Supporting Information

Near-Infrared Light-Responsive UCST-Nanogels Using An Efficient Nickel-bis(dithiolene) Photothermal Crosslinker

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1. Synthesis

1.1 Synthesis of the nickel-bis(dithiolene) complex $Ni(SC_{10}styr)_4$

All the reagents were purchased from commercial sources and used as received. 4-hydroxy styrene was synthesized as previously described.[1]

All synthetic manipulations were performed under an inert and dry nitrogen atmosphere using standard techniques. The reactions were followed by Thin Layer Chromatography (TLC) plates, revealed with a UV-lamp at 254 nm or iodine. Silica gel used in chromatographic separations was obtained from Acros Organics (Silica Gel, ultra-pure, 40-60 µm). Aluminium oxide 90 standardized from Merck KGaA was also used for chromatographic separations. 300 (^{1}H) and 75.5 MHz (^{13}C) NMR spectra were recorded on Bruker Avance 300 spectrometer at room temperature using perdeuterated solvents as internal standards. FT-IR spectra were recorded using a Bruker VERTEX 70 spectrometer equipped with an ATR apparatus. Elemental analyses were performed by the Service de Microanalyse, Institut de Chimie des Substances Naturelles, Gif sur Yvette, France. Mass spectra were recorded with a MALDI-TOF Microflex LT Bruker. UV-Vis-NIR absorption spectra in solution were recorded on a Shimadzu UV3600 Plus spectrophotometer. Samples were placed in 1 cm path length quartz cuvettes.

1-((10-bromodecyl)oxy)-4-styrene

4-hydroxy styrene (1.8 g, 15 mmol), dibromodecane (22.78g, 75 mmol), anhydrous K_2CO_3 (4.2 g, 30 mmol), and hydroquinone monomethyl ether (MEHQ) (0.038 g, 0.3 mmol) were dissolved in 50 mL butanone. The solution was heated at 60 °C under nitrogen for 48 H. After cooling, the solution was filtered and the crude product was deposited on celite prior to column chromatography on silica gel using a gradient of eluents for pure petroleum ether to 50/50 petroleum ether/CH_2Cl_2. The product was isolated as a white powder in 40 % yield (2.0 g).

^{1}H NMR (300 MHz, Chloroform-d) δ 7.39 – 7.23 (m, 2H), 6.91 – 6.80 (m, 2H), 6.66 (dd, J = 17.6, 10.9 Hz, 1H), 5.60 (dd, J = 17.6, 1.0 Hz, 1H), 5.12 (dd, J = 10.9, 1.0 Hz, 1H), 3.96 (t, J = 6.5 Hz, 2H), 3.41 (t, J = 6.9 Hz, 2H), 1.94 – 1.70 (m, 4H), 1.50 – 1.21 (m, 12H). ^{13}C NMR (75 MHz, Chloroform-d) δ 159.08 (Cq), 136.42 (CH styrene), 130.39 (Cq), 127.47 (CH), 114.63 (CH), 111.52 (CH_2 styrene), 68.15 (CH_2), 34.13 (CH_2), 32.97 (CH_2), 29.57 (CH_2), 29.49 (CH_2), 29.46 (CH_2), 29.39 (CH_2), 28.88 (CH_2), 28.30 (CH_2), 26.15 (CH_2). IR-ATR (cm^{-1}): 2934 (νCH_2Br), 2918 (νCH_2), 2850 (νCH_2), 1629 (νC=C styrene), 1605, 1574, 1510, 1473, 1463, 1439, 1435, 1410, 1394, 1313, 1301, 1292, 1279, 1248, 1217, 1175, 1118, 1038, 1011, 994 (δCH styrene), 959, 900 (δCH styrene), 837, 824, 737, 720, 646, 568, 499. UV-vis-NIR [CH_2Cl_2, λmax (nm) (ε (M^{-1}.cm^{-1}))]: 262 (25285), 296 (3940). MALDI-TOF-MS: m/z = 339.9 (M+H$^+$). Anal. Calc. for $C_{18}H_{27}BrO$ (%): C 63.72, H 8.02. Found (%): C 63.33, H 8.12.

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[1] Amir R.J., Zhong S., Pochan D.J., Hawker C.J., Enzymatically Triggered Self-Assembly of Block Copolymers, *J. Am. Chem. Soc.* ***2009****, 131, 13949-13951*

4,5-bis((10-(4-vinylphenoxy)decyl)thio)-1,3-dithiole-2-thione

Tetraethylammonium [bis(1,3-dithiole-2-thione-4,5-dithiolato)zincate(II)] ($[NEt_4]_2[Zn(dmit)_2]$) (1.0 g, 1.4 mmol), 1-((10-bromodecyl)oxy)-4-styrene (1.9 g, 5.6 mmol) and MEHQ (0.013 g, 0.12 mmol) were dissolved in 20 mL acetone. The solution was refluxed under N_2 for 72 H. After evaporation of the acetone, the crude product was dissolved in CH_2Cl_2. The solution was then filtered to remove the insoluble and dried over celite. The product was purified by column chromatography on silica gel using a gradient of eluents for pure petroleum ether to pure CH_2Cl_2. The product was isolated as a yellow powder in 86 % yield (1.77 g).

^{1}H NMR (300 MHz, Chloroform-d) δ 7.33 (dd, J = 8.9, 2.3 Hz, 4H), 6.94 – 6.79 (m, 4H), 6.66 (ddd, J = 17.6, 10.9, 2.0 Hz, 2H), 5.60 (dd, J = 17.6, 2.1 Hz, 2H), 5.12 (dd, J = 10.9, 2.1 Hz, 2H), 3.95 (t, J = 6.5 Hz, 4H), 2.87 (t, J = 7.3 Hz, 4H), 1.88 – 1.59 (m, 8H), 1.53 – 1.20 (m, 24H). ^{13}C NMR (75 MHz, Chloroform-d) δ 211.62 (Cq, C=S), 159.08 (Cq), 136.49 (Cq), 136.42 (CH styrene), 130.40 (Cq), 127.48 (CH), 114.64 (CH), 111.54 (CH_2 styrene), 68.15 (CH_2), 36.91 (CH_2), 29.80 (CH_2), 29.59 (CH_2), 29.52 (CH_2), 29.48 (CH_2), 29.41 (CH_2), 29.18 (CH_2), 28.62 (CH_2), 26.17 (CH_2). IR-ATR (cm^{-1}): 2915 (νCH_2), 2848 (νCH_2), 1628 (νC=C styrene), 1606, 1575, 1509, 1468, 1412, 1393, 1322, 1300, 1288, 1249, 1176, 1117, 1060, 1039, 1021, 1010, 991 (δCH styrene), 962, 902 (δCH styrene), 882, 838, 822, 811, 795, 738, 718, 639, 569, 554, 522, 494, 471, 451. UV-vis-NIR [CH_2Cl_2, λmax (nm) (ε (M^{-1}.cm^{-1}))]: 262 (58850), 296 (14300), 386 (15450). MALDI-TOF-MS: m/z = 715.1 (M+H$^+$). Anal. Calc. for $C_{39}H_{54}O_2S_5$ (%): C 65.50, H 7.61, S 22.41. Found (%): C 65.60, H 7.765, S 22.41.

$Ni(SC_{10}styr)_4$ complex

2.2 eq. of potassium tert-butoxide (0.218 g, 1.94 mmol) were added to a solution of 4,5-bis((10-(4-vinylphenoxy)decyl)thio)-1,3-dithiole-2-thione (0.634 g, 0.88 mmol) dissolved in 20 mL dry THF. The solution was stirred overnight under N_2 at room temperature. $NiCl_2.6H_2O$ (0.105 g, 0.44 mmol) dissolved in methanol (2 mL) was added to the solution and the mixture was stirred for 2 h. Bu_4NBr (0.142 mg, 0.44 mmol) dissolved in methanol was added and the solution was stirred overnight under N_2 at room temperature. The THF was evaporated and the residue was dissolved in CH_2Cl_2 prior to the addition of 1 eq. of I_2 (0.112 mg, 0.22 mmol). This solution was stirred for 3 hours under N_2 at room temperature. After evaporation of the solvent, the product was purified by column chromatography on silica gel using a gradient of eluents from 25/75 CH_2Cl_2/petroleum ether to pure CH_2Cl_2. The product was further purified by precipitation from a mixture of CH_2Cl_2/MeOH by slow evaporation of the CH_2Cl_2. After filtration and drying, the product was isolated as a brown powder in 50 % yield (0.313 g).

^{1}H NMR (300 MHz, Chloroform-d) δ 7.43 – 7.31 (m, 8H), 6.96 – 6.79 (m, 8H), 6.68 (dd, J = 17.6, 10.9 Hz, 4H), 5.62 (d, J = 17.6 Hz, 4H), 5.13 (d, J = 10.8 Hz, 4H), 3.97 (t, J = 6.5 Hz, 8H), 3.40 (t, J = 7.3 Hz, 8H), 1.98 – 1.68 (m, 16H), 1.61 – 1.18 (m, 48H). ^{13}C NMR (75 MHz, Chloroform-d) δ 176.27 (Cq), 159.08 (Cq), 136.42 (CH styrene), 130.37 (Cq), 127.47 (CH), 114.64 (CH), 111.50 (CH_2 styrene), 68.16 (CH_2), 36.80 (CH_2), 29.60 (CH_2), 29.50 (CH_2), 29.40 (CH_2), 29.24 (CH_2), 29.08 (CH_2), 28.58 (CH_2), 26.17 (CH_2). IR-ATR (cm^{-1}): 2920 (νCH_2), 2850 (νCH_2), 1626, 1606, 1574, 1510, 1466, 1406, 1392, 1319, 1301, 1287, 1248, 1225, 1203, 1182, 1173, 1114, 1101, 1040, 1012, 987 (δCH styrene), 931, 898 (δCH styrene), 831, 788, 737, 722, 638, 569, 554, 493, 474, 411. UV-vis-NIR [CH_2Cl_2, λmax (nm) (ε ($M^{-1}.cm^{-1}$))]: 262 (126430), 294 (53200), 354 (16590), 1010 (31920). MALDI-TOF-MS: m/z = 1401.5 (M^+). Anal. Calc. for $C_{76}H_{108}NiO_4S_8$, CH_3OH (%): C 64.54, H 7.88, S 17.90. Found (%): C 64.58, H 7.77, S 17.67.

1.2 Other synthesis

7-acryloyloxy-4-methylcoumarin (AOMC) monomer

The AOMC monomer was synthesized using method previously described[2]. In round bottom flask, 0.1 mol of 7-hydroxy-4-methylcoumarin, 0.1 mol of NaOH and were dispersed in 550 mL EtOH. The mixture was heated at 60°C to dissolve the coumarin compound. The flask was then cooled at room temperature and placed in ice bath. 0.1 mol of methacryloyl chloride was added dropwise. The mixture was maintained under magnetic stirring during 90 minutes. Ice water was then added to precipitate the AOMC monomer. The white compound was filtered and washed with cold water and finally dried under vacuum. Finally, the AOMC monomer was purified by recrystallization in methanol.

S,S'-Bis(α,α'-dimethyl-α''-acetic acid)-trithiocarbonate (BTC) chain transfer agent

The BTC chain transfer agent was synthesized following previous method[3]. In round bottom flask placed in ice bath, 2.74 g of carbon disulfide, 10.75 g of chloroform, 5.23 g of acetone and 241 mg of tetrapropylammonium hydrogen disulfate were dissolved in 12 mL of toluene. The mixture was placed under nitrogen atmosphere. 20.16 g of NaOH aqueous dissolved in water (50 wt%) were added dropwise and mixture was maintained at room temperature under magnetic stirring over-night. 90 mL of water was then added to dissolve the solid compound. The aqueous phase was extracted and neutralized with 12 mL of concentrated HCl solution. The brown compound formed was filtered, washed with water and dried under vacuum. The product was purified by washing in toluene/acetone mixture. After drying, the final product was isolated as a yellow powder.

2. Characterizations

2.1 Dosage of Ni element using Inductively-Coupled Plasma Mass Spectrometer (ICP-MS)

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[2] Patel M.G., Patel H. J., Patel A.K., Patel K.H., Patel R.M., Acrylic Copolymers Based on Coumarin Derivative : Synthesis and Characterization, *Malaysian Polymer Journal* ***2011,*** *6(1), 70-86*

[3] Lai J. T., Filla D., Shea R., Functional Polymers from Novel Carboxyl-Terminated Trithiocarbonates as highly Efficient RAFT Agents, *Macromolecules* ***2002,*** *35, 6754-6756*

The Ni element was quantified by elemental analysis. The digestion of organic matrix was performed using a MarsXpress microwave digester (CEM, Buckingham, UK). For digestion, few mg of lyophilized samples were transfer into a teflon tubes to which 10 mL of concentrated nitric acid were added. The temperature of digester was raised from 25°C to 200°C in 20 minutes, then maintained during 15 additional minutes. For analysis, the digested samples were diluted 10 times in MilliQ water to obtain a final concentration of 2 wt% of nitric acid. Germanium was used as internal standard. Moreover, standard curve for calculation is prepared from 100 ppm of element standard mixture (M2-QC26-100 Elemental Scientific). Finally, two blanks were prepared and analyzed; the blank of digestion and the blank of analysis.

2.2 Determination of the photothermal conversion efficiency (η)[4]

The variation of thermal energy of a system over time corresponds to the difference between the rate of radiative energy converted to heat by the system (Q_{in}) and the rate of heat dissipated (Q_{loss}):

$$\sum_i m_i C_i \frac{dT}{dt} = Q_{in} - Q_{loss} \qquad [1]$$

where m_i and C_i are the mass and specific heat capacity of components i, respectively. T is the temperature of system and t is the time.

The heat produced by the system {nickel-bis(dithiolene) + water} following the NIR-light absorption, is defined as:

$$Q_{in} = I(1 - 10^{-A_{980}})\eta \qquad [2]$$

where I is the incident laser power, A_{980} is the optical density of the system at 980 nm and η is the photothermal conversion efficiency.

The heat dissipated to the external environment is defined as:

$$Q_{loss} = \sum hS[T_t - T_0] \qquad [3]$$

where h is the heat transfer efficiency, S is the area interface between the sample and the external environment. T_t is the temperature of sample at time t and T_0 is the ambient temperature.

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[4] Roper D. K., Ahn W., Hoepfner M., Microscale Heat Transfer Transduced by Surface Plasmon Resonant Gold Nanoparticles. *J. Phys. Chem. C* ***2007****, 111 (9), 3636–3641*

Since the mass and the heat capacity of nickel-bis(dithiolene) are much lower than that of water, the equation 1 can be simplified as:

$$\frac{d\Delta T}{dt} = \frac{I(1 - 10^{-A_\lambda})\eta}{m_w C_w} - \frac{\sum hS\Delta T}{m_w C_w} = A - B\Delta T \qquad [4]$$

where m_w and C_w are, respectively, the mass of water and its heat capacity. A is the rate of energy absorption and B is defined as the constant rate of heat dissipation. ΔT is defined as $T_t - T_0$.

$$A = \frac{I\left(1 - 10^{-A_\lambda}\right)\eta}{m_w C_w} \qquad [5]$$

$$B = \frac{hS}{m_w C_w} \qquad [6]$$

Following the thermal equilibrium (T_m), the laser is turned off and the constant B can be determined by measuring the diminution of temperature over time. In this regime, the temperature profile is described by equation 7. As Figure S1 shows, the constant B correspond to the slope of $\ln\left[\frac{T(t) - T_0}{T_m - T_0}\right]$ as a function of time t.

$$T_t = T_0 + \left(T_m - T_0\right)\exp(-Bt) \qquad [7]$$

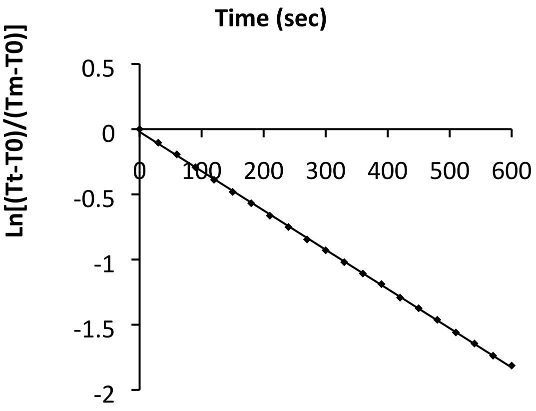

Figure S1. Determination of the constant B corresponding to the curve slope of Ln[(T_t-T_0)/(T_m-T_0)] as a function of time t.

When the laser is turned on, and at thermal equilibrium ($T_t \to T_m$), the photothermal conversion efficiency is determined as follows:

$$\frac{d\Delta T}{dt} = 0 \qquad [8]$$

$$\Delta T = T_m - T_0 = \frac{A}{B} \qquad [9]$$

$$\eta = \frac{B(T_m - T_0)m_w C_w}{I(1 - 10^{-A_{980\ nm}})} \qquad [10]$$

Using the B value extracted from Figure S1, and the measures of T_m, T_0, $A_{980\ nm}$ and I, the parameter η is determined by varying three parameters: light power density, nanogels concentration and solvent. The results are reported in Table SI.

The temperature change profile after the laser is turned on is given by equation 11.

$$T_t = T_0 + \frac{A}{B}(1 - \exp(-Bt)) \qquad [11]$$

Figure S2 shows the temperature rise profile measured during exposure to NIR-light, followed by the decay of temperature when the laser is turned off. The red dash line corresponds to the curve fitting using equations 7 and 11.

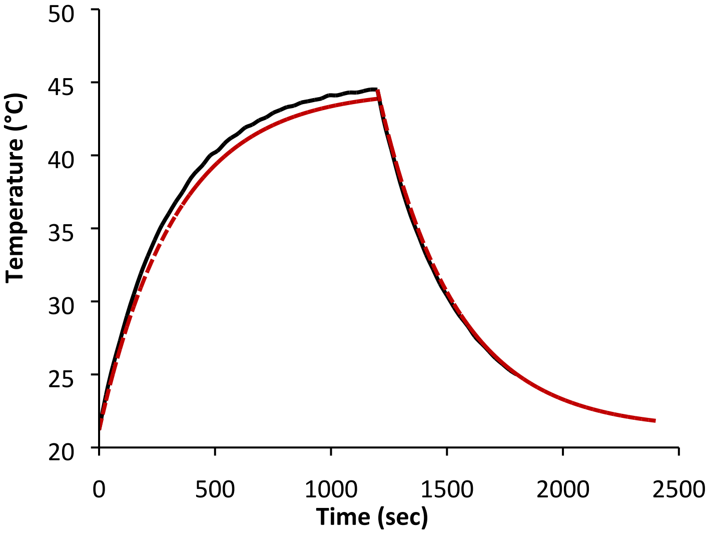

Figure S2. Black full-line corresponds to temperature profile of PDMA-UCST-C2 (0.1 wt% in water) under exposure to NIR laser (980 nm, 0.54 W/cm²), followed by decay of temperature when the laser source is turned off. Red dash-line is the curve fitting obtained using equations 7 and 11.

Table S1. Photothermal conversion efficiency (η) of PDMA-UCST-C2 for different conditions.

Concentration of nanogels	[Ni] µg/mL	Light power density W/cm²	Solvent	η
0.05 wt%	1.29	0.54	H_2O	0.649
0.1 wt%	2.58	0.15	H_2O	0,542
0.1 wt%	2.58	0.54	H_2O	0.540
0.1 wt%	2.58	0.74	H_2O	0.529
0.1 wt%	2.58	0.54	D_2O	0.492

2.3 Calibration of Nile Red content using the fluorescence emission

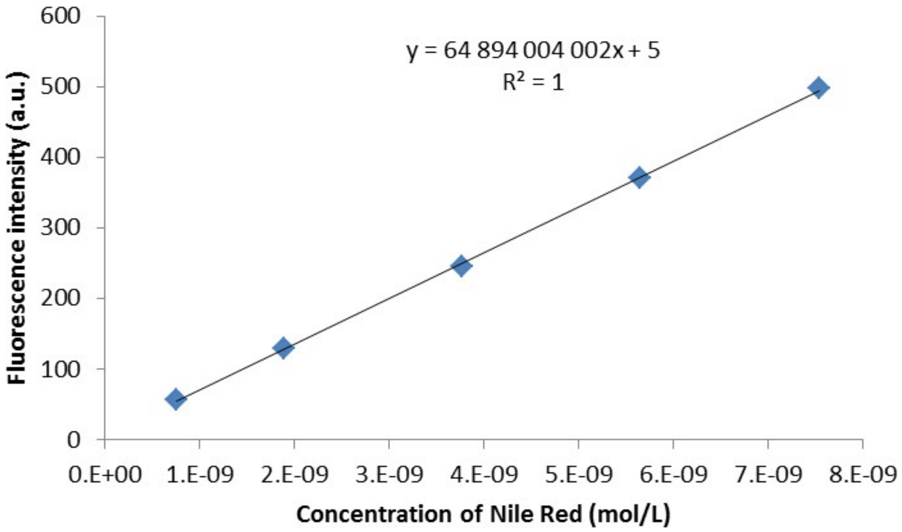

Figure S3. Calibration curve of Nile Red in DMSO obtained by fluorescence spectroscopy (λ_{exc}: 565 nm and λ_{em}: 600-800. Excitation and emission slits: 20 nm.)

2.4 Additional results

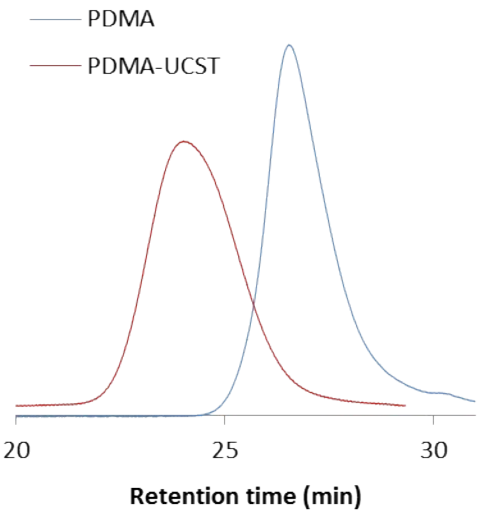

Figure S4. Chromatograms of PDMA and PDMA-UCST obtained by SEC, the polymers being dissolved in DMSO and poly(methyl methacrylate) used for calibration.

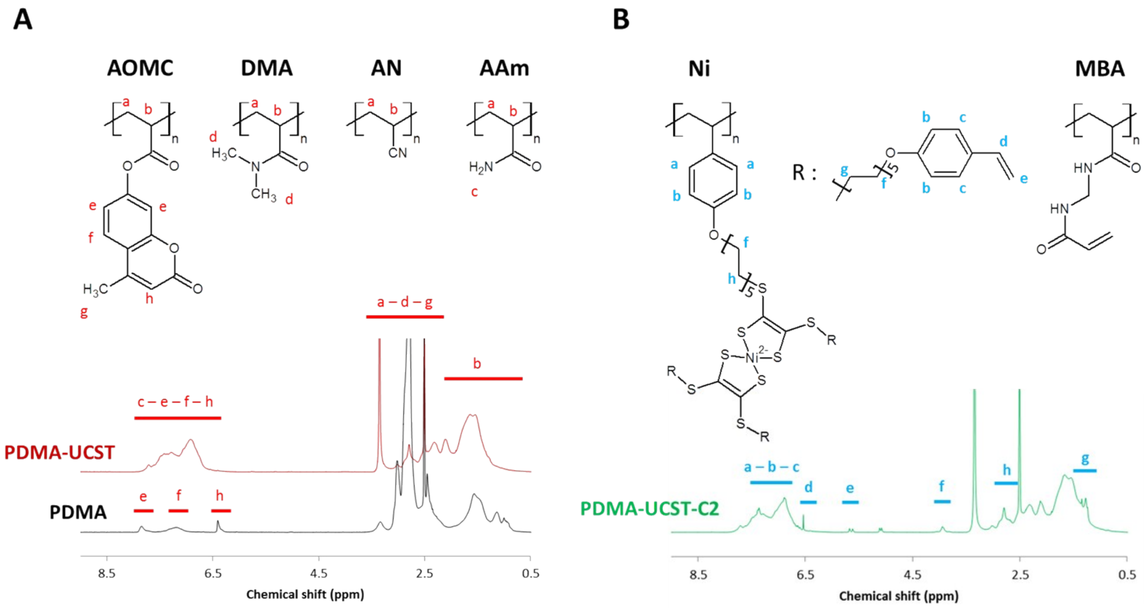

Figure S5. ^{1}H-NMR spectra of (A) PDMA and PDMA-UCST and (B) PDMA-UCST-C2 in d6-DMSO.

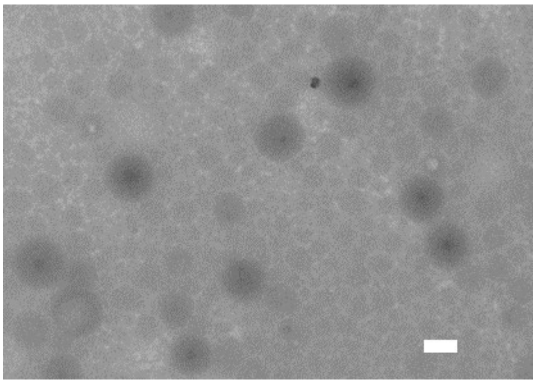

Figure S6. TEM images of PDMA-UCST-C1 nanoparticles (scale bar: 100 nm).

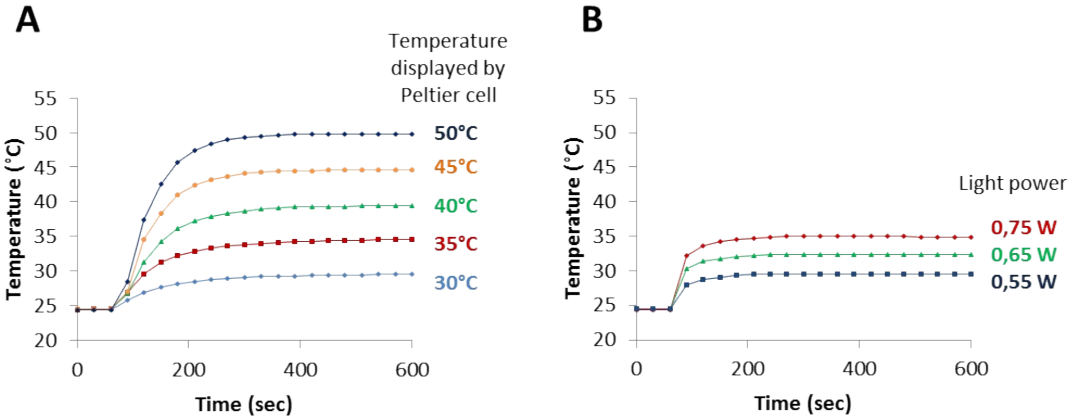

Figure S7. Temperature change profiles over time for PDMA-UCST-C1 (0.1 wt% in water): (A) for sample thermostated at different temperatures via a Peltier cell, and (B) for sample upon exposure to NIR light for several laser powers.

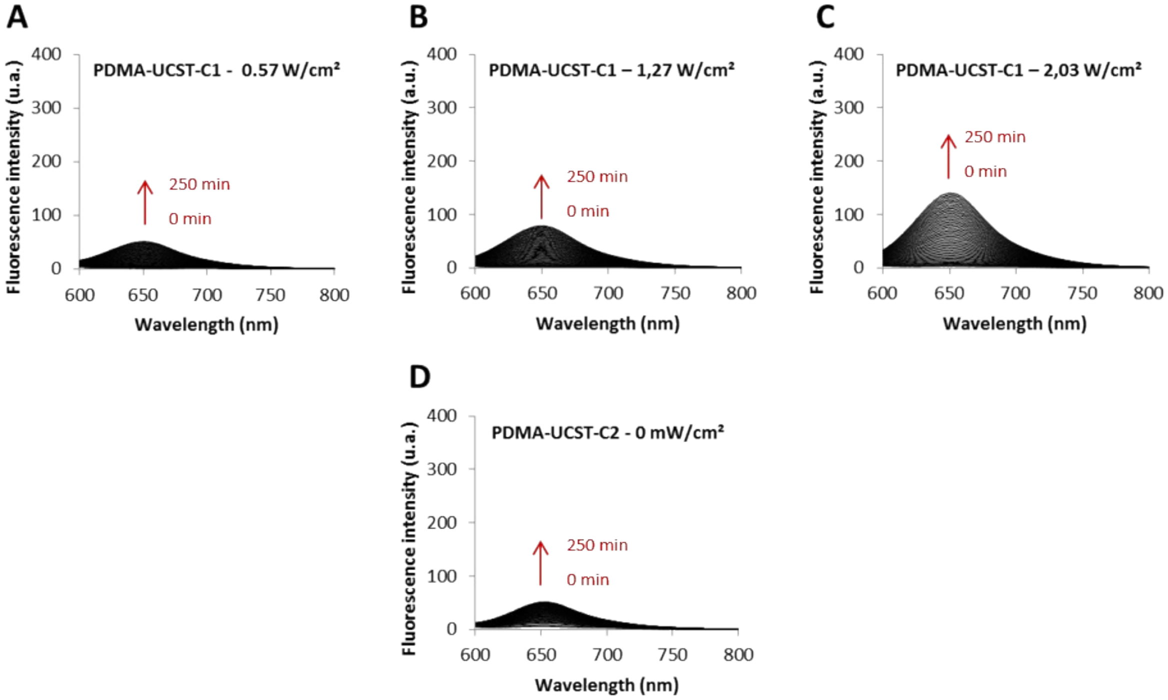

Figure S8. Fluorescence emission spectra of Nile Red released from PDMA-UCST-C1 exposed to NIR light with various light power densities: (A) 0.57 W/cm² (B) 1.27 W/cm² and (C) 2.03 W/cm². (D) Fluorescence spectra of Nile Red released from PDMA-UCST-C2 without laser irradiation.