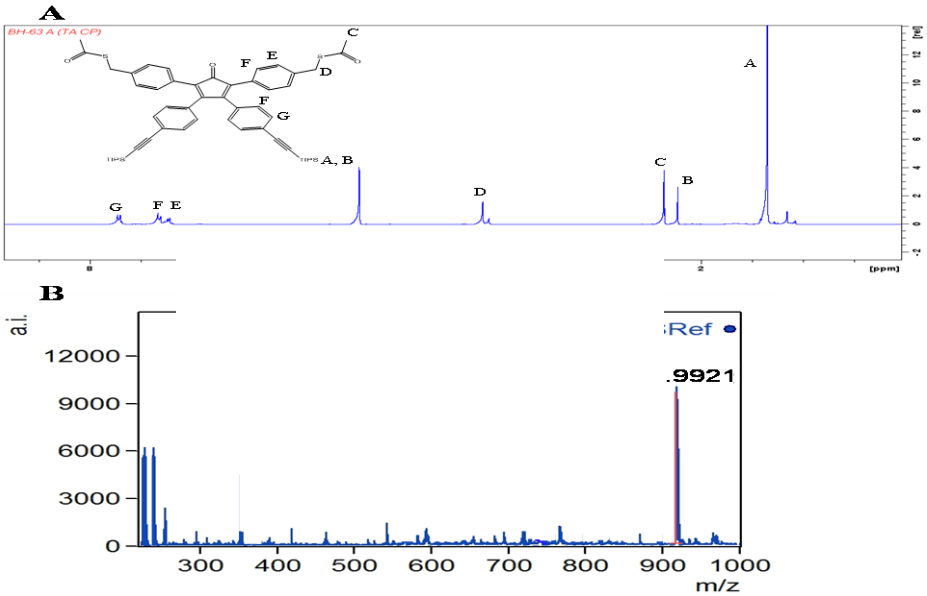
The synthetic scheme for 1,3,6,8-tetrakis(4'-ethynyl-[1,1'-biphenyl]-4-yl)pyrene (**1**) is shown in **Scheme 1**. A 2 M solution of pyrene in trichlorobenzene was reacted with bromine (16 M) at 120 °C for 24 hours under an argon atmosphere. The tetra-brominated pyrene precipitated in the solution, was filtered, washed with diethyl ether, and dried as a white powder in 78 % yield. Solid state MALDI-TOF mass spectrometry confirmed the molecular weight of the product to be 513.93 g/mol ($[M/Z]_{theor.}$= 513.72 g/mol). The tetra-bromopyrene (1.2 g, 2.34 x 10^{-3} mol) was reacted with bis(pinacolato)diboron (2.9 g, 1.14 x 10^{-2}) with Pd(dppf)Cl_2 (98 mg, 1.2 x 10^{-4} mol) and potassium acetate (2.3 g, 2.32 x 10^{-2} mol) in toluene (45 mL) at 90 °C for 24 h under an argon atmosphere. The solution was washed with water, extracted with dichloromethane, and the organic phase was dried by rotary evaporation. The crude product was purified by silica gel column chromatography using hexane:toluene (60:40 vol. %) as the eluent to achieve a bright yellow powder in 72 % yield. ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 1.2 (48 H), 7.5 (4 H), and 7.7 (2 H) ppm. MALDI-TOF found [M/Z] = 705.13 g/mol. with theoretical [M/Z] = 706.42 g/mol. This compound (0.5 g, 7.10 x 10^{-4} mol) underwent Suzuki coupling with 4,4'-dibromobiphenyl (2.2 g, 7.05 x 10^{-3} mol) with tetrakis(triphenylphosphine)palladium (0) (46 mg, 4.10 x 10^{-5} mol) and potassium carbonate (0.2 g, 1.45 x 10^{-2} mol) as the catalyst in toluene/H_2O (20 mL each) at 105°C for 24 h under an argon atmosphere. The organic phase collected and dried by rotary evaporation. The product was purified by column chromatography successively using hexane, and hexane:toluene (75:25 vol. %) as the eluents to afford 1,3,6,8-tetrakis(4'-bromo-[1,1'-biphenyl]-4-yl)pyrene as a yellow powder in 86 % yield. ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 7.2 (16 H), 7.4 (16H), 7.7(4H), and 8.2 (2H) ppm. MALDI-TOF found [M/Z] = 1122.15 g/mol. with theoretical [M/Z] = 1121.97 g/mol. The tetrabiphenyl functionalized pyrene (0.5 g, 4.52 x 10^{-4} mol) underwent Sonogashira coupling with TIPS-acetylene (0.8 mL, 3.36 x 10^{-3} mol) with Pd(Ph_3P)Cl_2 (16 mg, 2.00 x 10^{-5} mol), CuI (5.7 mg, 3.00 x 10^{-5} mol), and TEA (0.8 mL, 6.00 x 10^{-3} mol) as the catalyst system in toluene at 80 °C for 12 h under an argon atmosphere. The reaction was washed with water and the organic phase was dried and purified by column chromatography with hexane:toluene (75:25 vol. %) as the eluent to produce the product as a yellow powder in 77% yield. ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 0.9 (72 H), 2.1 (4 H), 7.2 (16 H), 7.6 (16H), 7.7 (4H), and 8.2 (2H) ppm. ^{13}C NMR (300 MHz, CD_2Cl_2, 298 K, δ): 81.5, 83.2, 118-142 ppm. MALDI-TOF found [M/Z] = 1531.05 g/mol. with theoretical [M/Z] = 1530.86 g/mol. Finally, this compound (0.35 g, 2.30 x 10^{-4} mol) was reacted with tetrabutylammonium fluoride (2.75 mL, 2.75 x 10^{-3} mol) in THF (10 mL) at room temperature for 3 hours. The reaction was quenched with water and extracted with dichloromethane. The product was filtered through a silica gel column with toluene as the eluent and dried under reduced pressure to yield 1,3,6,8-tetrakis(4'-ethynyl-[1,1'-biphenyl]-4-yl)pyrene core (**1**) as a bright yellow powder in 86% yield. ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 3.1 (4 H), 7.2 (16 H), 7.5 (16H), 7.7 (4H), and 8.2 (2H) ppm. ^{13}C NMR (300 MHz, CD_2Cl_2, 298 K, δ): 81.5, 83.2, 118-142 ppm. MALDI -TOF found [M/Z] = 906.12 g/mol. (**SI-Figure 1**) with theoretical [M/Z] = 906.33 g/mol.



SI Figure 1: MALDI-TOF spectrum of 1,3,6,8-tetrakis(4'-ethynyl-[1,1'-biphenyl]-4-yl)pyrene (**1**).

***Synthesis of S,S'-(((2-oxo-4,5-bix(4-((triisopropyl)silyl)ethynyl)phenyl)cyclopenta-3,5-diene-1,3-diyl)bis(1,4-phenylene)bis(methylene)diethanethioate (2)*:**

4-Bromobenyzlacetic acid (2.0 g, 8.73 x 10^{-3} mol) was reacted with potassium thioacetate (1.2 g, 1.05 x 10^{-2}) in THF (30 mL) at 50 °C for 6 h. The solution was filtered through a plug of silica gel and dried under reduced pressure to obtain the product as a white powder at 80 % yield. ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 2.3 (3 H), 3.5 (2 H), 4.2 (2H) and 7.1 (4H) ppm. 2-(4-(Acetylthiomethyl)phenyl)acetic acid (2.0 g, 8.90 x 10^{-3} mol) was reacted with N,N'-dicyclohexylcarbodiimide (DCC) (1.9 g, 9.00 x 10^{-3} mol) with 4-dimethylaminopyridine (DMAP) (0.27 g, 2.41 x 10^{-3} mol) as the catalyst in dichloromethane (40 mL) at room temperature for 18 h under an argon atmosphere. The solution was filtered, dried under reduced pressure, and the product was purified by silica gel column chromatography using petroleum ether:THF (80:20 vol. %) as the eluent. ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 2.3 (3 H), 3.4 (2 H), 4.3 (2H), and 7.1-7.2 (4H) ppm. 1,2-Bis(4((triisopropylsilyl)ethynyl)phenyl)ethane-1,2-dione was synthesized as previously reported.[SI-1] ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 1.2 (36 H), 2.0 (6 H), 7.7 (4H), and 7.9 (4H) ppm. MALDI-TOF found [M/Z] = 570.32 g/mol. with theoretical [M/Z] = 570.33 g/mol. The thioacetate functionalized propanone (1.5 g, 3.89 x 10^{-3}) was reacted with 1,2-bix(4((triisopropylsilyl)ethynyl)phenyl)ethane-1,2-dione (2.2 g, 3.89 x 10^{-3}) in the presence of n-butyl ammonium hydroxide (1 mL, 1 x 10^{-3} mol) in THF (30 mL) at room temperature for 1 h under an argon atmosphere. The solution was concentrated by rotary evaporations and purified by silica gel column chromatography using petroleum ether:THF (85:15 vol. %) as the eluent to achieve compound **2** as a dark red solid in 46 % yield. ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 1.3 (36 H), 2.2 (6H), 2.4 (6 H), 4.1 (4H), 7.2 (4H), 7.3 (8 H), and 7.7 (4H) ppm. ^{13}C NMR (300 MHz, CD_2Cl_2, 298 K, δ): 18, 23, 32, 33, 97, 104, 125-140, 194 ppm. MALDI-TOF found [M/Z] = 920.99 g/mol. (**SI-Figure 2**) with theoretical [M/Z] = 920.41 g/mol.



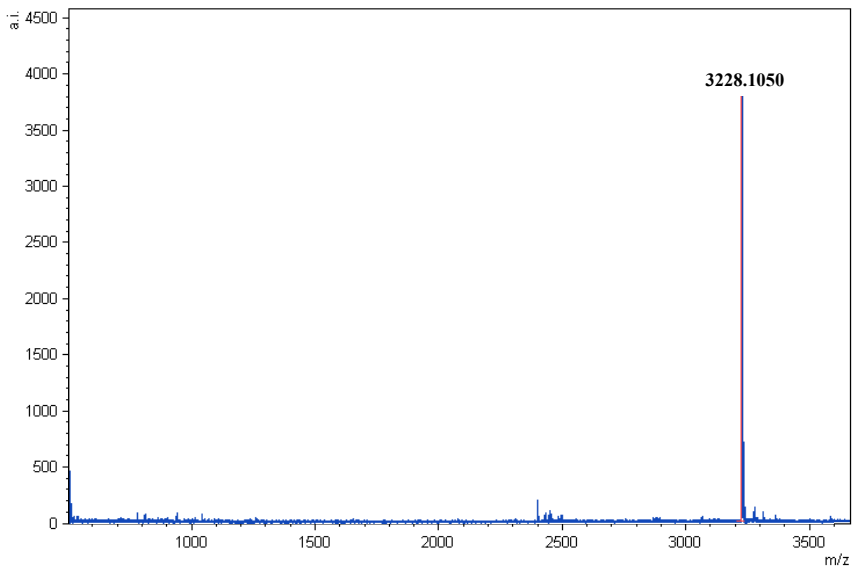
SI Figure 2: MALDI-TOF spectrum of S,S'-(((2-oxo-4,5-bix(4-((triisopropyl)silyl)ethynyl)phenyl)cyclopenta-3,5-diene-1,3-diyl)bis(1,4-phenylene)bis(methylene)diethanethioate (2).

***Synthesis of 2,3,4,5-tetraphenylcyclopenta-3,5-diene-1-one (3)*:**

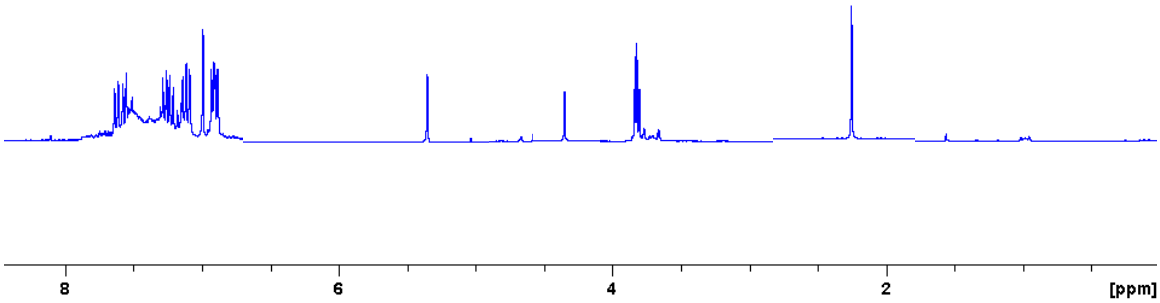
Compound 3 was synthesized according to literature.[SI-1] ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 7.2-7.7 (20 H) ppm. ^{13}C NMR (300 MHz, CD_2Cl_2, 298 K, δ): 99, 100, 101, 101, 125-140, 199 ppm. MALDI-TOF found [M/Z] = 385.06 g/mol. with theoretical [M/Z] = 384.67 g/mol.

Synthesis of SI-PPD1:

The general procedure for the synthesis of a 1st generation PPD goes as follows: cyclopentadienone **2** (0.25 g, 2.70 x 10^{-4} mol) was mixed with the pyrene core **1** (45 mg, 5.00 x 10^{-5} mol) in *o*-xylene (10 mL) and heated at 160 °C for 24 h. The solution was cooled to room temperature and precipitated in methanol. The precipitate was filtered through a small plug of silica gel sequentially rinsing with hexanes, hexane:dichloromethane (80:20), and THF, respectively. The THF fraction was concentrated by rotary evaporation, and then filtered through a GPC column backed with polystyrene beads with THF as the eluent. The PPD was collected, dried by rotary evaporation, and then reacted with n-butyl ammonium fluoride (10:1 molar ratio to dendrimer) in THF at room temperature for 3 h. Water was added to the reaction and allowed to stir for 30 min. The dendrimer was extracted with dichloromethane, run through a small plug of silica gel, and dried under reduced pressure to yield 1st generation **SI-PPD 1** in 54 % yield as a light yellow solid. ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 2.3 (3 H), 3.9 (2 H), 4.3 (1H), and 7.0-7.5 (aromatic) ppm (**SI-Figure 4**). ^{13}C NMR (300 MHz, CD_2Cl_2, 298 K, δ): 32, 35, 125-140, and 195 ppm. MALDI-TOF found [M/Z] = 3228.10 g/mol. with theoretical [M/Z] = 3230.95 g/mol, as shown in **SI-Figure 3**.



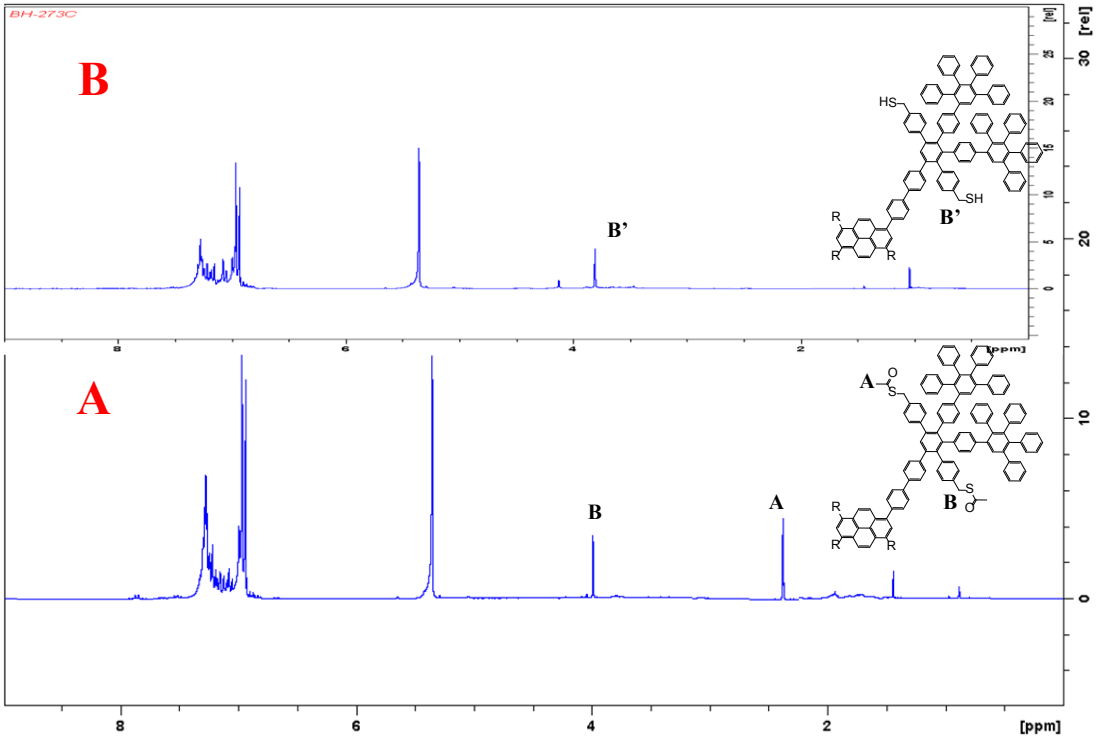
SI Figure 3: MALDI MS spectrum of SI-PPD 1.



SI Figure 4: ^{1}H NMR spectrum of SI-PPD 1 in deuterated methylene chloride.

***Synthesis of SI-PPD 2*:**

The synthesis of SI- PPD **2** was accomplished by reacting SI-PPD1 (125 mg, 4.00 x 10^{-5} mol) with cyclopentadienone **3** (92 mg, 2.40 x 10^{-4} mol) in *o*-xylene (5 mL) and heated at 165 °C for 48 h. The solution was cooled to room temperature and precipitated in methanol. The crude product was purified by silica gel column chromatography with petroleum ether, then dichloromethane, and finally THF as the eluents, respectively. The THF fraction was dried by rotary evaporation to yield SI-PPD 2 as yellow/orange solid in 45% yield. ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 2.4 (3 H), 4.0 (2 H), and 7.0-7.5 (aromatic) ppm (**SI-Figure 5A**). ^{13}C NMR (300 MHz, CD_2Cl_2, 298 K, δ): 32, 35, 120-142, and 195 ppm. MALDI-TOF for SI-PPD 2 [M/Z] =6082.54 g/mol with theoretical [M/Z] = 6081.21 g/mol.



SI-Figure 5: ^{1}H NMR spectra of A) SI-PPD 2 and B) PPD 1 in deuterated methylene chloride; R= dendrimer arm.

***Synthesis of 2-(4-nitrophenoxy)ethanethiol (4)*:**

4-Nitrophenol (1 g, 7.19 x 10^{-3} mol) was reacted with 1,2-dibromoethane (6.75 g, 3.59 x 10^{-2} mol) in THF (25 mL) at 60 °C for 12 h. The solution was concentrated and the compound was purified by silica gel column chromatography using petroleum ether:THF (70:30 vol. %) as the eluent to achieve the product as a white powder in 73 % yield. This compound (1.2 g, 4.88 x 10^{-3} mol) was reacted with potassium thioacetate (2.75 g, 2.45 x 10^{-2} mol) in THF (30 mL) at 40 °C for 6 h. The reaction was concentrated and purified by silica gel column chromatography with hexane:THF (50:50) as the eluent to achieve compound **4** as a white powder in 79 % yield. ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 2.9 (2 H), 4.1 (2 H), 7.3 (2H), and 8.1 (2H) ppm. ^{13}C NMR (300 MHz, CD_2Cl_2, 298 K, δ): 26, 79, 118, 124, 140, 161 ppm.

***Deprotection of the thioacetate groups and reaction with 2-(4-nitrophenoxy)ethanethiol (4)* :**

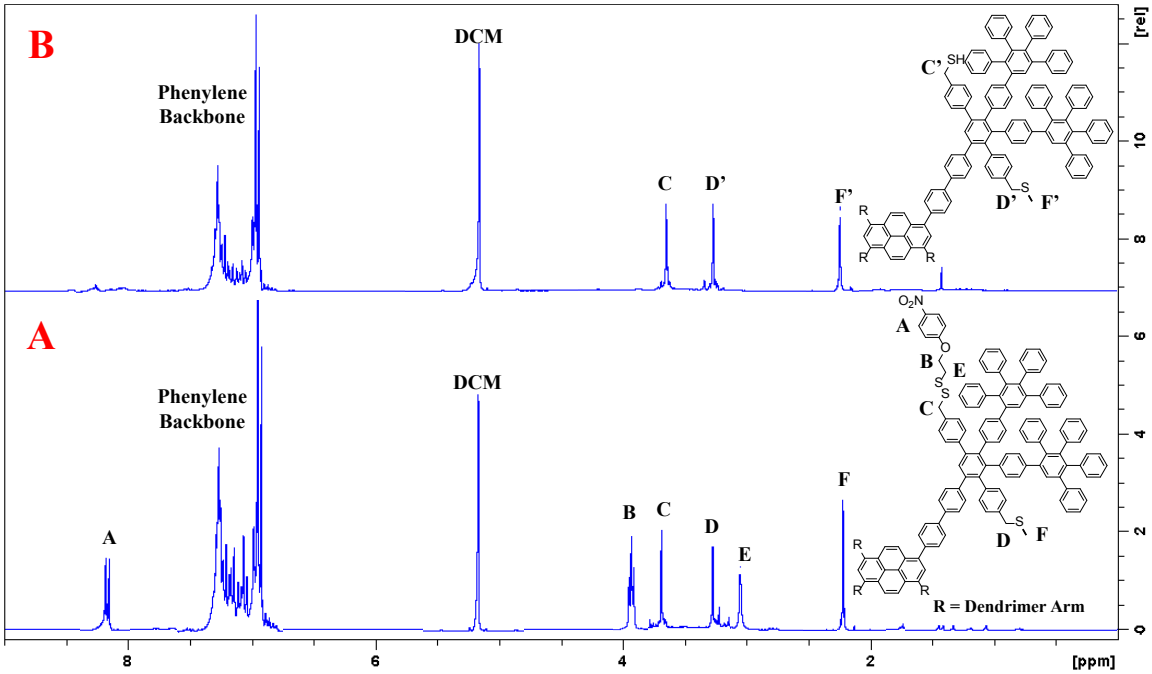
SI PPD **2** (100 mg, 2.00 x 10^{-5} mol) was mixed with 2-(4-nitrophenoxy)ethanethiol (200 mg, 1.00 x 10^{-3} mol) in the presence of dimethyl amine (1mL, 1.00 x 10^{-3}) in THF (8 mL) at RT for 24 h opened to atmospheric oxygen. The polymer was precipitated in methanol three times, and purified by dialysis (benzoylated dialysis tubing with a molecular weight cut-off of 2,000 g/mol) in THF for 24 h. The functionalized dendrimer was achieved as a light yellow powder. ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K, δ): 3.1 (2 H), 3.65 (2H), 3.9 (2H, CH_2), 6.9-7.4 (m), and 8.2 (2H) ppm. ^{13}C NMR (300 MHz, CD_2Cl_2, 298 K, δ): 28, 38, 44, 70, 119-144, and 168 ppm. MALDI-TOF [M/Z] = 6535.10 g/mol. with theoretical (for 4 4-nitrophenol) [M/Z] = 6534.96 g/mol (**Figure 2 B**).

***Methyl End-Capping Procedure*:**

PPD functionalized with 4-nitrophenol derivatives (75 mg, 1.00 x 10^{-5} mol) were reacted with methylbromide (0.5 mL, 5.00 x 10^{-3} mol) in the presence of TEA(50 µL, 5.00 x 10^{-3} mol) in THF (5 mL) at 60 °C for 12 h. The polymer was repeatedly precipitated in methanol, and again purified by dialysis in THF for 24 h to remove unreacted molecules from the dendrimers to yield **PPD 2**. **^{1}H** NMR (300 MHz, CD_2Cl_2, 298 K, δ): indicated a new signal related to the methyl groups attached to the sulfurs at 2.3 (3H) ppm (**Figure 3 A**). ^{13}C NMR (300 MHz, CD_2Cl_2, 298 K, δ): indicated a new signal at 19 ppm. MALDI-TOF showed a [M/Z] = 6590.78 g/mol. with theoretical (for *four* 4-nitrophenol) [M/Z] = 6590.24 g/mol (**Figure 2 C**).

***Reduction of Disulfide Bonds for Molecular Release to yield PPD 3*:**

PPD 2 (60 mg, 9.10 x 10^{-6} mol) was reacted with DL-dithiothreitol (30 mg, 1.95 x 10^{-4} mol) in THF (3 mL) at 60 °C for 2 h under an argon atmosphere. The dendrimer was precipitated in methanol and purified by dialysis in THF for 24 h. The THF solution was dried to yield **PPD 3** as a yellow solid. **^{1}H** NMR (300 MHz, CD_2Cl_2, 298 K, δ): 2.25 (3 H), 3.40 (2 H), 3.65 (2H), and 7.00-7.50 (aromatic) ppm (**Figure 3 B**). ^{13}C NMR (300 MHz, CD_2Cl_2, 298 K, δ): 19, 29, 36, and 120-145 ppm. MALDI-TOF showed a /Z] = 5801.33 g/mol. with theoretical [M/Z] = 5800.56 g/mol (**Figure 2 D**).



SI-Figure 6: ^{1}H NMR spectra of A) **PPD 2** and B) **PPD 3** in deuterated methylene chloride.