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Reactive Oxygen Species (ROS) Responsive PEG-PCL Nanoparticles with pH-Controlled Negative-to-Positive Charge Reversal for Intracellular Delivery of Doxorubicin

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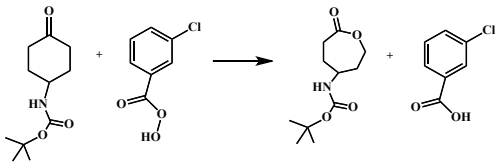
Materials

Methoxy poly (ethylene glycol) (mPEG, Mn = 5.0×10^3 g/mol), stannous octoate ($Sn(Oct)_2$), ε-caprolactone (ε-CL), 4-(tert-butyloxycarbonylamino) cyclohexanone and m-chloroperoxybenzoic acid were purchased from Sigma-Aldrich (Milwaukee, USA). Prior to use, PEG was dried by an azeotropic distillation in toluene and ε-CL was dried over calcium hydride (CaH_2) for 48 h at room temperature and distilled under reduced pressure.

Synthesis of γ-(carbamic acid tert-butyl ester)-ε-caprolactone (CATCL)

As shown in **Scheme S1**, γ-(carbamic acid tert-butyl ester)-ε-caprolactone (CATCL) was prepared through a Baeyer-Villiger oxidation. 4-(tert-butyl oxycarbonylamino)cyclohexanone (21.3 g, 0.1 mol) and 3-chloroperoxybenzoic acid (20.6 g, 0.12 mol) were dissolved in dichloromethane (100 mL) and the mixture was refluxed for 15 h at 43 °C. After the dichloromethane was evaporated, CATCL was obtained through recrystallization in diethyl ether. Yield: 77%.



Scheme S1. Synthesis route of CATCL

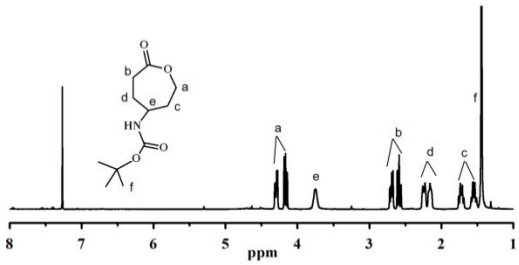


Fig. S1 The ^{1}H-NMR spectra of CATCL

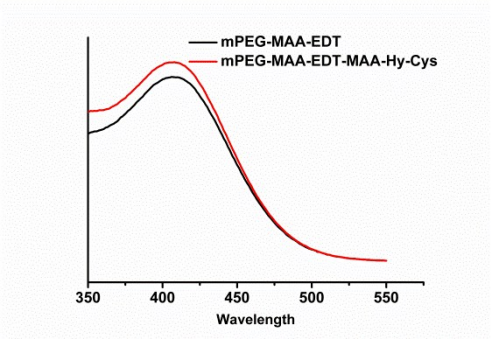


Fig. S2 The concentration of the thiol groups of copolymers was measured using Ellman reagent 5, 5-dithio-bis(2-ni-trobenzoci acid)

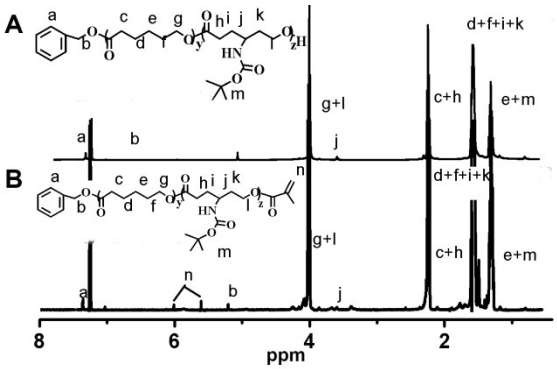


Fig. S3 ^{1}H-NMR characterization of PA-P(Cl-co-CATCL) (A) and PA-P(Cl-co-CATCL)-MAA (B).

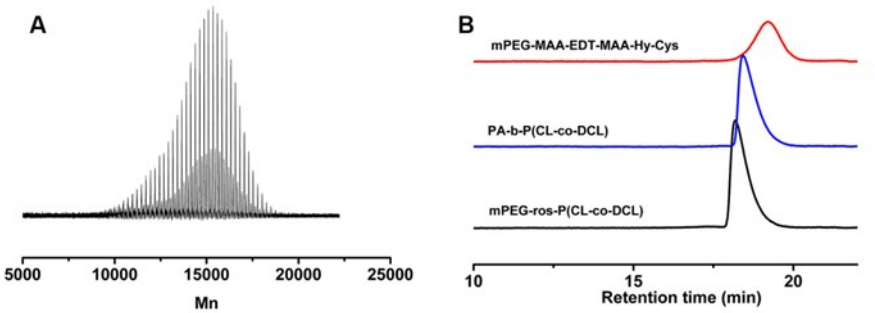


Fig. S4 MALDI-TOF-MS analysis of the conjugation of mPEG-ros-P(CL-co-DCL) (A). GPC elution chromatograms of mPEG-MAA-EDT-MAA-Hy-Cys, PA-b-P(CL-co-DCL) and mPEG-ros-P(CL-co-DCL) (B).

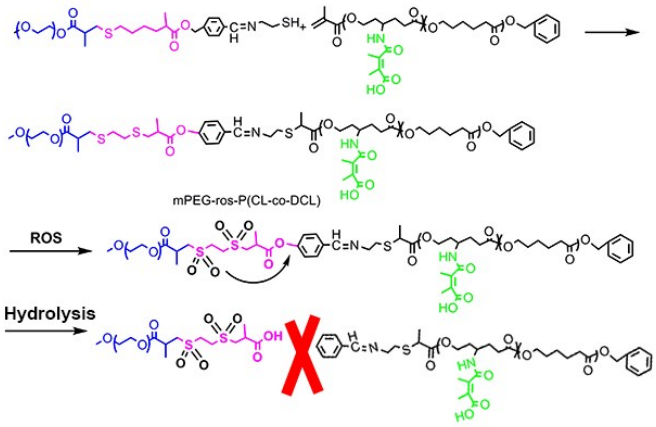


Fig. S5 The ROS responsive mechanism of thioether.

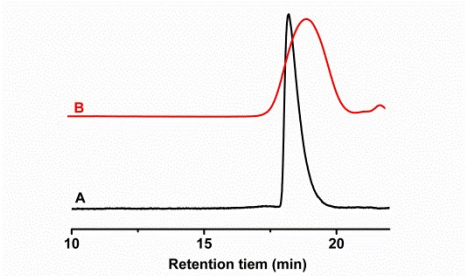


Fig. S6 GPC charts of mPEG-ros-P(CL-co-DCL) before (A) and after treated with 10 mM H_2O_2 for 12 h (B).

Table S1. Stability of blank and DOX-loaded mPEG-ros-P(CL-co-DCL) NPs

Copolymers	Blank NPs				DOX-loaded NPs			
	Size (nm)[a]	PDI [a]	Size (nm)[b]	PDI[b]	Size (nm)[a]	PDI [a]	Size (nm)[b]	PDI [b]
$mPEG_{113}$-b-PCL_{67}	98 ± 6	0.11	105 ± 6	0.12	108 ± 10	0.11	110 ± 8	0.11
$mPEG_{113}$-ros-P(CL_{42}-co-DCL_{10})	103 ± 8	0.12	115 ± 9	0.11	95 ± 8	0.12	101 ± 7	0.12
$mPEG_{113}$-ros-P(CL_{41}-co-DCL_{22})	119 ± 10	0.12	126 ± 8	0.13	112 ± 11	0.14	116 ± 8	0.13
$mPEG_{113}$-ros-P(CL_{43}-co-DCL_{33})	141 ± 12	0.13	148 ± 10	0.11	132 ± 13	0.13	141 ± 10	0.12

[a]Determined using Laser particle size analyzer at 25°C in PBS (10 mM, pH 7.4).

[b] Determined using Laser particle size analyzer at 25°C in PBS (10 mM, pH 7.4) containing 10% (v/v) FBS .