*Electronic Supplementary Information (ESI)*

# Synthesis of Multifunctional Poly(carbamoyl ester)s Containing Dual-Cleavable Linkages and AIE Luminogen via Passerini-type Multicomponent Polymerization

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**Experiment sections:**

**Characterization.** Gel permeation chromatography (GPC) were conducted at 40 °C (eluent: tetrahydrofuran (THF); flow rate: 1 mL/min) and equipped with two PSS SDV columns (Linear S and 100 Å pore size), Waters 515 pump, and Waters 410 RI detector. Sample characterization (i.e., $M_n$, $M_w$, and PDI (= $M_w/M_n$)) was estimated from a calibration curve using polystyrene standards with different molecular weights and narrow molecular distributions. FT-IR spectra were conducted by a Nicolet Avatar 320 FT-IR Spectrometer at a resolution of 8 $cm^{-1}$ with 64 scans. The samples were dissolved in chloroform and casted on a KBr plate. Proton and carbon nuclear magnetic resonance ($^1H$ and $^{13}C$ NMR) spectra were measured by a Bruker 500 NMR and calibrated by a solvent standard of $CDCl_3$ (δ = 7.26 ppm) or DMSO-$d_6$ (δ = 2.49 ppm). The molecular masses of the A4 and A3 monomers were determined using a Bruker amazon SL mass spectrometer equipped with an electrospray ionization source (ESI-MS, Bruker amaZon SL). Ultraviolet–visible (UV–Vis) measurements were carried out by collecting the absorbance from a Hitachi U-3900 spectrophotometer. Fluorescence (FL) measurements were conducted by using a HITACHI F-2500 fluorescence spectroscopy with a scanning range of 250–750 nm and using 330 nm as the excitation wavelength. Particle sizes were measured by dynamic light scattering (DLS) of a commercial spectrometer (Brookhaven NanoBrook ZetaPALS) equipped with a BI-SCGO cell, BI-SREL electrode, and a BI-9000AT digital autocorrelator. A 35 mW vertically diode laser (630 nm) was used as the light source. Scanning electron microscopy (SEM) images were acquired by a JEOL JSM 7401F FE-scanning electron microscope operating at a voltage of 100 kV. Prior to the measurements of DLS and SEM, the solutions were filtered with a PTFE filter head (0.45 μm). For SEM analysis, the solutions were separately dropped on wafers and freeze-dried the drops.

**Materials.** Terephthalaldehyde (98% (named as A1 monomer)), glutaraldehyde aqueous solution (25 wt% (A2 monomer)), malonic acid (98% (B1 monomer)), 3,3'-dithiodipropionic acid (99% (B2 monomer)), zinc powder (99%), titanium tetrachloride (98%), 4-bromobenzophenone (97%), tetrakis(triphenylphosphine) palladium ($Pd(PPh_3)_4$, 98+%) and benzaldehyde (99%) were purchased from Aldrich. Cyclohexyl isocyanide (99% (C monomer)), benzoic acid (99.6%), butyraldehyde (98+%), octanoic acid (99%), curcumin (Cur, 98%), sodium hydrogen carbonate (98%), dithiothreitol (DTT, 98%), and rhodamine B (Rh, 99%) were ordered from ACROS. All solvents were purified and stored with molecular sieves prior to use.

**Synthesis of 1,2-bis (4-bromophenyl)-1,2-diphenylethene (TPE-2Br) (i.e., step i in Scheme S1).** In a flame-dried three-neck flask under $N_2$ atmosphere, an ice-cooled (–5 °C) suspension of zinc powder (12.50 g, 191.19 mmol) in THF (240 mL) was prepared and titanium tetrachloride (20.00 mL, 181.81 mmol) was slowly added to the suspension. The resulting mixture was refluxed for 4 h. After cooling to room temperature, a solution of 4-bromobenzophenone (10.00 g, 38.30 mmol) in THF (50 mL) was slowly added to the mixture, and the mixture was then refluxed overnight. After cooling to room temperature, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution and stirred for 5 h. The mixture was filtered, and the filtrate was separated into an organic and an aqueous layer. The aqueous layer was extracted thrice with dichloromethane, and the combined organic layer was dried over $MgSO_4$ and the solvent was evaporated under the reduced pressure. The resulting white crude product was purified by silica gel column chromatography using hexane as eluting solvent to afford a white powder of TPE-2Br product.

**Synthesis of dialdehyde-functionalized tetraphenylethane (TPE) monomer [(*E*)-4',4'''-(1,2-diphenylethene-1,2-diyl)bis([1,1'-biphenyl]-4-carbaldehyde (A3 monomer (i.e., step ii in Scheme S1))]**. The TPE-2Br (1.50 g, 3.03 mmol) and 4-formylphenylboronic acid (1.14 g, 7.60 mmol) were dissolved in dry THF (80 mL). The solution was mixed with an aqueous solution containing $K_2CO_3$ (2.09 g, 5.20 mmol) and water (15 mL) and $Pd(PPh_3)_4$ catalyst (15.20 mg) was gradually added. The reaction mixture was then immersed in a thermostated oil bath at 85 °C for two days. After cooling the reaction solution to room temperature, the reaction mixture was mixed with water and the organic layer was extracted three times by DCM. The resulting product was purified by silica gel column chromatography using hexane/$CH_2Cl_2$ (v/v = 2:1) to afford a light-yellow solid (1.09 g, yield = 67%). δ (ppm, $CDCl_3$): 9.78 (s, 2H), 7.41–7.92 (m, 26H). $^1$H NMR spectrum of the A3 monomer is shown in Figure S1a. $^1$H NMR (500 MHz, $CDCl_3$, Fig. S1a): δ 10.04 (s, 2H, CHO group), 7.89–7.13 (m, 26H). $^{13}$C NMR (125 MHz, $CDCl_3$, Fig. S2a): 191.87 (C=O), 146.56, 144.00, 143.32, 140.84, 137.42, 135.05, 131.99, 131.37, 130.21, 127.94, 127.34, 126.83, 126.53, 77.32, 77.00, 76.68. FTIR (KBr, $cm^{-1}$, Fig. S3a): 3050 (CH aromatic), 2842.77 and 2738.99 (CHO group). (+)ESI-MS (m/z), $[C_{40}H_{28}O_2+Na]^+$ calculated: 563.3 [Fig. S4].

**Synthesis of mono-aldehyde functionalized TPE monomer [4-(1,2,2-triphenylvinyl)benzaldehyde (A4 monomer)].** Our synthetic procedures are modified based on the previous reports.[1-3] Bromotriphenylethylene (2.00 g, 6 mmol) was added to a mixture of 4-formylphenylboronic acid (1.20 g, 8 mmol), methylbenzene (100 mL) and methanol (100 mL) and kept at 25 °C for an hour. Then $K_2CO_3$ (3.4 g, 24.5 mmol) and $Pd(PPh_3)_4$ (0.25 g, 0.20 mmol) were added to the mixture and stirred at 75 °C for overnight under $N_{2(g)}$. The reaction flask was opened to the air and extracted with dichloromethane (DCM) for three times. The organic layers were

collected and concentrated. The crude was purified by fresh silica column chromatography using hexane and DCM (v/v = 10:1) as the eluent. We then obtained mono-aldehyde functionalized A4 monomer as a green-yellow solid (1.5 g, yield = 79%). δ (ppm, DMSO-$d_6$): 9.90 (s, 1H), 7.62–7.01 (m, 19H). $^1$H NMR (500 MHz, $CDCl_3$, Fig. S1b): 9.90 (s, 1H), 7.62–7.01 (m, 19H). $^{13}$C NMR (125 MHz, $CDCl_3$, Fig. S2a): 191.89 (C=O), 150.53, 143, 142.96, 142.86, 139.72, 134.23, 131.91, 131.25, 129.13, 127.89, 127.71, 126.84. FTIR (KBr, $cm^{-1}$, Fig. S3b): 3050 (CH aromatic), 2924.9 and 2859.2 (CHO group). (-)ESI-MS (m/z), [$C_{27}H_{20}O$] calculated: 360.6 [Fig. S5].

**Synthesis of Poly(carbamoyl ester)s (PCEs) via Passerini-type Multicomponent Polymerization (P-MCP).** Taking the A1B1C combination as an example: A1 monomer (0.27 g, 2 mmol), B1 (0.13 mL, 2 mmol), C (0.50 mL, 4 mmol), and a proper solvent amount (3.4 mL) were mixed in a Schlenk flask (A1/B1/C = 1/1/2). The P-MCP was then carried out at 30 °C under nitrogen atmosphere. After the reaction completed, the mixture was stopped by dilution of dichloromethane (DCM). By repeating two times for purification, the mixture was concentrated and precipitated into ether. White powder was collected and dried in a vacuum oven to afford PCE P1. The other combinations of P-MCPs were synthesized and purified based on the above-mentioned procedures. The chemical structures of PCEs P1–P6 are illustrated in Scheme 1 and their corresponding co-monomers are summarized in Table 1.

**Micellizations and Measurements of Critical Micelle Concentration (CMC) of PCEs.**

(i) Micellization procedures: PCEs P1–P6 (7 mg) were individually dissolved in THF (1 mL) and stirred at room temperature for overnight. The mixtures were added dropwise to deionized water

(DIW) (7 mL) through a microsyringe pump at a rate of 1 mL/h and stirred at room temperature for an additional day. The mixtures were concentrated to remove THF, filtrated by PTFE filters (0.45 μm) to remove impurities, and afforded PCE-micellized solutions.

(ii) Measurements of CMC: A solution of pyrene/acetone was prepared (15 mg/100 mL) and gradually added into DIW for the dilution of 500 folds. The mixture was kept stirring for further few hours. The small amounts of acetone were evaporated out under reduced pressure to prepare a pyrene aqueous stock solution. Various concentrations of PCE aqueous solutions were prepared (i.e., 0.5–$10^{-3}$ mg/mL) and then individually mixed with the pyrene stock solution in a ratio of 1:1 by volume. FL spectroscopy of each solution was measured in a range of 250–750 nm with an excitation wavelength of 330 nm. Relative intensities between 392 and 372 nm (i.e., $I_{392}/I_{372}$) were plotted with respect to the corresponding PCE aqueous solutions. From each plot, one intersection can be acquired and determined as the CMC value.

**Tests of drug loading and releasing.** In the case of rhodamine B (Rh), a PCE sample and Rh were mixed in MeOH and the mixture was dropwise added into DIW via a microsyringe pump to afford a micelle solution of Rh/PCE/DIW mixture (= 0.5 mg/0.5 mg/1 g). The mixture was further stirred for overnight and removed MeOH via vacuum. The free Rh was removed by centrifuging thrice of removable of the supernatant and re-dispersing of the precipitate in a fresh DIW rapidly. The drug release was subjected to *in vitro* tests to discuss the influence of DTT-based redox reactions. Solutions without and with the DTT (i.e., 0 and 10 mM) were individually mixed with the $PMs_{(aq)}$ samples (5 mL) and were placed in a dialysis bag (MWCO = 3.5 kDa). The bags were separately immersed in beakers having 15 mL of DIW and kept at 37 °C with regular stirring. For comparisons, various aqueous mixtures of P4 and Rh/P4 monitored under UV light (λ = 365 nm).

The drug-containing DIWs were sampling at regular intervals to trace the release profiles by FL spectrometer, DLS, SEM, and GPC analyses. In the case of curcumin (Cur), P4 (or polyethylene glycol (PEG)) sample and Cur were mixed in THF and the mixture was dropwise added into DIW via a microsyringe pump to obtain a micelle solution of Cur/PCE (or PEG)/DIW mixture (= 1 mg/0.5 mg/1 g). The mixture was stirred for overnight and removed THF via vacuum. For comparisons, various aqueous mixtures of Cur, Cur/PEG, and Cur/P4 were passed through PTFE filters (0.45 μm) and monitored under UV light.

**Examinations of aggregation-induced emission (AIE) behaviors and redox reaction of PMc comprising AIE luminogen and disulfide linkages.**

(i) Examinations of AIE behaviors: Stock solutions of PCEs/DMSO (0.4 mg/mL) were prepared. The stock solutions were individually mixed with various concentration of DMSO/DIW and fixed the total solution amounts (3 mL). To test AIE behaviors, the FL measurements were conducted by using a 330 nm excitation wavelength.

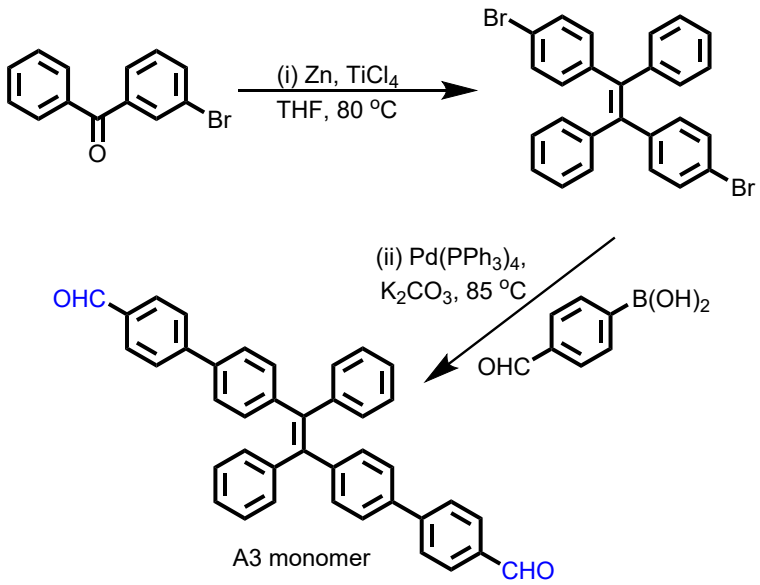
(ii) Examinations of AIE "Switch-off" property: The above-mentioned 70 wt% DIW/DMSO solution containing P5 (0.2 mg/mL) was mixed with DTT solution (10 mM). The mixture was monitored by FL spectrometer ($\lambda_{ex}$ = 330 nm) and inspected under UV light to trace the changes of AIE property

**Table S1.** Characterization of aggregation-induced FL emission property of P2, P5, and P6 PCEs from **Fig. S12**.

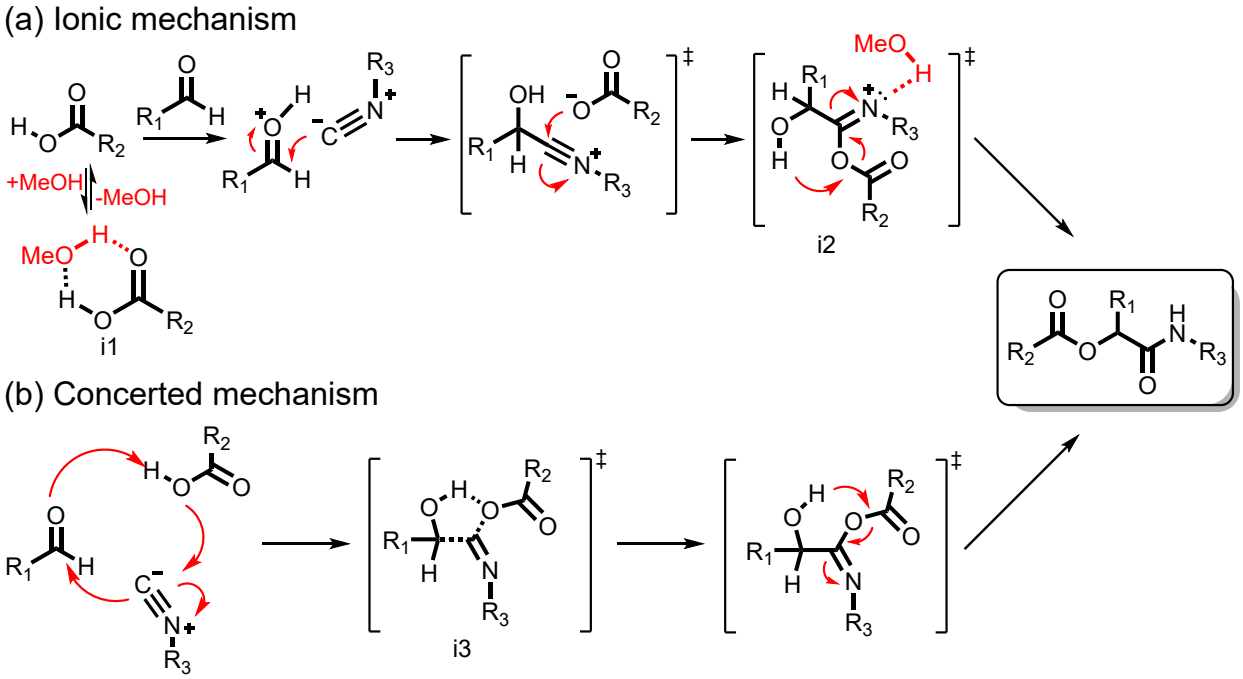
| PCE sample[a] | $\Delta I$ (= $I_{max}$-$I_{sol}$)[b] | $\Delta I$/V (in per voltage) |
|---|---|---|
| P2 | 32 | 0.08 |
| P5 | 9190 | 36.7 |
| P6 | 4690 | 11.7 |

[a] P2: without TPE moiety; P5 and P6: with TPE moiety.

[b] $I_{max}$: FL intensity from the maximum PCE aggregates; $I_{sol}$: FL intensity of PCE in the reference solution.




**Scheme S1.** Synthetic routes for (i) TPE-2Br precursor and (ii) A3 monomer.




**Scheme S2.** Plausible Passerini multicomponent reactions of (a) ionic and (b) concerted mechanisms influenced by different solvents.

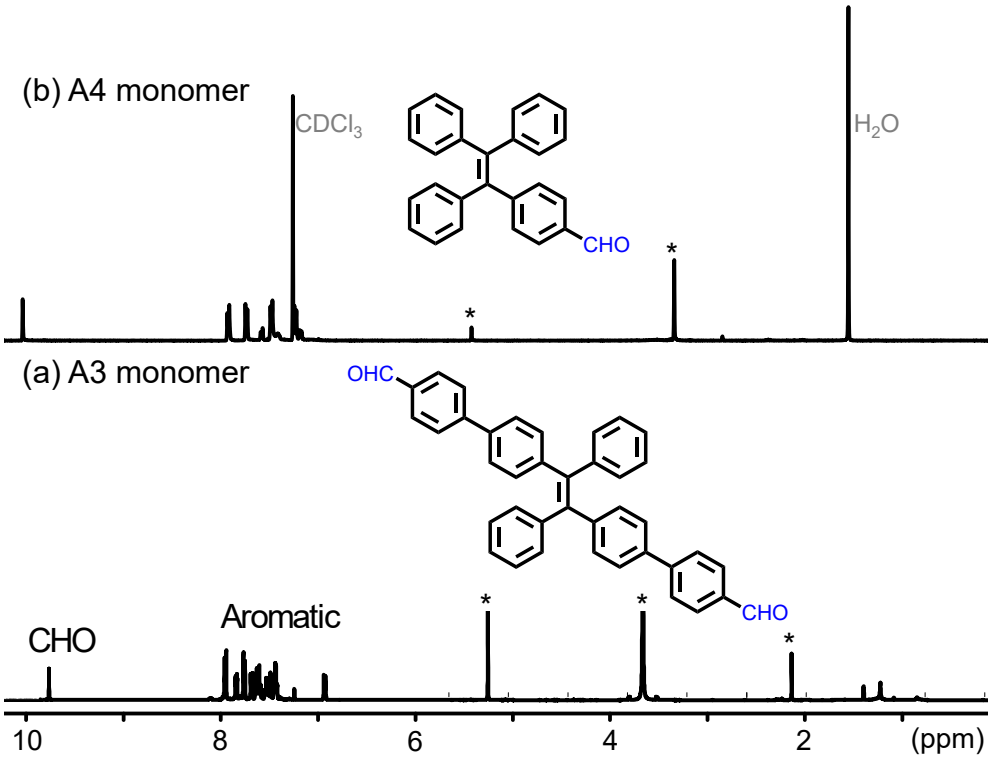



**Figure S1.** $^{1}$H NMR (400 MHz, $CDCl_3$) spectra of (a) A3 and (b) A4 monomers (*: solvent peaks).

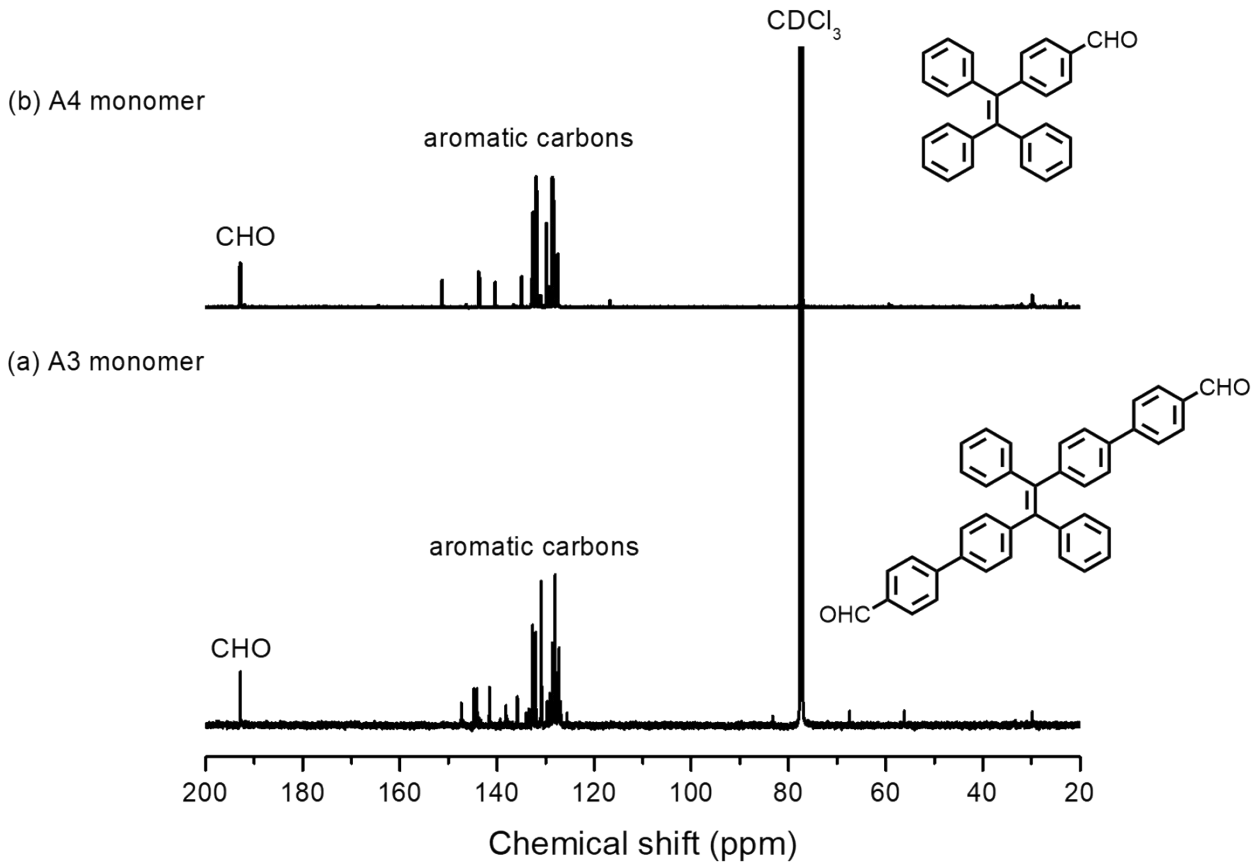



**Figure S2.** $^{13}C$ NMR (400 MHz, $CDCl_3$) spectra of (a) A3 and (b) A4 monomers.

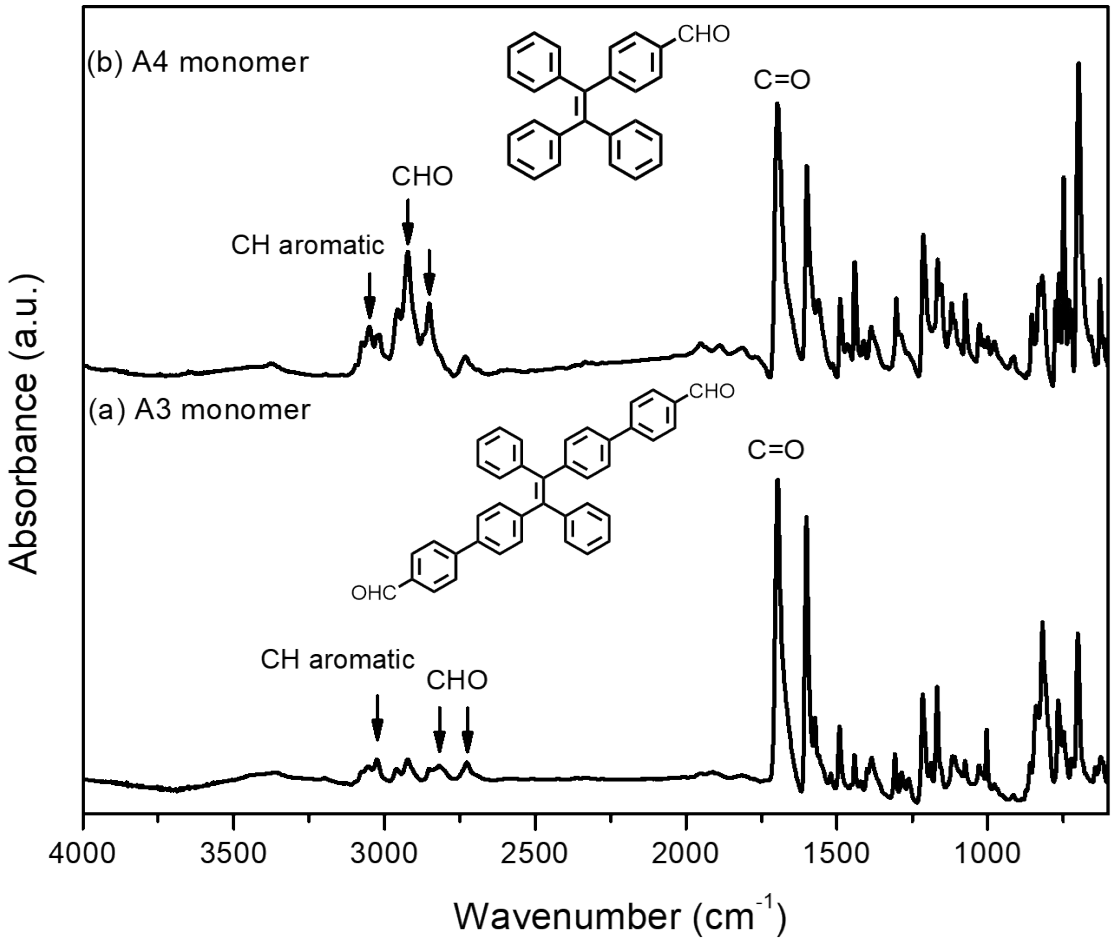



**Figure S3.** FT-IR spectra of (a) A3 and (b) A4 monomers.

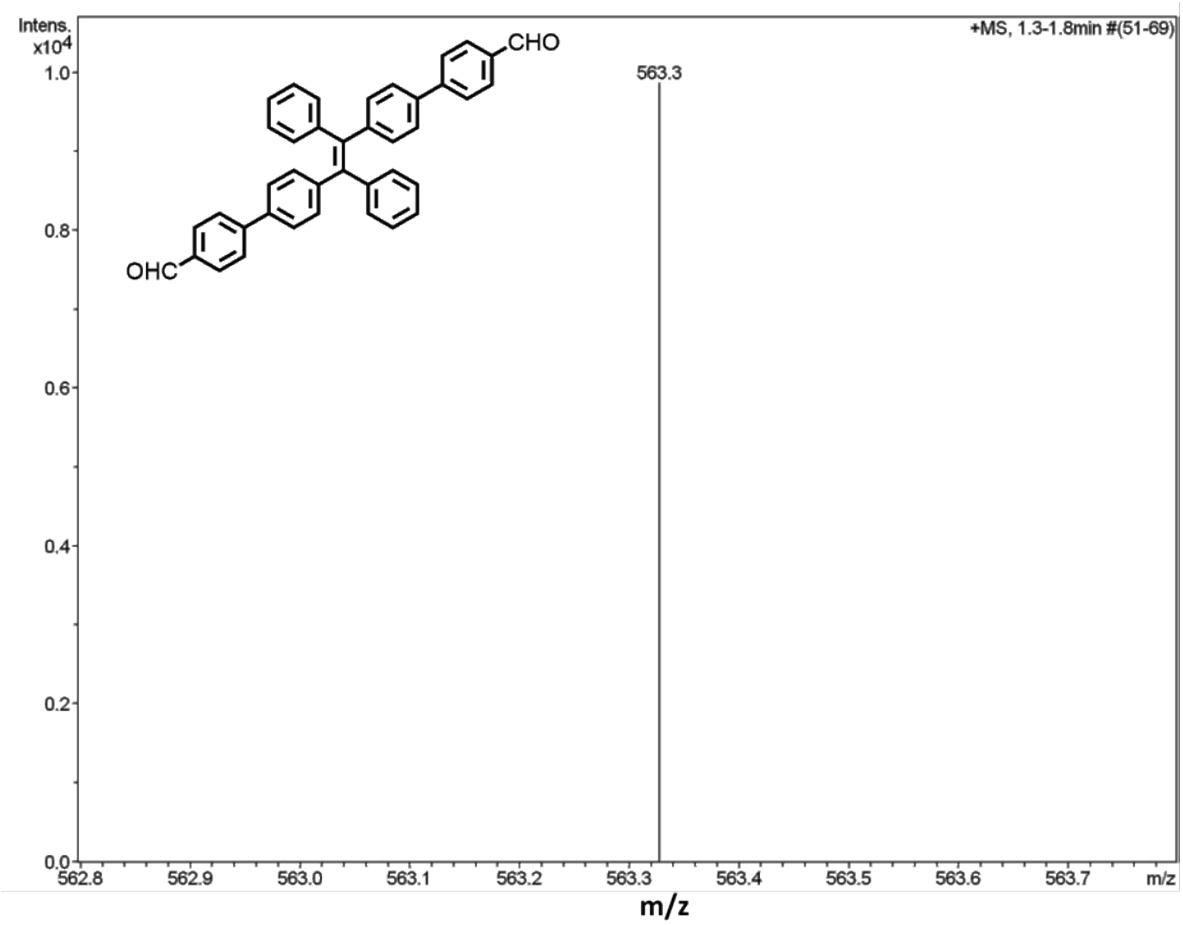



**Figure S4.** ESI-MS spectrum of A3 monomer.

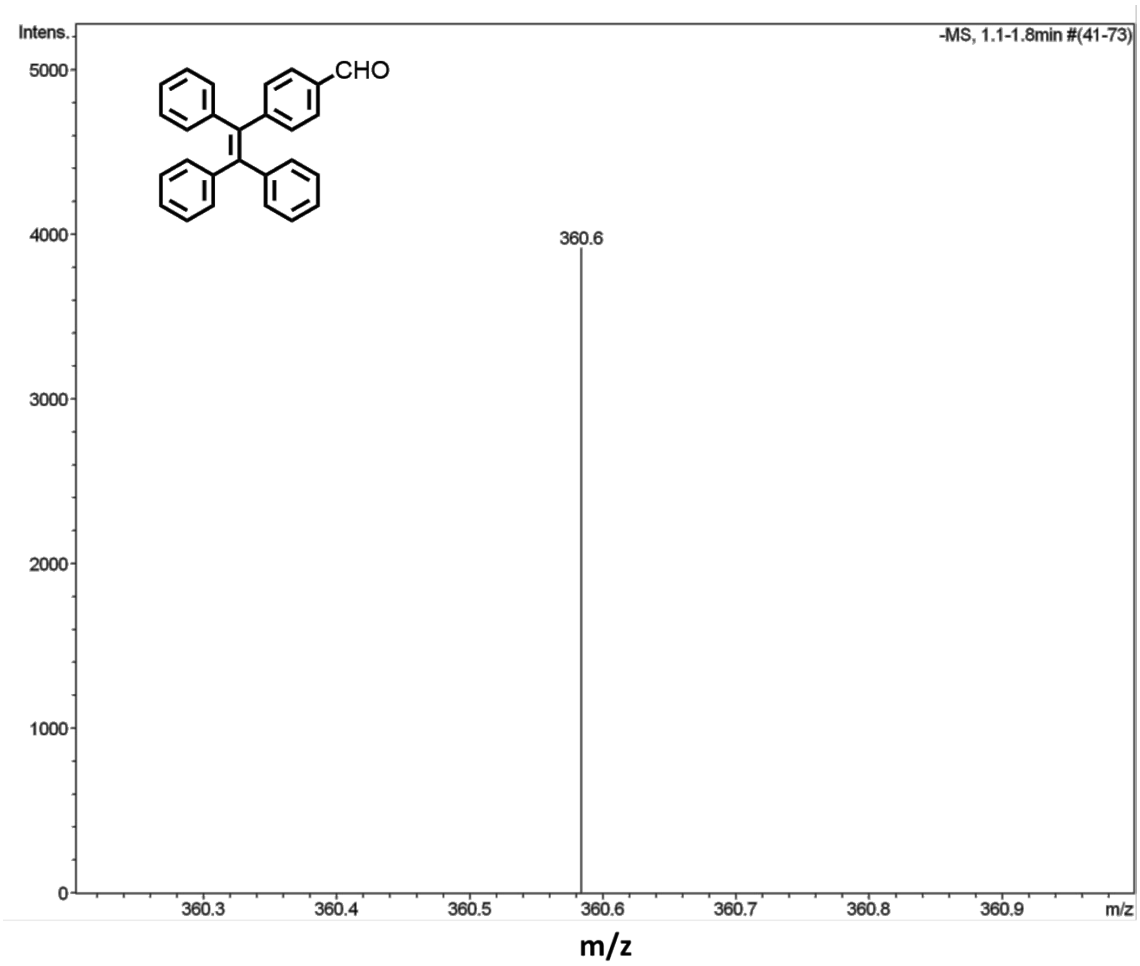



**Figure S5.** ESI-MS spectrum of A4 monomer.

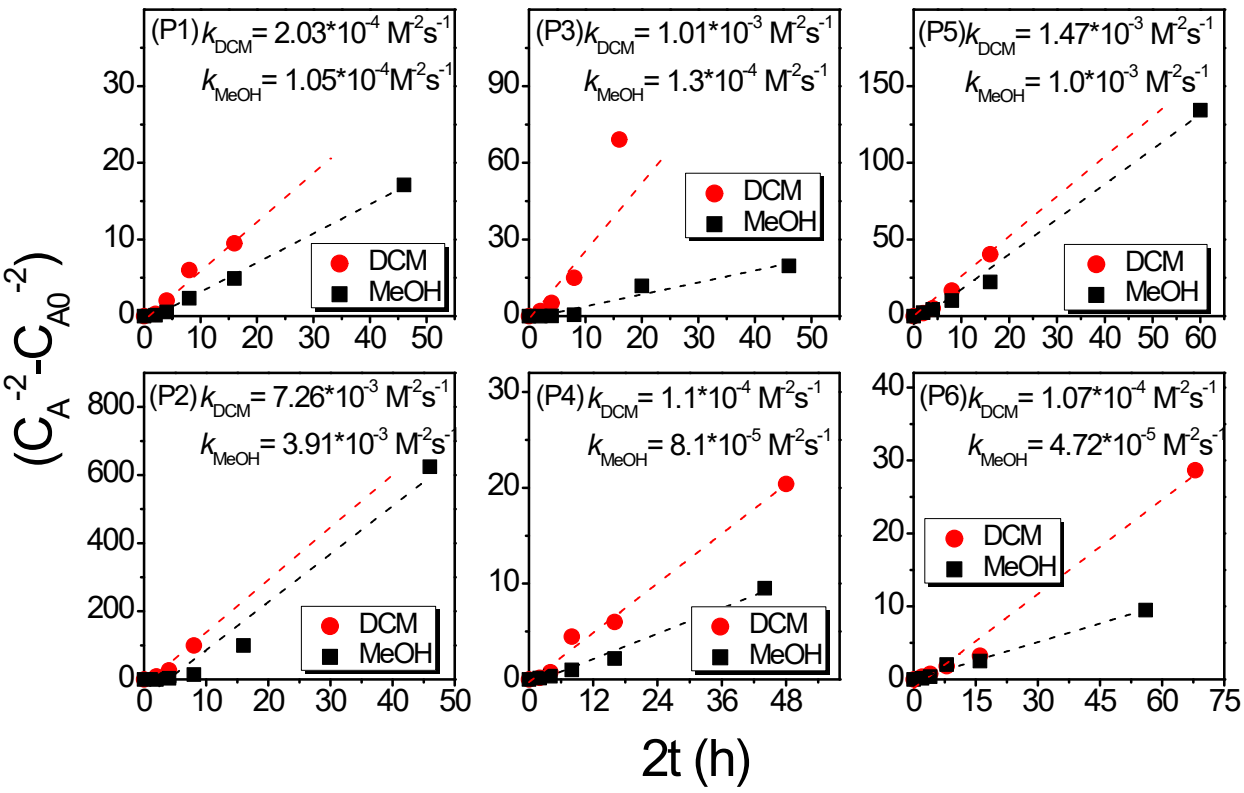



**Figure S6.** Kinetic analysis of P-MCPs in various solvents with the approach of 3$^{rd}$-order reactions.

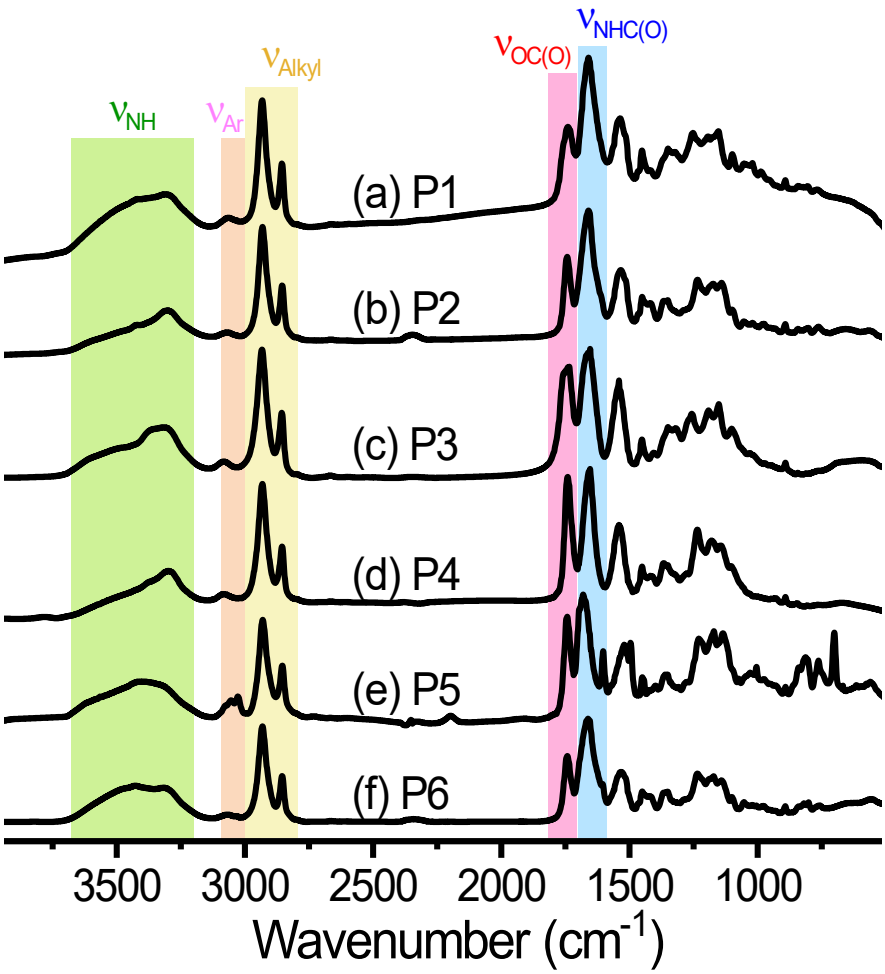



**Figure S7.** FT-IR spectra (3900−400 $cm^{-1}$) of (a–f) P1–P6 functional PCEs.

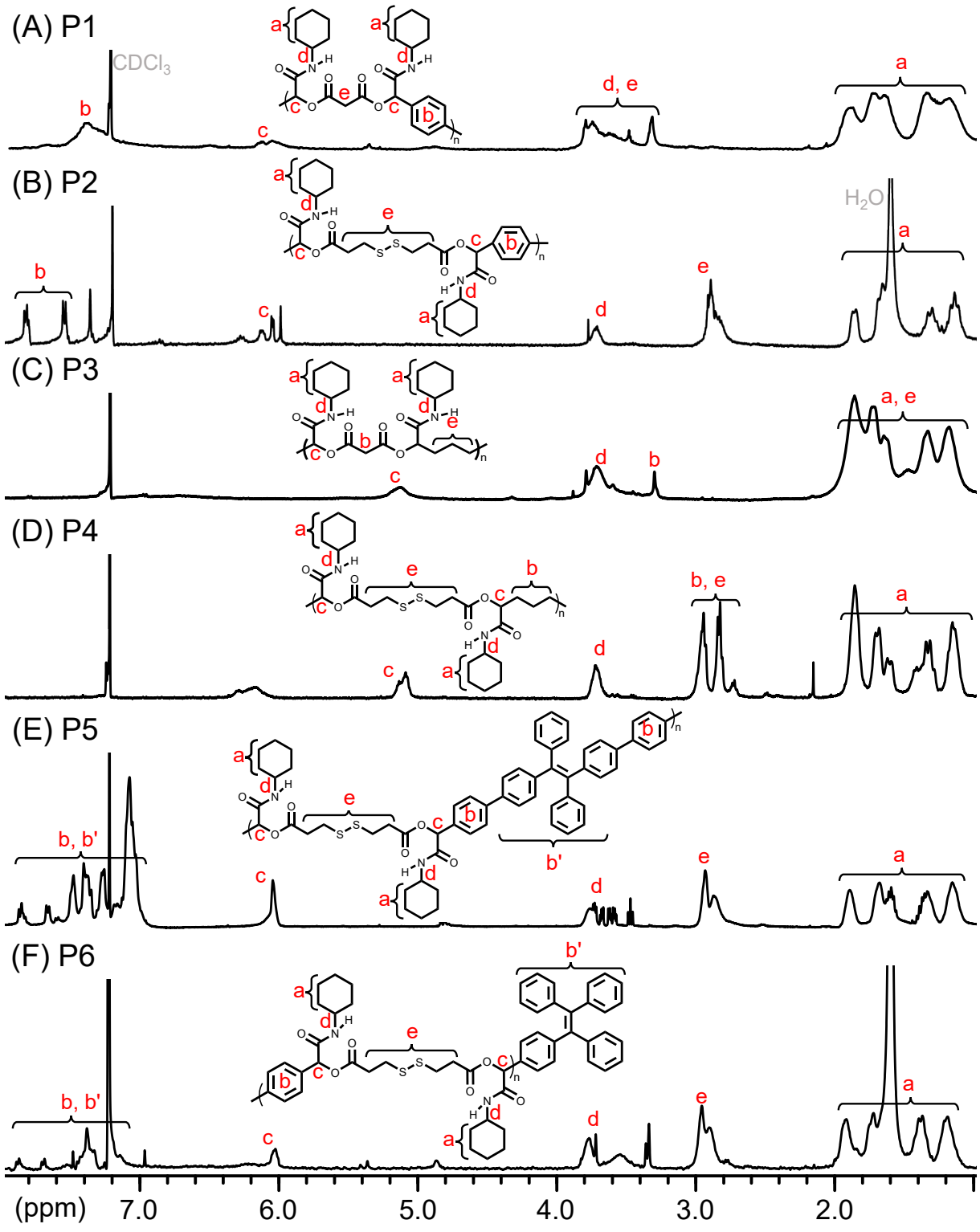



**Figure S8.** $^{1}$H NMR (400 MHz, $CDCl_3$) spectra of (A–F) P1–P6 functional PCEs.

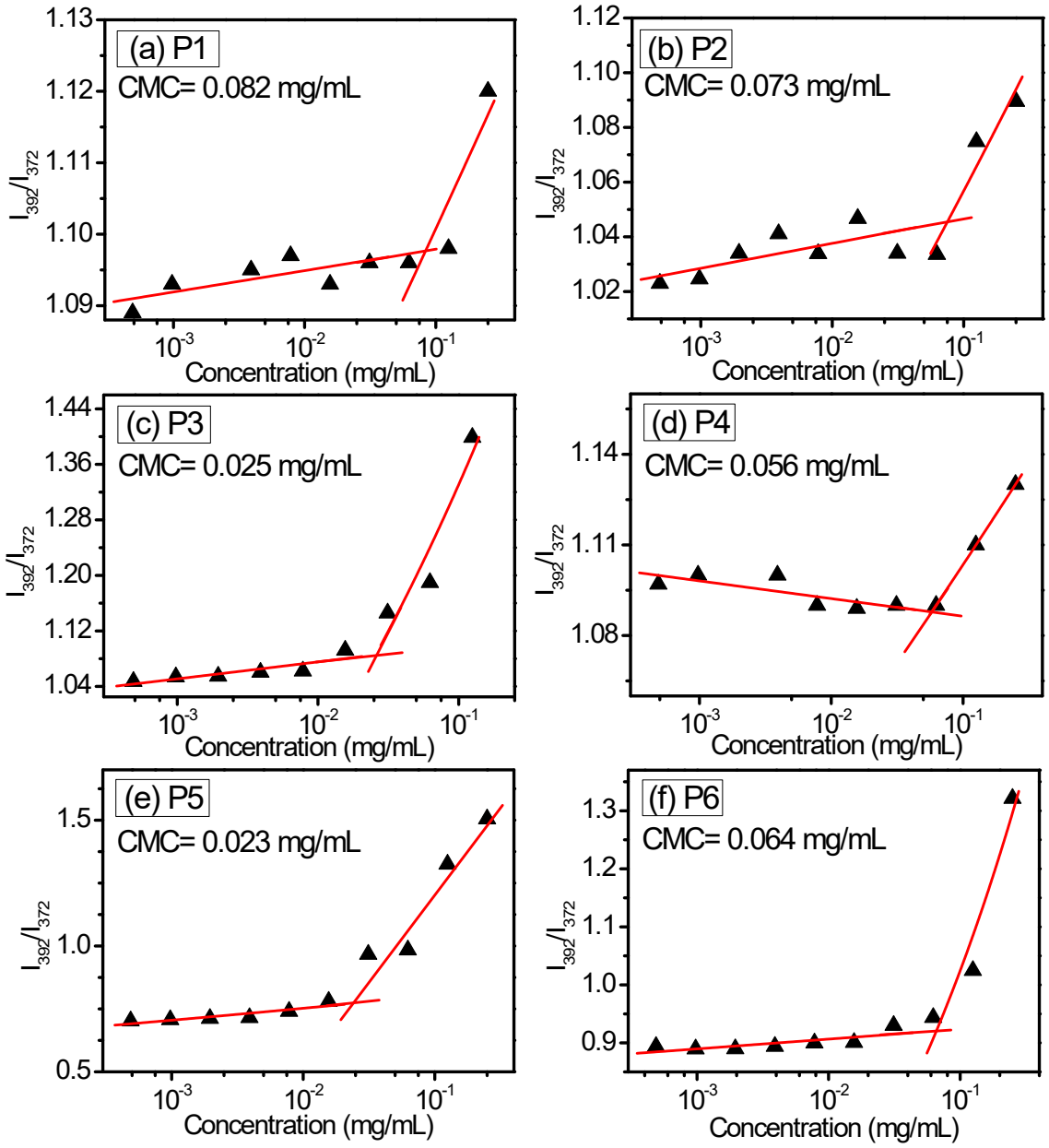



**Figure S9.** CMC plots of (a–f) P1–P6 traced by FL spectrometer.

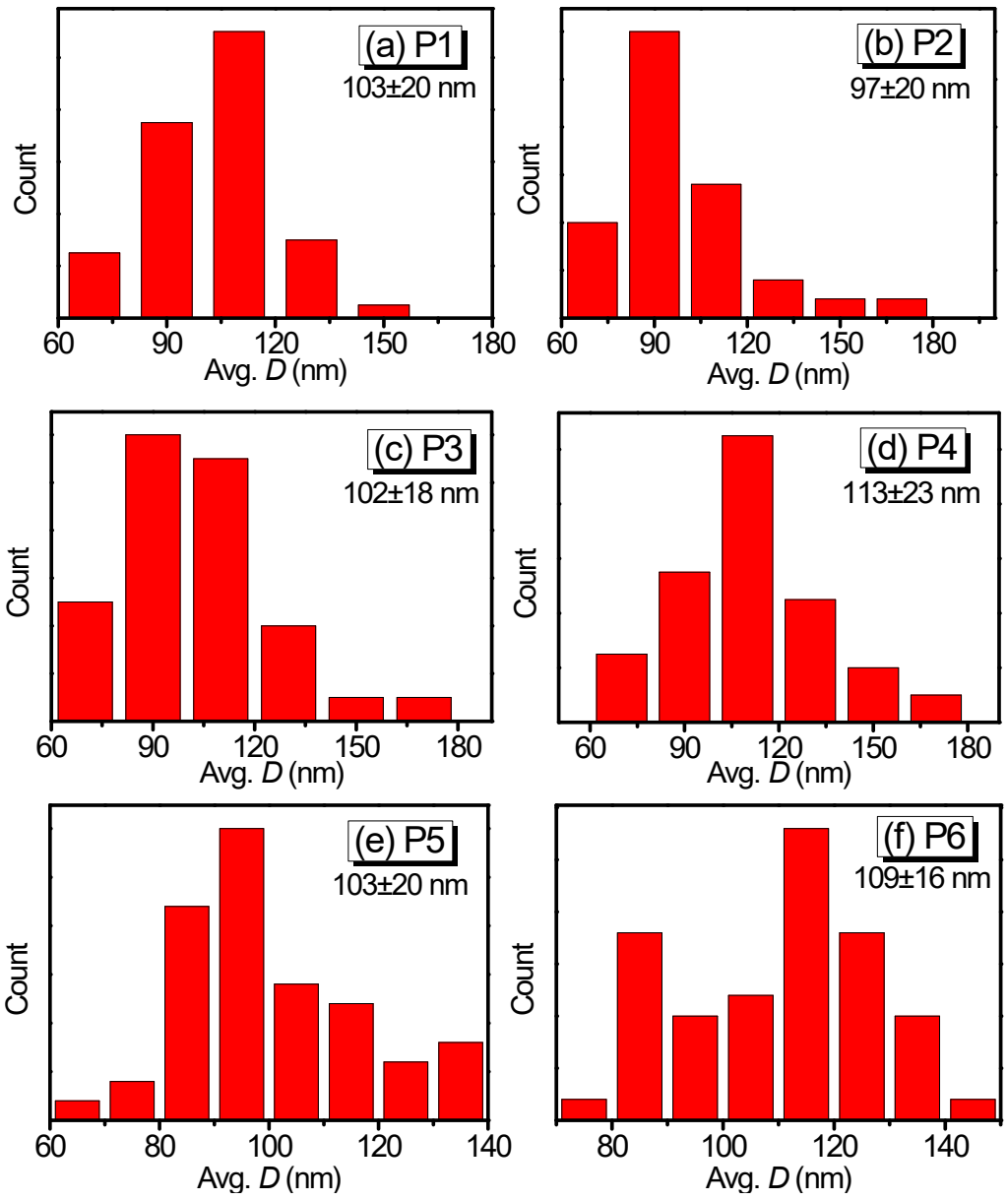



**Figure S10.** Particle diameter (*D* (nm)) counts and distributions of P1–P6 estimated from SEM images.

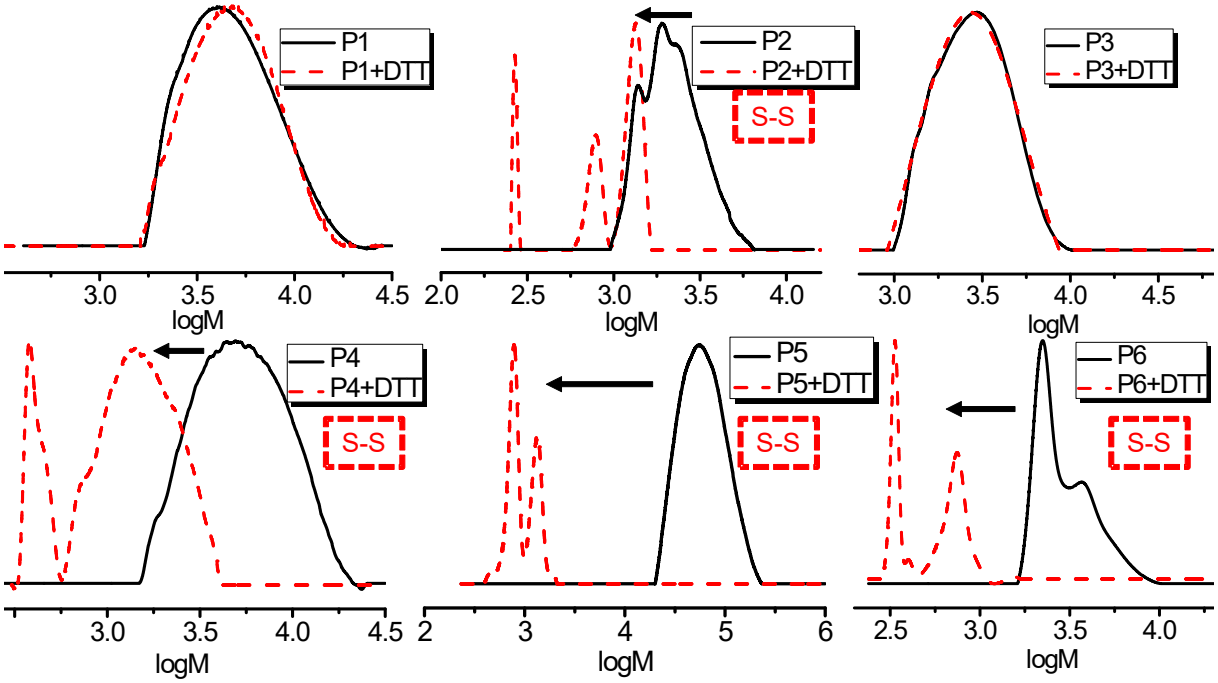



**Figure S11.** GPC traces of P1–P6 before (solid curves) and after (dash curves) DTT cleavages (S-S: containing disulfide linkages).

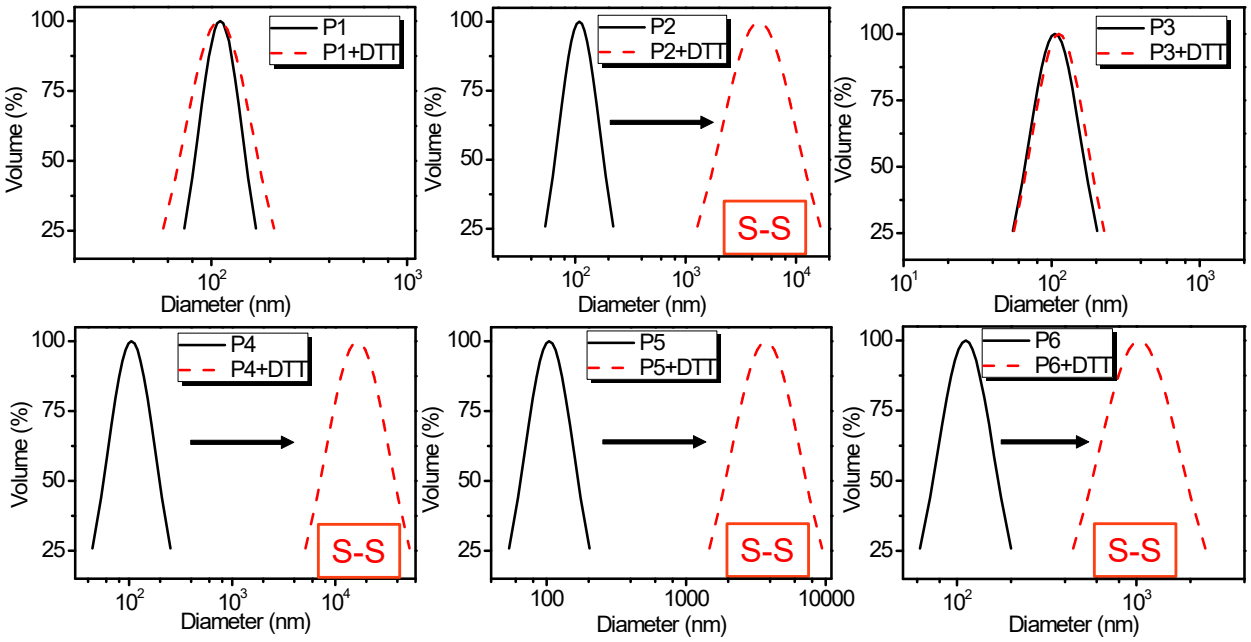



**Figure S12.** DLS differences of P1–P6 before and after DTT cleavages (S-S: containing disulfide linkages).

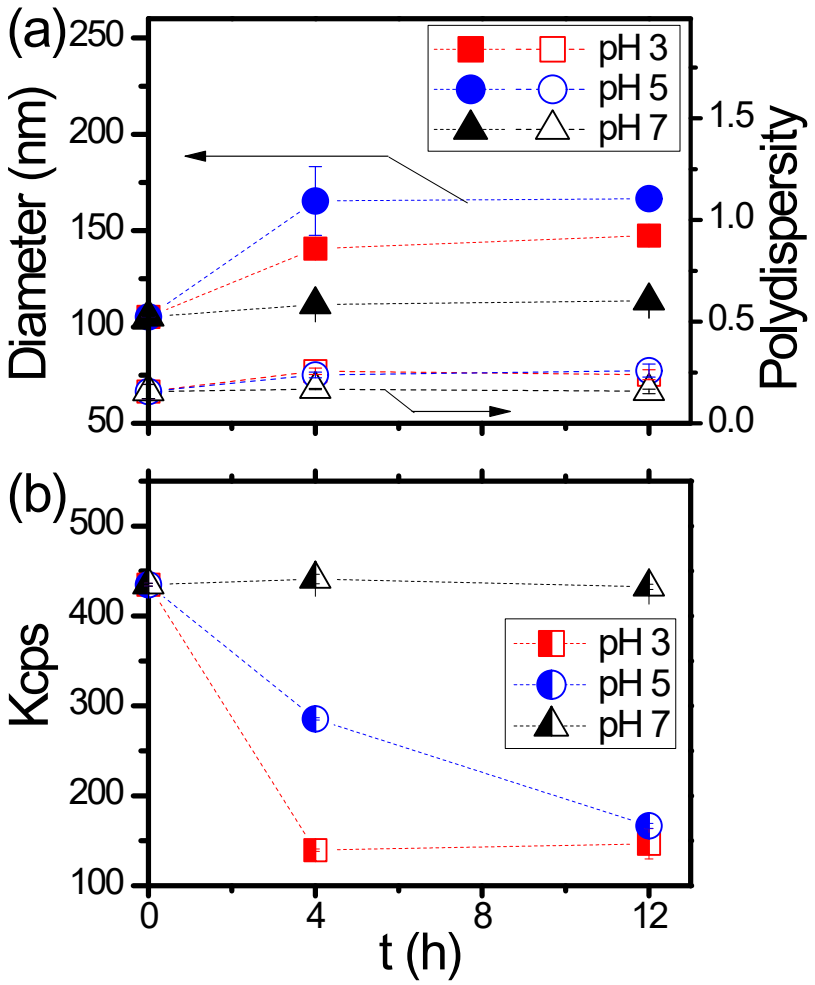



**Figure S13.** Micelle stabilities in different aqueous environments (i.e., pH = 3, 5, and 7 in 12 h at ambient) of P1–P6 measured by DLS.

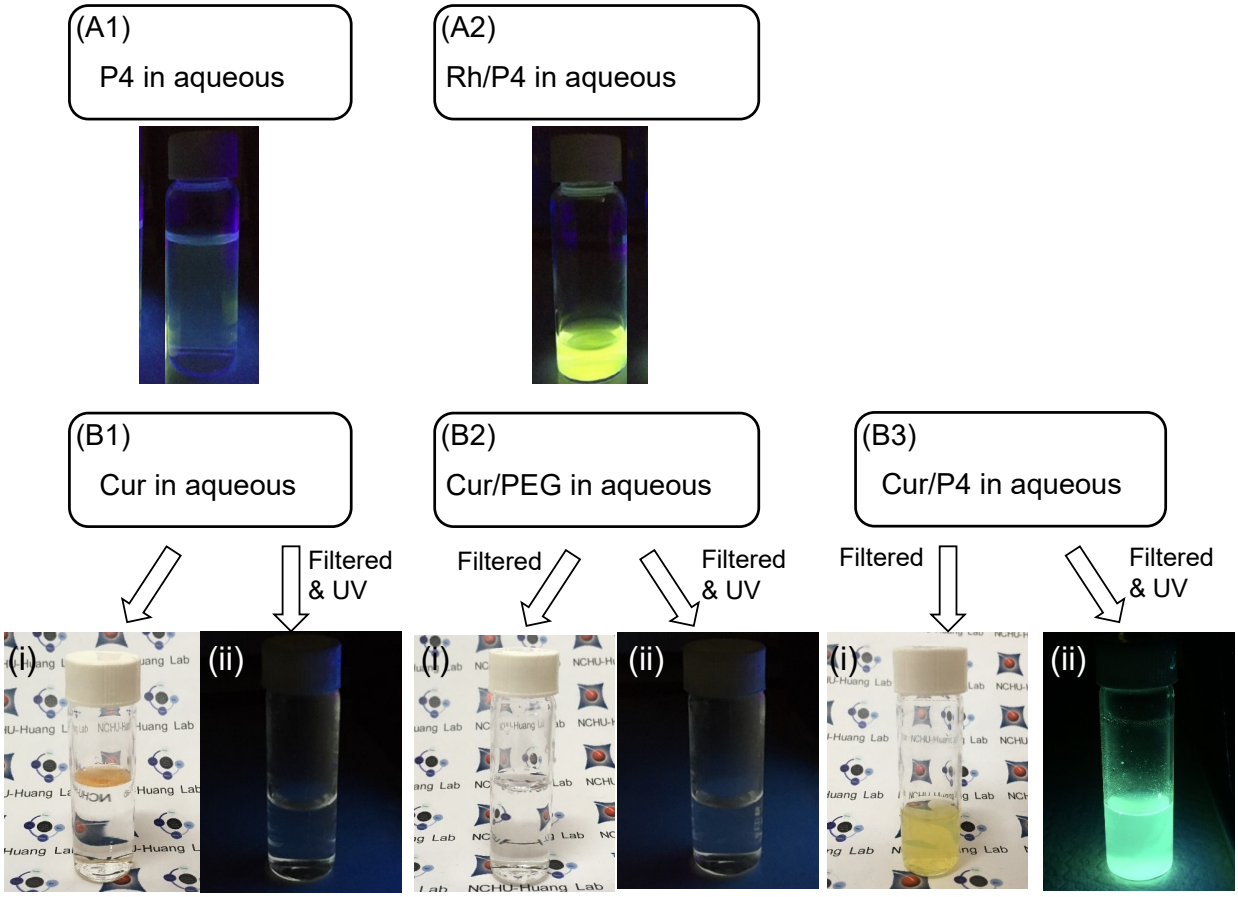



**Figure S14.** Rhodamine B (Rh) encapsulations photos of (A1) neat $P4_{(aq)}$ and (A2) $Rh/P4_{(aq)}$. Curcumin (Cur) encapsulations photos of (B1) neat Cur dispersed in DIW, (B2) $Cur/PEG_{(aq)}$, and (B3) $Cur/P4_{(aq)}$.

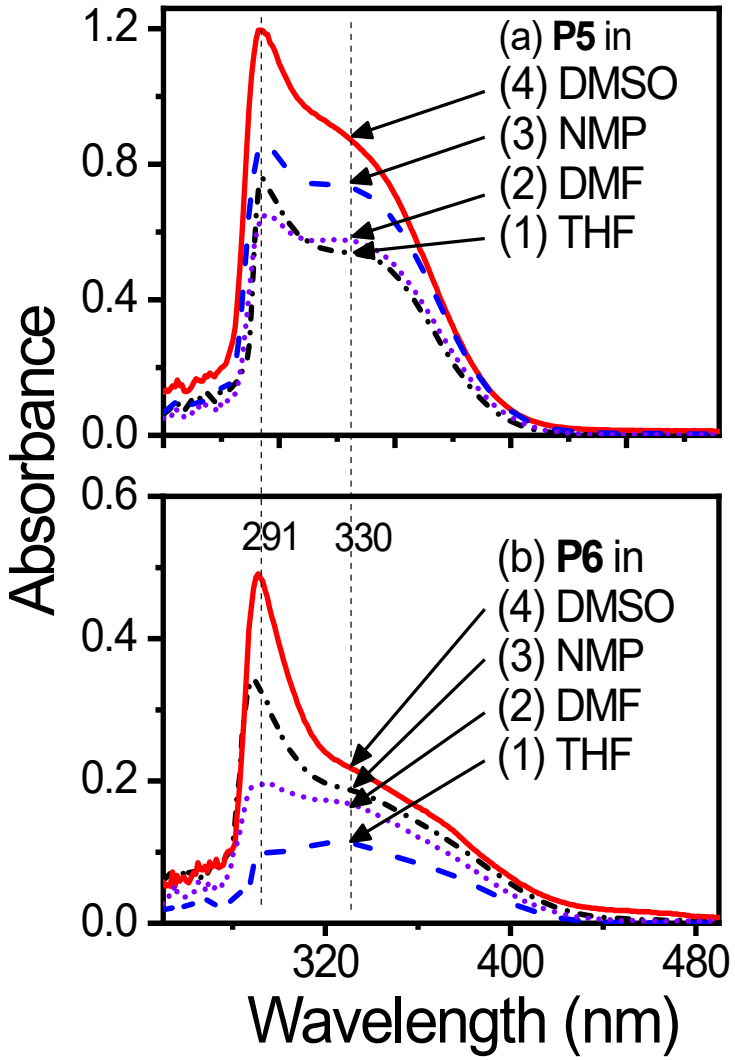



**Figure S15.** UV–Vis spectra of (a) P5 and (b) P6 in different solvents: (1) THF, (2) DMF, (3) NMP, and (4) DMSO.

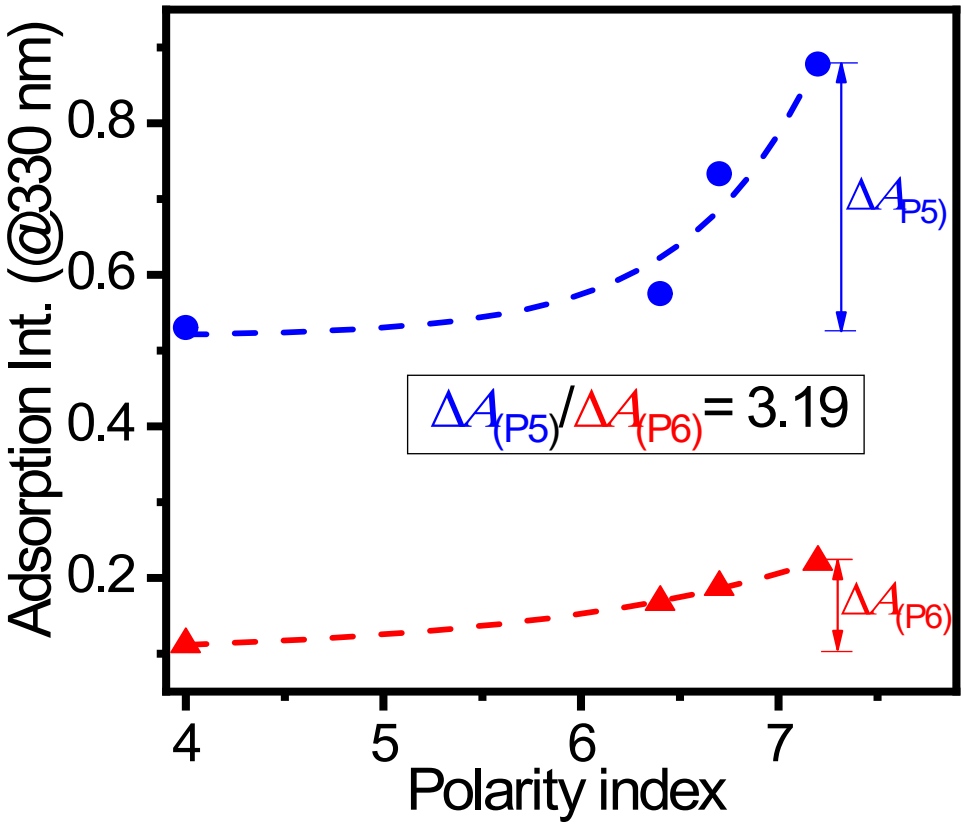



**Figure S16.** Relative trends of UV–Vis adsorption intensity variations ($\Delta A$) at 330 nm vs polarity index of solvents of (a) P5 and (b) P6 estimated from UV–Vis spectra (i.e., **Fig. S15**).

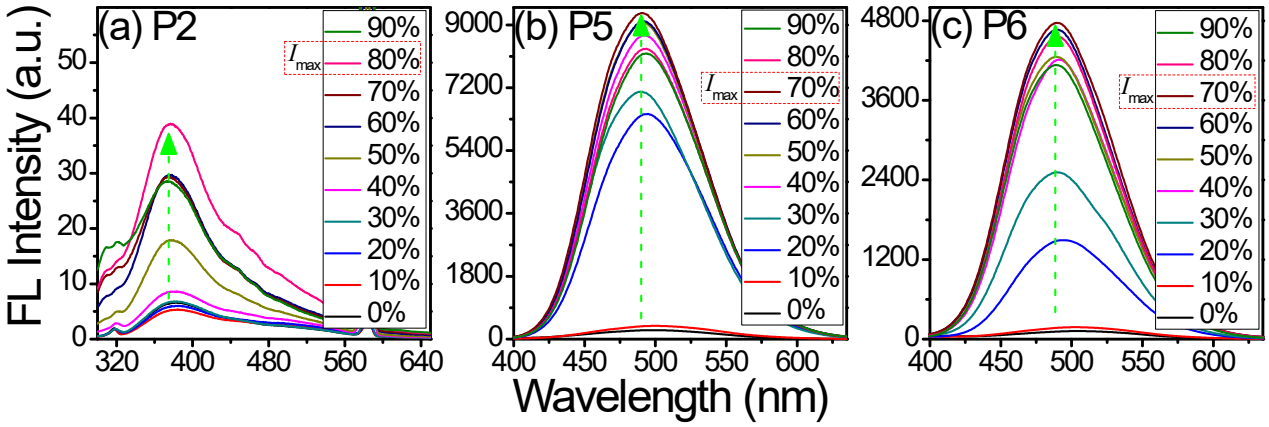



**Figure S17.** FL spectra of (a) P2 (400 V), (b) P5 (250 V), and (c) P6 (400 V) with various water vol.% in water and DMSO mixtures ($\lambda_{ex}$ = 330 nm; V: voltage).

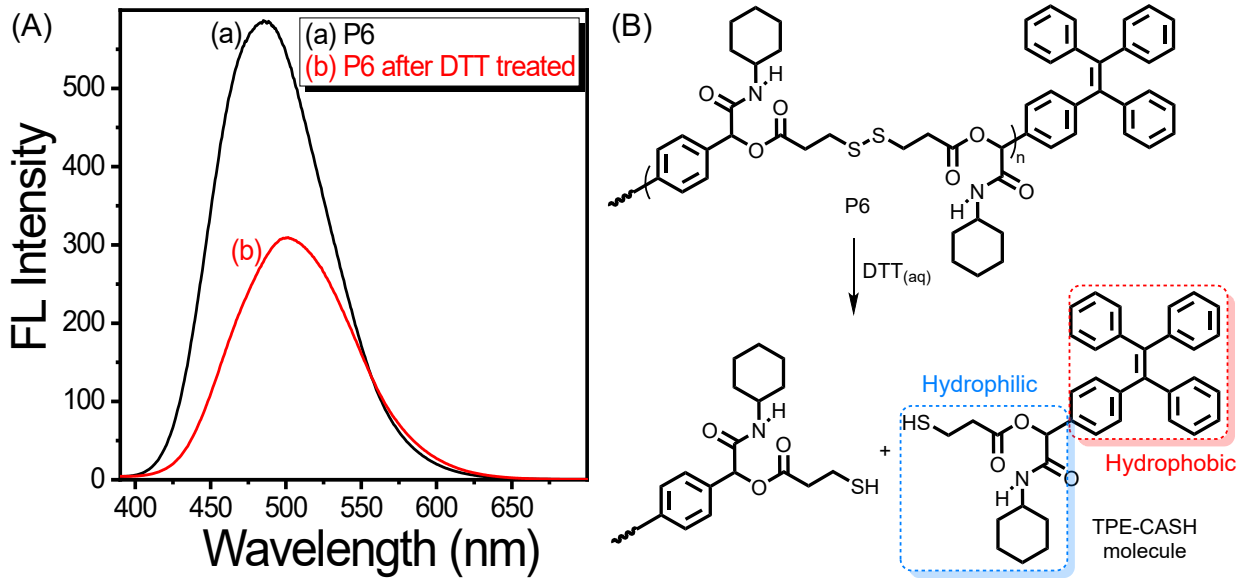



**Figure S18.** (A) FL spectra of DTT treatment of P6 (10 $mM_{(aq)}$, 0.5 h). (B) Plausibly chemical structure after chain end cleavage of P6.

## REFERENCES


1. Samy, M. M.; Mohamed, M. G.; Kuo, S. W., *Compos. Sci. Technol.* **2020,** *199*, 108360.
2. Mohamed, M. G.; Chen, T. C.; Kuo, S. W., *Macromolecules* **2021,** *54*, 5866.
3. Weng, M. T.; Elsyed, A. F. N.; Yang, P. C.; Mohamed, M. G.; Kuo, S. W.; Lin, K. S., *J. Taiwan Inst. Chem. Eng.* **2022,** *133*, 104238.