Supporting Information

Photo-Redox Activated Drug Delivery Systems Operating Under Two Photon Excitation in the Near-IR

Tania M. Guardado-Alvarez[a], Lekshmi Sudha Devi[a], Jean-Marie Vabre[b], Travis Pecorelli[a], Benjamin J. Schwartz[a], Jean-Olivier Durand[c], Olivier Mongin[b,d], Mireille Blanchard-Desce[b,e] and Jeffrey I. Zink[a]

[a]*Department of Chemistry and Biochemistry and California NanoSystems Institute, University of California, Los Angeles, California 90095-1569.*

[b]*Chimie et Photonique Moléculaires, CNRS UMR 6510, Université de Rennes 1, Campus de Beaulieu, F-35042 Rennes Cedex (France)*

[c]*Institut Charles Gerhardt Montpellier, UMR 5253 CNRS-UM2-ENSCM-UM1, CC1701 Place Eugène Bataillon, 34095 Montpellier Cedex 05, France. e-mail : jean-olivier.durand@um2.fr, yannick.guari@um2.fr fax 0033467143852*

[d]*Institut des Sciences Chimiques de Rennes, CNRS UMR 6226, Université de Rennes 1, Campus de Beaulieu, 35042 Rennes Cedex, France*

[e]*Univ. Bordeaux, Institut des Sciences Moléculaires, CNRS UMR 5255, 351 Cours de la Libération, F-33405 Talence Cedex, France*

Experimental materials

Distilled, deionized H_2O was obtained using a Millipore water purification system. Reagent grade chemicals were used as purchased: tetraethoxysilane (TEOS) [98%, Aldrich] ,Hexadecyltrimethylammonium bromide [99% Aldrich], methanol [99.9%, Fisher], 2-mercaptoethanol [14.3 M pure liquid, Aldrich], 3-isocyanatopropyltriethoxysilane [95%, Aldrich], 3-(triethoxysilyl)-1-propanethiol [80 %, Aldrich], 3-aminopropyltriethoxysilane [99%, Aldrich], lead(II) thiocyanate [99.5%, Aldrich], bromine [99.9%, Aldrich], 1-Adamantanethiol [95 %, Aldrich], and β-cyclodextrin (β-CD) [98 %, Aldrich], Rhodamine B [95% Sigma], 1,1′-Diethyl-2,2′-carbocyanine iodide .

General methods

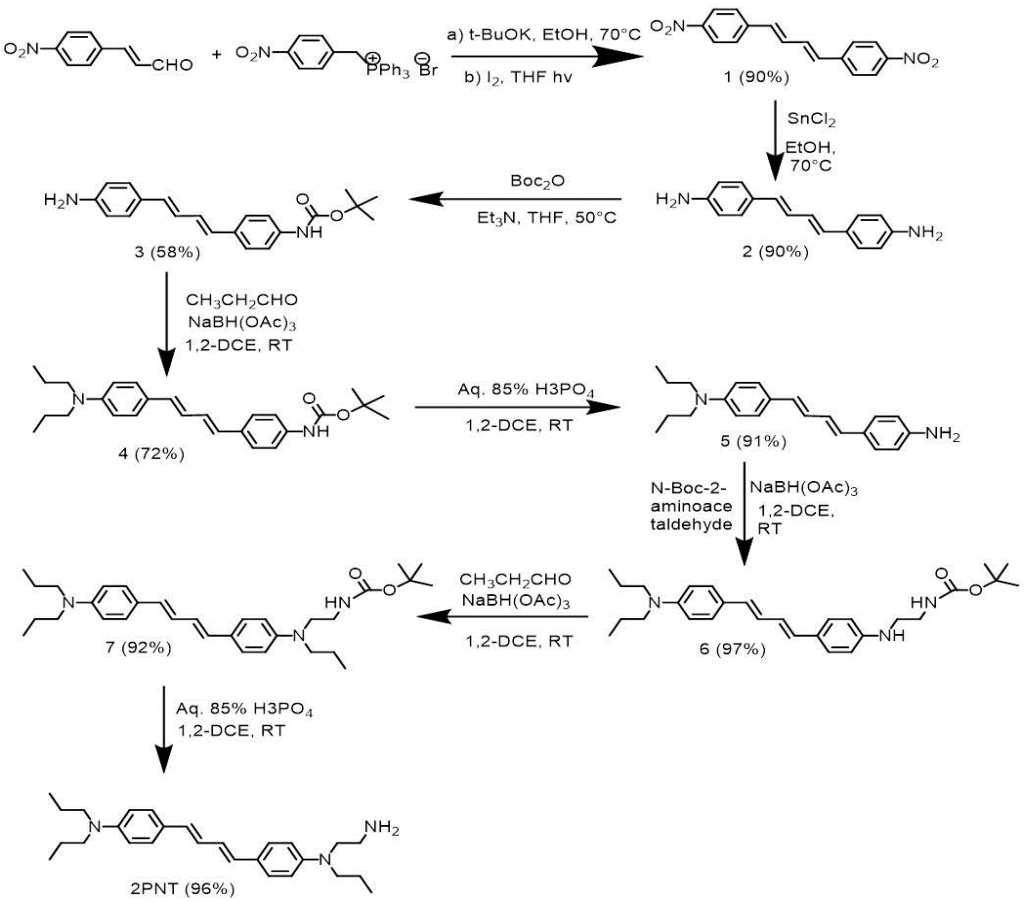
Transmission electron microscopy (TEM) images were collected on a JEM1200-EX (JEOL) instrument in the California NanoSystem Institute (CNSI). Microfilms for TEM imaging were made by placing a drop of the particle suspension in methanol onto a 200-mesh copper TEM grid (Ted Pella, Inc., Redding, CA) and dried at room temperature. Powder X-ray diffraction (XRD) patterns were collected using a Philips X'Pert Pro diffractometer equipped with Cu KR radiation. UV-Vis spectra were collected using a Cary 5000 UV-Vis-NIR spectrophotometer. The photo-continuous fluorescence spectroscopy was done using a monochromator connected to an Acton SpectraPro 2300i spectrometer coupled to a CCD and a coherent cube laser. A femtosecond Ti:Sapphire amplifier (Coherent, Legend Elite) seeded with a broadband Ti:Sapphire oscillator (Coherent, Mantis) was used for the two photon excitation. The amplifier output consisting of 40 fs, 60 μJ pulses centered around 800 nm (at 1 kHz repetition rate) was focused to a 2.5 mm spot size. Nuclear magnetic resonance (NMR) spectra were recorded by a Bruker DSX 300 at room temperature. N_2 adsorption-desorption isotherms were obtained at 77 K on a Quandrchrome Surface Area and Pore size analyzer. The emission spectra were measured on an Edinburgh FLS-920 spectrophotometer.

Synthesis of 2PNT

(E,E)-1,4-Bis(4-nitrophenyl)-1,3-butadiene (1). In a 1 L round bottom flask, trans-4-nitrocinnamaldehyde (6.0 g, 33.9 mmol) and (4-nitrobenzyl)triphenylphosphonium bromide (16.2 g, 33.9 mmol) were mixed in absolute EtOH (68 mL). The solution was purged with argon before dropwise addition of t-BuOK (11.4 g, 102.0 mmol) in absolute EtOH (205 mL). The mixture was stirred at room temperature for 12 h. Distilled water (200 mL) was added and the precipitate was filtrated, washed with

water/EtOH (40:60) and dried at 50 °C. The resulting powder was dissolved in 230 mL of THF and solution of (0.032 g, 0.127 mmol) iodine in THF (27 mL) was then added. The solution was stirred for 48 h under irradiation (75 W tungsten lamp). The solution was then treated with a saturated Na2S2O3 solution. The precipitate was filtered, washed with water, and dried at 50°C to afford 1 (9.04 g, 90%).

Scheme S1. Synthesis of the 2PNT



4,4'-(1E,3E)-1,3-Butadiene-1,4-diylbis(benzenamine) (2). In a 1 L round bottom flask, a solution of 1 (9.20 g, 31.1 mmol) in EtOH (123 mL) was purged with argon. Anhydrous tin (II) chloride (59.0 g, 311 mmol) was added and the mixture was stirred for 14 h at 70 °C. Aqueous NaOH was added until pH 8. The mixture was then filtered and the filtrate was extracted with AcOEt. After drying and evaporation under reduced pressure, the resulting solid was refluxed with AcOEt (750 mL) for 12 h under vigorous stirring. The mixture was filtered and rinsed with hot AcOEt. The solvent was evaporated and the residue was dried to afford 2 (6.61 g, 90%).

Carbamate 3. A solution of 2 (3.10 g, 13.1 mmol) in THF (136 mL) was cooled to 0 °C and Et3N (2.2 mL, 16.3 mmol) was added. A solution of di-tert-butyl dicarbonate (2.86 g, 13.1 mmol) in THF (50 mL) was added drop by drop (10 mL/h) at 65 °C for 5 h. THF was evaporated under reduced pressure and AcOEt and water were added. The organic layer was dried (MgSO4), filtered and evaporated. The residue was purified by flash chromatography on silica gel (AcOEt/heptane 1:3) to afford compound 3 (2.58 g, 58%).

Compound 4. To a solution of 3 (1.09 g, 3.24 mmol) in anhydrous 1,2-dichloroethane (20 mL) under argon, was added a solution of propanol (0.555 mL) in anhydrous 1,2-dichloroethane (5 mL). The mixture was stirred at room temperature for 3 h. Sodium triacetoxyborohydride (1.58 g, 7.45 mmol) was added and the mixture was stirred at room temperature for 12 h. A saturated sodium bicarbonate solution was then added until pH 7-8. After evaporation of 1,2-dichloroethane, the aqueous layer was

extracted with AcOEt. The organic phase was then washed with water and brine, dried over Na2SO4 and evaporated under reduced pressure. The residue was purified by flash chromatography (AcOEt/heptane/Et3N 30:70:0.1) to afford 4 (0.98 g, 72%).

Compound 5. To a solution of 4 (0.84 g, 2.0 mmol) in anhydrous 1,2-dichloroethane (25 mL, was added dropwise 85 % phosphoric acid (3.3 mL). The mixture was then stirred for 15 h at room temperature. Saturated sodium bicarbonate was added (100 mL) until pH 7-8. Dichloroethane was evaporated, and the mixture was extracted with AcOEt. The organic layer was washed with water and brine and dried over Na_2SO_4. After evaporation of the solvents under reduced pressure, the residue was purified by flash chromatography (AcOEt/heptane/Et3N 30:70:0.2) to afford 5 (0.582 g, 91%).

Compound 6. To a solution of 5 (0.54 g, 1.68 mmol) in anhydrous 1,2-dichloroethane (11 mL) under argon, was added N-Boc-2-aminoacetaldehyde (0.32 g, 2.02 mmol). The reaction was stirred at room temperature for 3 h. Sodium triacetoxyborohydride (0.46 g, 2.18 mmol) was then added and the mixture stirred for 5 h. A saturated sodium bicarbonate solution was then added until pH 7-8. After evaporation of 1,2-dichloroethane, the aqueous layer was extracted with AcOEt. The organic phase was then washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography (AcOEt/heptane/Et3N 30:70:0.1) to afford 6 (0.76 g, 1.63 mmol, 97%)

2PNT. To a solution of 7 (0.82 g, 1.63 mmol) in anhydrous 1,2-dichloroethane (20 mL, was added dropwise 85 % phosphoric acid (2.8 mL). The mixture was then stirred for 3 h at room temperature. Saturated sodium bicarbonate was added until pH 7-8. Dichloroethane was evaporated, and the mixture was extracted with AcOEt. The organic layer was washed with water and brine and dried over Na_2SO_4. The solvents were evaporated under reduced pressure 2PNT (0.63 g, 96%).

The characterizations for the synthesis of the 2PNT were done using NMR spectroscopy. For compound 1; 1H NMR (DMSO-d6, 300.13 MHz): δ 6.99 and 7.41 (AA'BB', 4H), 7.63 and 8.24 (AA'XX', JAX = 8.9 Hz, 8H); 13C NMR (DMSO-d6, 75.46 MHz): δ 124.1, 127.5, 133.0, 133.5, 143.4, 146.4. For compound 2; 1H NMR (DMSO-d6, 300.13 MHz,): δ 5.23 (s, 4H),δ 6.37 and 6.65 (AA'BB', 4H), 6.50 and 7.11 (AA'XX', JAX = 8.5 Hz, 8H); 13C NMR (DMSO-d6, 75.46 MHz): δ 114.4, 125.4, 125.8, 127.5, 131.1, 148.7. For compound 3; 1H NMR (DMSO-d6, 300.13 MHz,): δ 1.47 (s, 9H), 5.30 (s, 2H), 6.45-6.83 (m, 4H), 6.53 and 7.14 (AA'XX', JAX = 8.5 Hz, 4H), 7.34 and 7.38 (AA'BB', 4H), 9.38 (s, 1H); 13C NMR (DMSO-d6, 75.46 MHz): δ 28.1, 79.1, 113.9, 118.2, 124.2, 124.9, 126.3, 127.4, 128.4, 129.3, 131.5, 132.8, 138.5, 148.6, 152.7. For compound 4; 1H NMR (DMSO-d6, 300.13 MHz): d 0.87 (t, J = 7.3 Hz, 6H), 1.52 (m, 4H), 1.48 (s, 9H), 3.23 (t, J = 7.3 Hz, 4H), 6.46-6.96 (m, 4H), 6.59 and 7.26 (AA'XX', JAX = 8.4 Hz, 4H), 7.33 and 7.40 (AA'BB', JAB = 8.4 Hz, 4H), 9.40 (s, 1H); 13C NMR (DMSO-d6, 75.46 MHz) d 11.1, 20.0, 28.1, 51.8, 79.0, 111.4, 118.1, 124.0, 124.3, 126.3, 127.5, 128.4, 129.3, 131.5, 132.4, 138.5, 147.4, 152.6. For compound 5; 1H NMR (DMSO-d6, 300.13 MHz): d 0.87 (t, J = 7.3 Hz, 6H), 1.51 (sext, J = 7.5 Hz, 4H), 3.22 (t, J = 7.3 Hz, 4H), 5.26 (s, 2H), 6.53 and 6.68 (AA'BB', 4H), 6.50 and 7.12 (AA'XX', JAX = 8.5 Hz, 4H), 6.57 and 7.22 (AA'XX', JAX = 8.9 Hz, 4H). For Compound 6; 1H NMR (DMSO-d6, 300.13 MHz) : d 0.87 (t, J = 7.3 Hz, 6H), 1.37 (s, 9H), 1.51 (sext, J = 7.5 Hz, 4H), 3.06 (m, 4H), 3.22 (t, J = 7.3 Hz, 4H), 5.83 (br s, 1H), 6.42 and 6.70 (AA'BB', 4H), 6.91 (br s, 1H), 6.52 and 7.19 (AA'XX', JAX = 8.6 Hz, 4H), 6.57 and 7.23 (AA'XX', JAX = 8.9 Hz, 4H); 13C NMR (DMSO-d6, 75.46 MHz) d 11.3, 20.1, 28.3, 30.7, 42.7, 52.0, 77.8, 111.5, 112.0, 124.5, 125.1, 125.5, 127.2, 127.3, 130.4, 130.6, 147.1, 148.1, 155.8. For compound 7; 1H NMR (DMSO-d6, 300.13 MHz): d 0.87 (t, J = 7.3 Hz, 9H), 1.37 (s, 9H), 1.51 (sext, J = 7.5 Hz, 6H), 3.03 (m, 2H), 3.22 (t, J = 7.3 Hz, 6H), 3.31 (m, 2H), 6.44 and 6.72 (AA'BB', 4H), 6.58 and 7.23 (AA'XX', JAX = 8.7 Hz, 4H), 6.72 and 7.23 (AA'XX', JAX = 8.7 Hz, 4H), 6.94 (t, J = 6.0 Hz, 1H). For compound 8; 1H NMR (DMSO-d6, 300.13 MHz): d 0.87 (t, J = 7.3 Hz, 9H), 1.51 (sext, J = 7.5 Hz, 6H), 2.67 (br s, 2H), 3.31-3.23 (m, 10H), 6.43 and 6.71 (AA'BB', 4H), 6.58 and 7.23 (AA'XX', JAX = 8.9 Hz, 4H), 6.62 and 7.23 (AA'XX', JAX = 8.9 Hz, 4H); 13C NMR (DMSO-d6, 75.46 MHz) d 11.1, 19.9, 20.0, 30.6, 51.8, 52.0, 111.3, 111.4, 124.3, 124.6, 124.9, 125.1, 127.0, 127.1, 130.1, 130.3, 147.0, 147.1; HRMS (ES+) calculated for C27H39N3 (M+.) m/z 405.3144, found 405.3135.

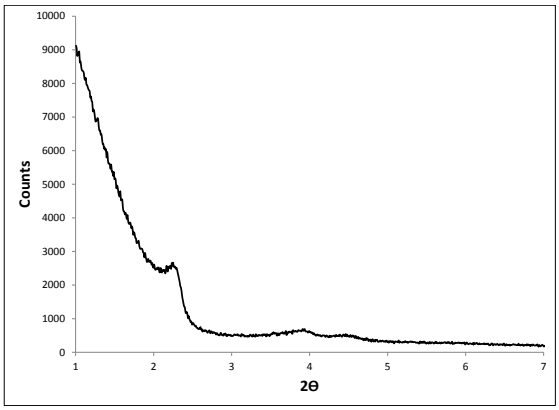


Fig. S1. Powder XRD of the surfactant extracted MCM-41 silica nanoparticles.

The Fig. S1 represents the powder X-ray diffraction of MCM-41 nanoparticles. The higher-order peaks observed in the powder XRD can be indexed as the (1 0 0), (1 1 0) and (2 0 0) planes with a lattice spacing of 4 nm. The observed peaks are typical of an MCM-41.

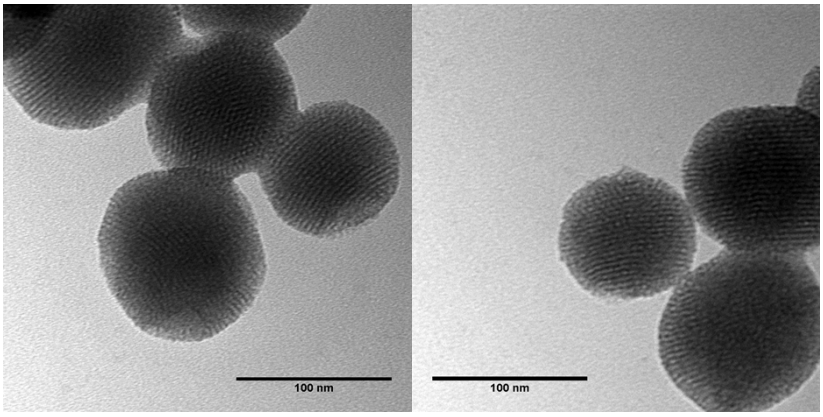


Fig. S2. Transmission electron microscopy of the surfactant extracted MCM-41 silica nanoparticles.

The TEM images showed a particle diameter of about 100 nm (Fig. S2). The images also showed a hexagonal pores structure that is consistent with MCM-41 type mesoporous silica nanoparticles (MSNs). The nanoparticles were well dispersed and the pore structure well defined.

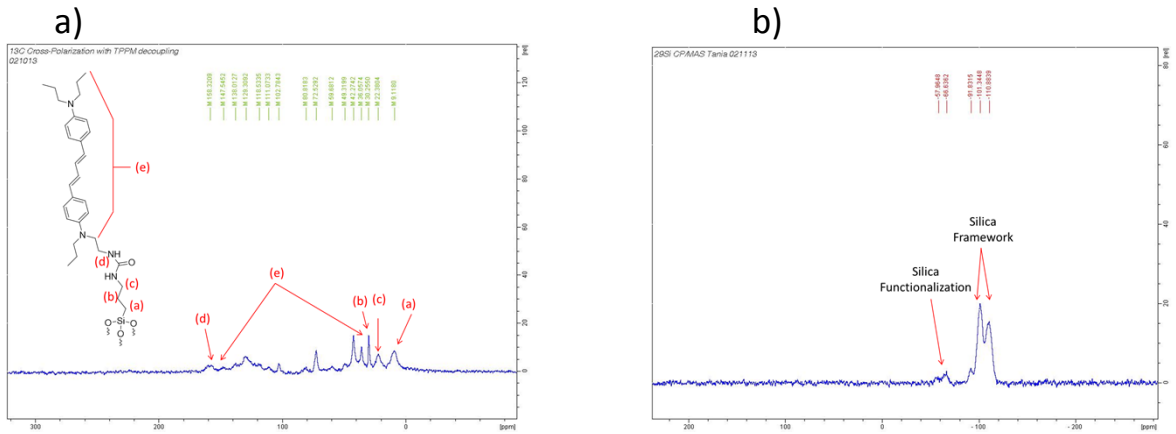


Fig. S3. a)[13] C solid state NMR Characterization of the 2PNT on the MSNs. b) [29] Si solid state NMR characterization of the 2PNT on the MSNs.

The [13]C chemical shifts in Fig. S3 a) labeled a, b, c and d belong to the linker where the d represents the carbonyl carbon. The region labeled as e represents chemical shifts belonging to the nanotrigger molecule portion responsible for the electron transfer. Fig. S3 b) shows the [29]Si chemical shifts for the silica framework at 91 ppm, 101 ppm and 110 ppm. Also shown is the chemical shift for the functionalized silica at 66 ppm.

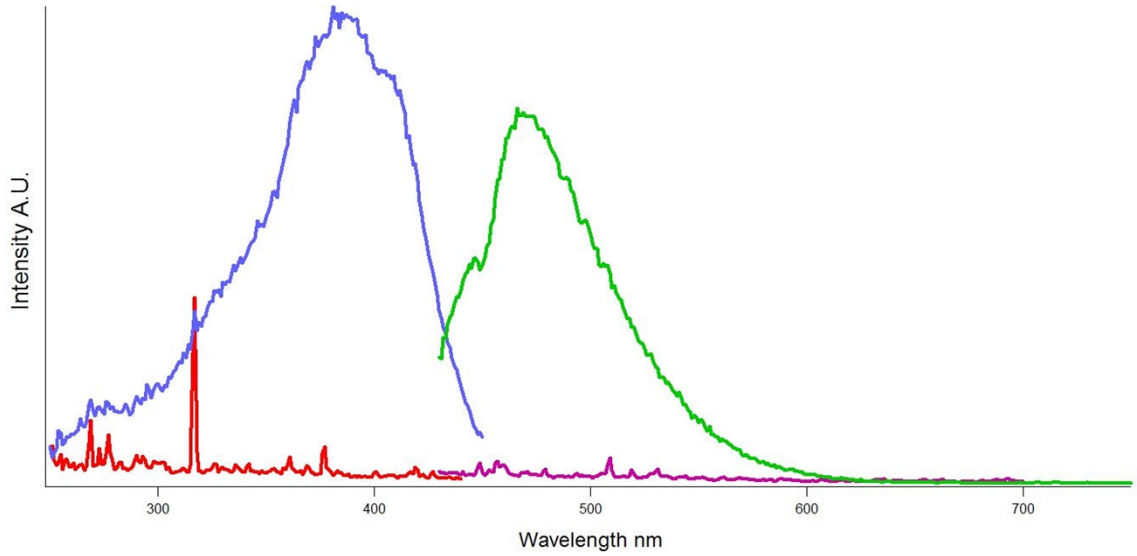


Fig. S4. Excitation spectrum of the bare MSNs (red), emission spectrum of the bare MSNs (purple), excitation spectrum of the 2PNT-MSNs (blue) and, emission spectrum of the 2PNT-MSNs (green).

In order to further confirm the attachment of the 2PNT on the surface of the MSNs an excitation-emission spectra was taken. An excitation (blue) and emission (green) spectra of the surfactant extracted 2PNT functionalized MSNs was taken and a signal was observes at ~350 nm for the excitation and ~480 nm for the emission. Additionally an excitation (red) and emission (purple) spectra of the surfactant extracted unfunctionalized MSNs was taken and no signal was observed providing evidence of the 2PNT attachment on the MSNs surface.

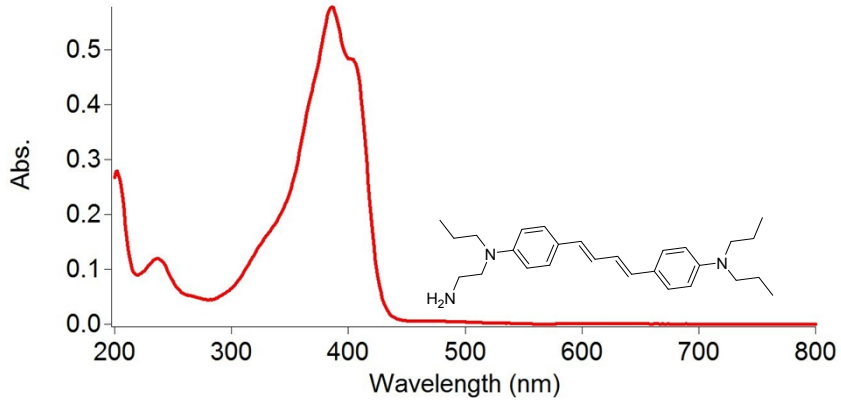


Fig. S5. UV-Vis spectra of the 2PNT in methanol.

Fig. S5 shows a UV-vis of the 2PNT in a methanol solution and confirms that there is no absorption of the 2PNT around the 800

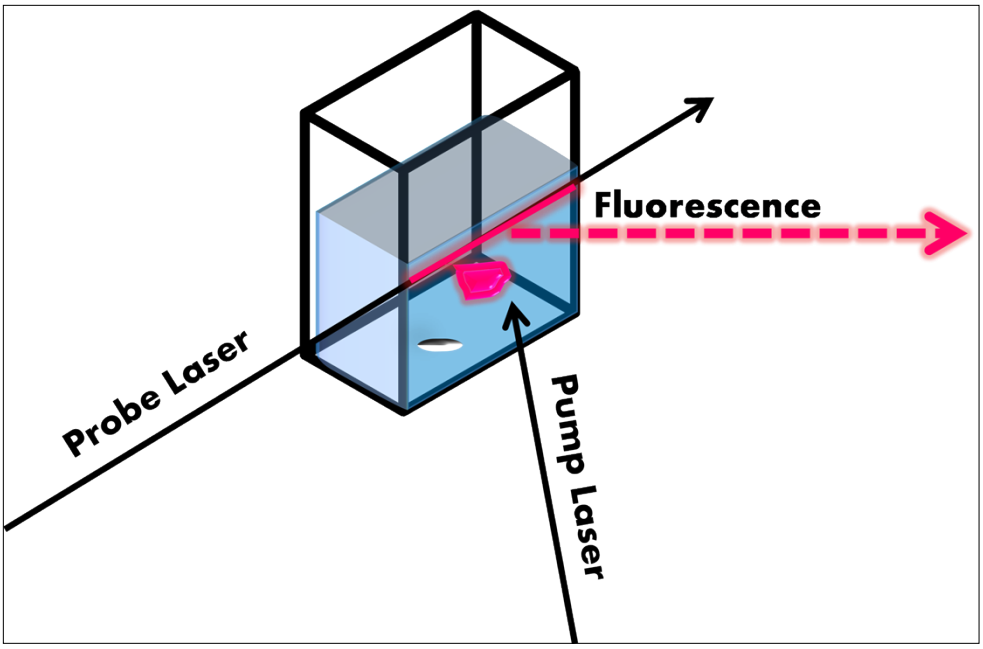


Fig. S6. Pictorial representation of detection set-up for the one photo-continuous fluorescence spectroscopy experiments

nm region.

The release profiles for the one photon experiments were performed following the set up depicted in Fig. S6.

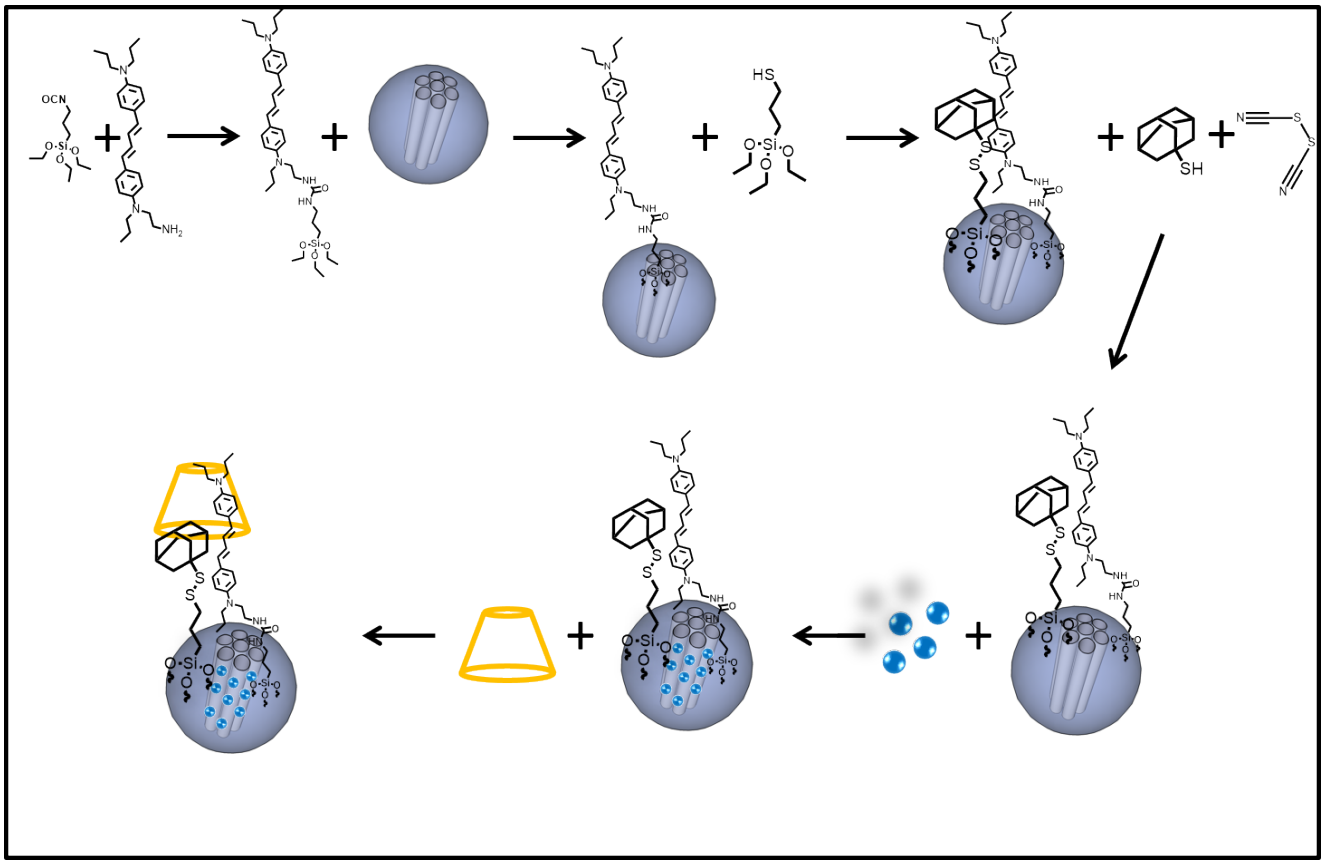


Fig. S7. Schematic representation of the synthesis of fully assembled snap-top with 2PNT system.

The schematic representation of the synthesis of the 2PNT-snap-too is shown on Fig. S7.