Programmable self-assembly of cystamine-block copolymer in response to pH and progressive reduction-ionization-oxidation

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Electronic Supporting Information (ESI)

Synthesis of poly(2-hydroxypropylmethacrylamide) macromolecular chain transfer agent (PHPMA macro-CTA)

Typical protocol for the synthesis is as follows: HPMA (5.965 g, 41.7 mmol), CEP (0.0727 g, 0.276 mmol) and SPTP (0.0215 g, 0.0692 mmol) were dissolved in 2-butoxyethanol/water (30:70 wt./wt., 5.925 g) in a 25 mL flask. The flask was sealed with rubber septa and immersed into water bath at 25°C. The solution was bubbled with argon gas in the dark for 40 min, and then irradiated with visible light for 105 min. The reaction was quenched by exposure to air and addition of hydroquinone inhibitor. ^{1}H NMR revealed that 60% HPMA was polymerized. The polymer was precipitated from excess of acetone, washed 3 times in the precipitation solvent, and dried under vacuum at 25°C for 3 days.

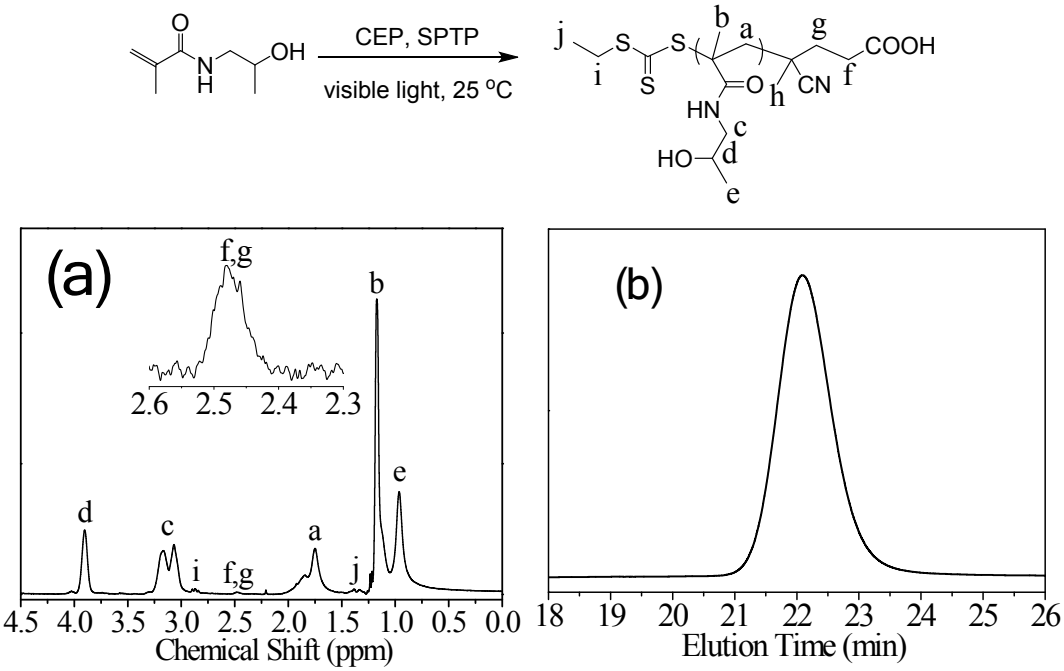


Fig. S1 (a) ^{1}H NMR spectrum and (b) GPC trace of PHPMA synthesized via RAFT polymerisation at a $[HPMA]_0$=3.46 M and a $[HPMA]_0/[CEP]_0/[SPTP]_0$=150:1:0.25 in BOE/water (30:70, wt./wt.) under visible light irradiation at 25°C for 105 min (^{1}H NMR: 60% conversion).

^{1}H NMR results confirmed extremely high fidelity of the CEP chain-ends of as-obtained polymer, and can serve as macromolecular chain transfer agent. The molecular structure $PHPMA_{90}$, i.e. DP=90, was determined by ^{1}H NMR studies according to $DP=4\times I_d/I_{f+g}$, in which I_d is the integral signal *d* within HPMA units, and I_{f+g} are integral signals *f*, *g* at CEP chain-ends. The SEC trace is perfectly unimodal and symmetrical. The analysis indicated M_n of 28.2 kDa and M_w/M_n of 1.07.

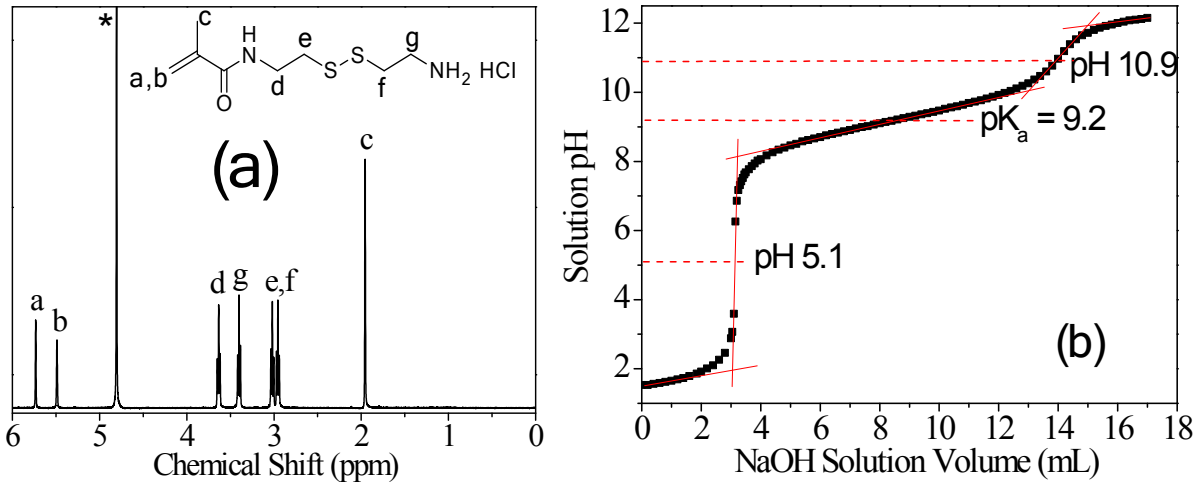


Fig. S2 (a) ^{1}H NMR spectrum and (b) the acid-base titration plot of cystamine methacrylamide hydrochloride (CysMA) monomer.

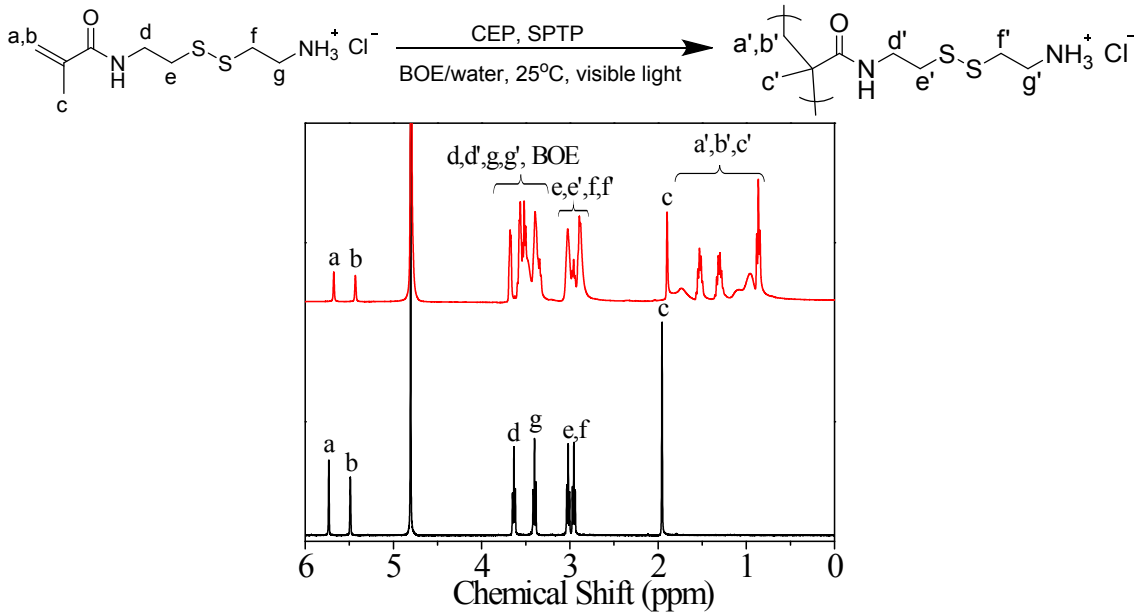
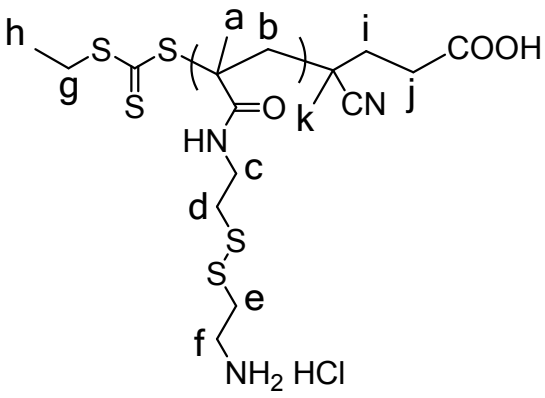


Fig. S3 ^{1}H NMR spectra of CysMA and the solution at $[CysMA]_0$=1.95 M, $[CysMA]_0/[CEP]_0/[SPTP]_0$=300:1:0.25 after visible light irradiation at 25°C for 2 h.

Monomer conversions were calculated according to Equation S1, in which I_b is the integral signal *b* (one proton of CH_2=CCH_3 within CysMA), and $I_{e+e'+f+f'}$ are integral signals *e, f, e', f'* within both the monomer and polymer unit.

$$Conversion = \frac{I_{e+e'+f+f'} - 4 \times I_b}{I_{e+e'+f+f'}} \qquad \text{(S1)}$$



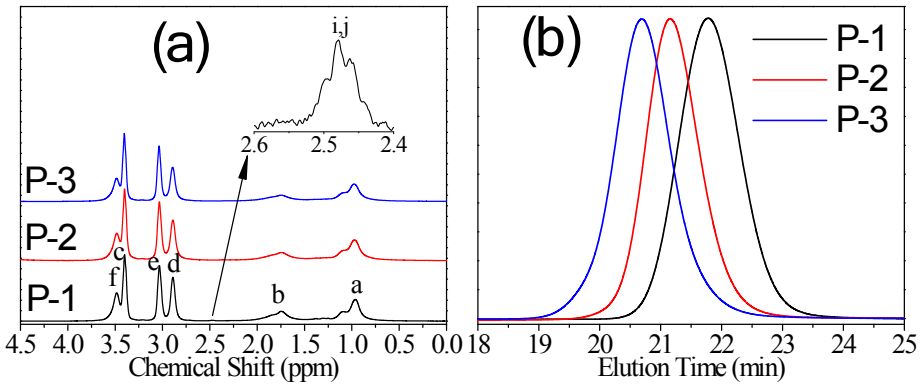


Fig. S4 ^{1}H NMR spectra (a) and SEC traces (b) of as-purified polymer samples including PCysMA$_{96}$ (*black*), PCysMA$_{198}$ (*red*) and PCysMA$_{303}$ (*blue*).

The degree of polymerization of as-purified polymer (DP) were assessed according to Equation S2, in which I_{d+e} are the integral signals *d, e* within CysMA units, and I_{i+j} are the integral signals *i, j* in the CEP chain-ends (Fig. S4a). Accordingly, the polymer samples are termed as PCysMA$_{96}$, PCysMA$_{198}$ and PCysMA$_{303}$, in which the subscripts are the DP values.

$$DP = \frac{I_{d+e}}{I_{i+j}} \qquad \text{(S2)}$$

As shown in Fig. S4b, their SEC traces are perfectly unimodal and symmetrical. Analysis results indicate that these polymer samples are well-defined with intact CysMA unit structures at M_n=37.1 kDa and M_w/M_n=1.10 for PCysMA$_{96}$, M_n=59.2 kDa and M_w/M_n=1.12 for PCysMA$_{198}$, and M_n=90.4 kDa and M_w/M_n=1.14 for PCysMA$_{303}$.

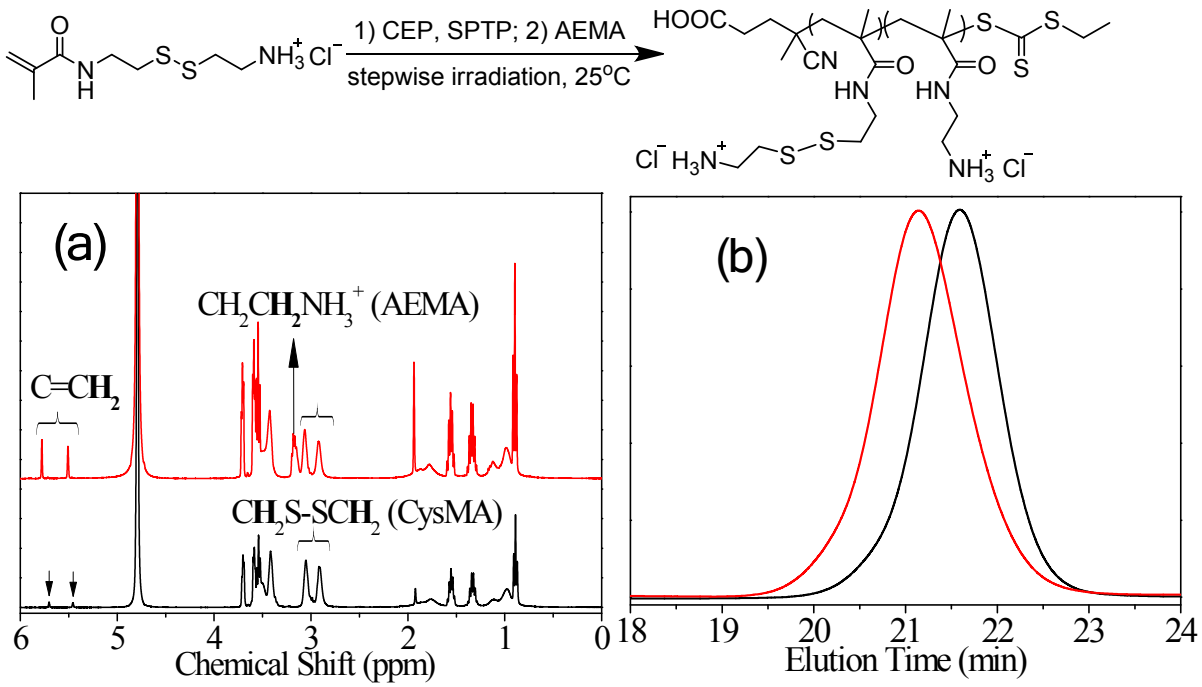


Fig. S5 (*Top*) schematic illustration for one-pot synthesis of PAEMA-*b*-PCysMA; (*bottom*) ^{1}H NMR spectra (a) and GPC traces (b) of reaction firstly at $[CysMA]_0$=1.99 M and $[CysMA]_0/[CEP]_0/[SPTP]_0$=100:1:0.25 under irradiation for 2.5 h (*black*), and then addition of AEMA up to $[AEMA]_0=[CysMA]_0$ and irradiation for 1 h (*red*).

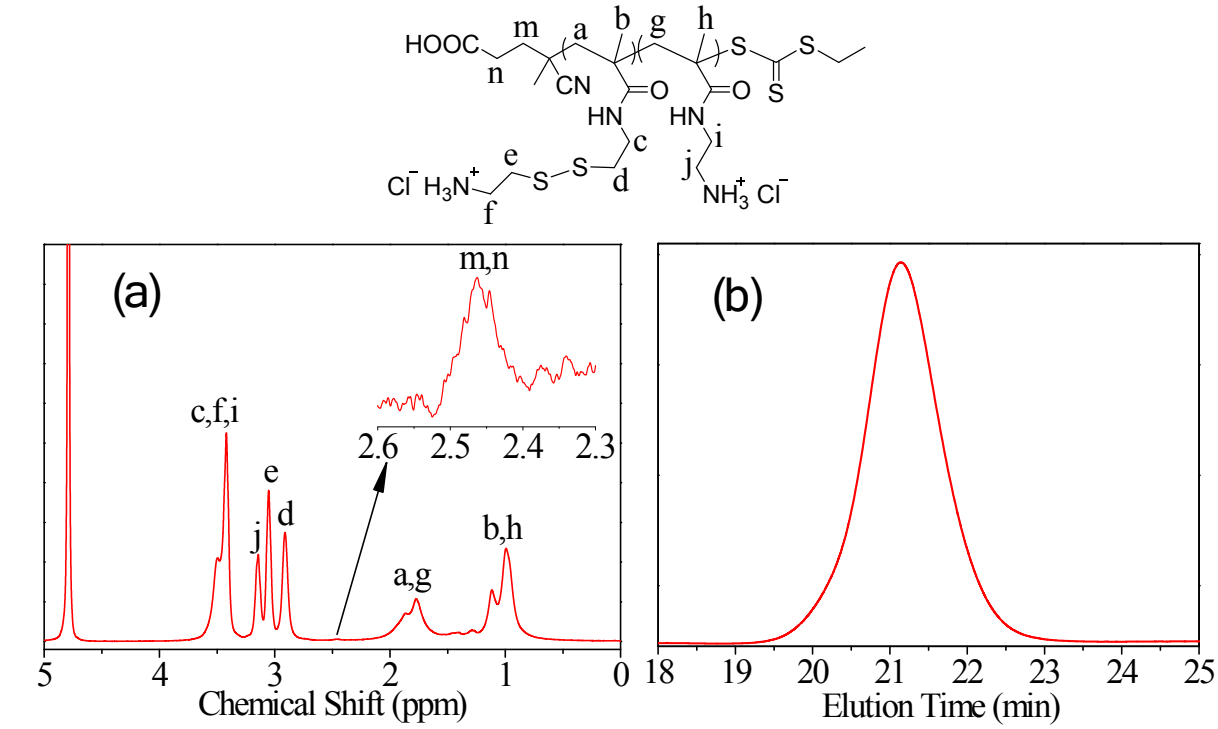


Fig. S6 ^{1}H NMR spectrum (a) and SEC trace (b) of as-purified $PAEMA_{67}$-*b*-$PCysMA_{98}$ block copolymer (P-5).

The degrees of polymerization were assessed according to Equations S3 and S4, in which I_{d+e+j} are integral signals *d, e* within CysMA units and *j* in AEMA units, I_d are the integral signal *d* in CysMA units, and I_{m+n} are integral signals *m, n* in the CEP chain-ends (Fig. S6a). These results indicate the molecular structure of $PAEMA_{67}$-*b*-$PCysMA_{98}$. The SEC trace of as-purified sample is unimodal and symmetrical (Fig. S6b). Analysis results revealed the well-defined block copolymer with intact CysMA units at M_n = 53.0 kDa and M_w/M_n = 1.13.

$$DP_{AEMA} = \frac{2 \times (I_{d+e+j} - 2 \times I_d)}{I_{m+n}} \quad \text{(S3)}$$

$$DP_{CysMA} = \frac{2 \times I_d}{I_{m+n}} \quad \text{(S4)}$$

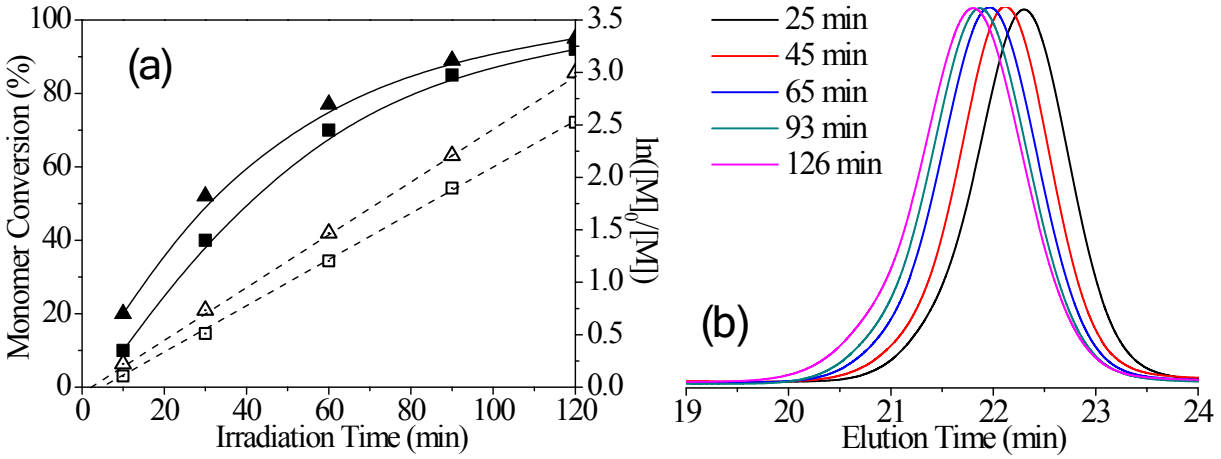


Fig. S7 (a) The kinetic plots of copolymerization of CysMA (■) and AEMA (▲) monomers at $[CysMA]_0/[AEMA]_0$=4, $[monomers]_0$=1.95 M, and $[monomers]_0/[CEP]_0/[SPTP]_0$=100:1:0.25 in BOE/water (20:80, wt./wt.) under visible light irradiation at 25°C; (b) The shift of GPC traces with irradiation time.

Table S1. Kinetic data for assessment of the reactivity ratios in copolymerization of CysMA and AEMA monomers at $[CysMA]_0/[AEMA]_0$ = 0.25 or 4, $[monomers]_0$=1.95 M, and $[monomers]_0/[CEP]_0$=100, under visible light irradiation at 25°C.

M1[a]	Conversion [b] (%)	$[M1]_t/[M1]_0$ [b]	$[M2]_t/[M_2]_0$ [b]	r_1	Averaged r_1	F_1	Averaged F_1
AEMA	28	0.72	0.76	1.20	1.16	0.820	0.811
	47	0.53	0.58	1.17		0.811	
	57	0.43	0.47	1.12		0.804	
CysMA	70	0.3	0.25	0.87	0.88	0.807	0.822
	86	0.14	0.11	0.89		0.819	
	94	0.06	0.04	0.87		0.839	

(a) M1 is major one and M2 is minor one; (b) monomer conversions, $[M1]_t/[M1]_0$, $[M2]_t/[M2]_0$ were determined by ^{1}H NMR studies.

The reactivity ratios of r_{CysMA}=0.88 and r_{AEMA}=1.16 were assessed according to Jaacks Equation (Equations S5, S6), in which $[M]_0$ and $[M]_t$ are the monomer concentrations at the beginning and predetermined time points, respectively.

$$\log \frac{[M_1]_t}{[M_1]_0} = r_1 \times \log \frac{[M_2]_t}{[M_2]_0} \quad \text{(S5)}$$

$$F_1 = \frac{r_1 \times f_1}{r_1 \times f_1 + f_2} \quad \text{(S6)}$$

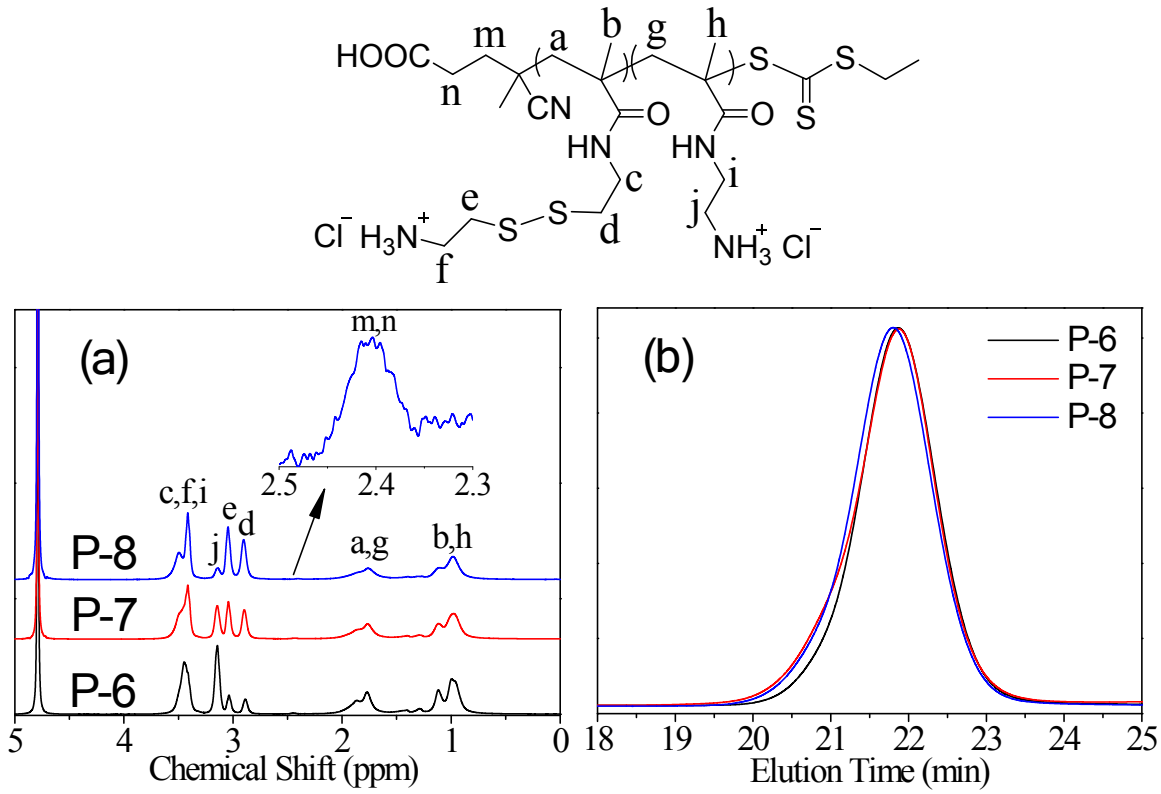


Fig. S8 ^{1}H NMR spectra (a) and GPC traces (b) of as-purified P(AEMA$_{79}$-*stat*-CysMA$_{19}$) (*black*), P(AEMA$_{49}$-*stat*-CysMA$_{46}$) (*red*) and P(AEMA$_{22}$-*stat*-CysMA$_{82}$) (*blue*).

The degrees of polymerization of as-purified statistic copolymers were assessed by ^{1}H NMR according to Equations S3 and S4. The SEC traces are unimodal and reasonably symmetrical. Analysis results indicate the well-defined molecular structures with intact CysMA units: P(AEMA$_{79}$-*stat*-CysMA$_{19}$) at M_n=34.1 kDa, M_w/M_n=1.13; P(AEMA$_{49}$-*stat*-CysMA$_{46}$) at M_n=35.2 kDa, M_w/M_n=1.16; P(AEMA$_{22}$-*stat*-CysMA$_{82}$) at M_n=37.8 kDa, M_w/M_n=1.15.

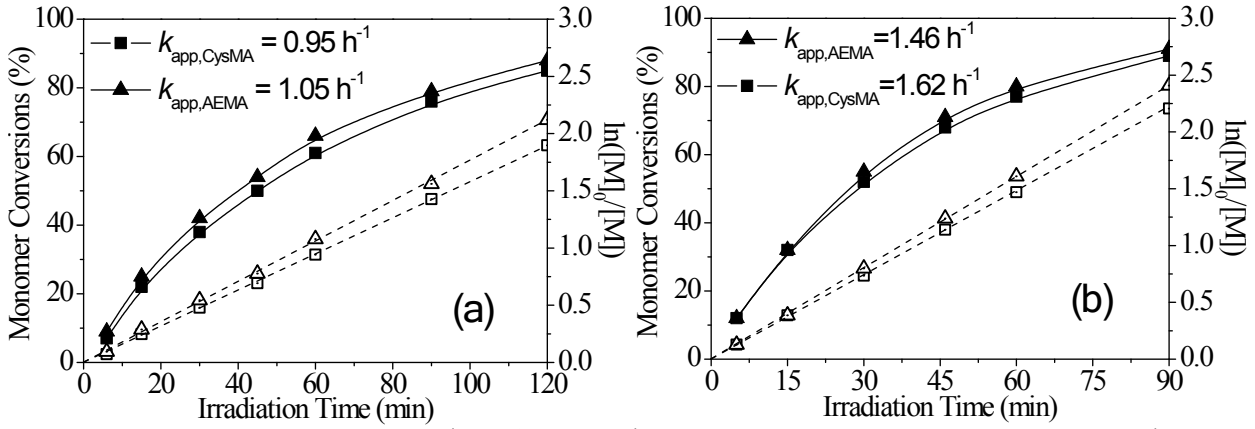


Fig. S9 The kinetic plots of copolymerization of CysMA (■)/AEMA (▲) at [CysMA]$_0$/[AEMA]$_0$=0.25 (a) and 4 (b), [monomers]$_0$=1.30 M and [monomers]$_0$/[PHPMA$_{90}$]$_0$ = 100 under visible light irradiation at 25°C.

Table S2. Kinetic data for the reactivity ratio assessment for the copolymerization of CysMA/AEMA using a $PHPMA_{90}$ Macro-CTA at $[CysMA]_0/[AEMA]_0$=0.25 and 4, $[monomers]_0$=1.95 M, $[monomers]_0/[PHPMA_{90}]_0$=100, under visible light irradiation at 25°C.

M1 [a]	Conversion [b] (%)	$[M1]_t/[M1]_0$ [b]	$[M2]_t/[M2]_0$ [b]	r_1	Averaged r_1	F_1	Averaged F_1
AEMA	9	0.91	0.93	1.30	1.17	0.836	0.814
	25	0.75	0.78	1.16		0.817	
	42	0.58	0.62	1.14		0.810	
CysMA	54	0.46	0.5	1.12		0.805	
	66	0.34	0.39	1.15	0.95	0.800	0.806
	12	0.88	0.88	1.00		0.800	

(a) M1 is the major one and M2 is the minor one; (b) the monomer conversions, $[M1]_t/[M1]_0$ and $[M2]_t/[M2]_0$ were determined by ^{1}H NMR studies.

Reactivity ratios of r_{CysMA}=0.95 and r_{AEMA}=1.17 were determined according to Jaacks Equation (S5, S6).

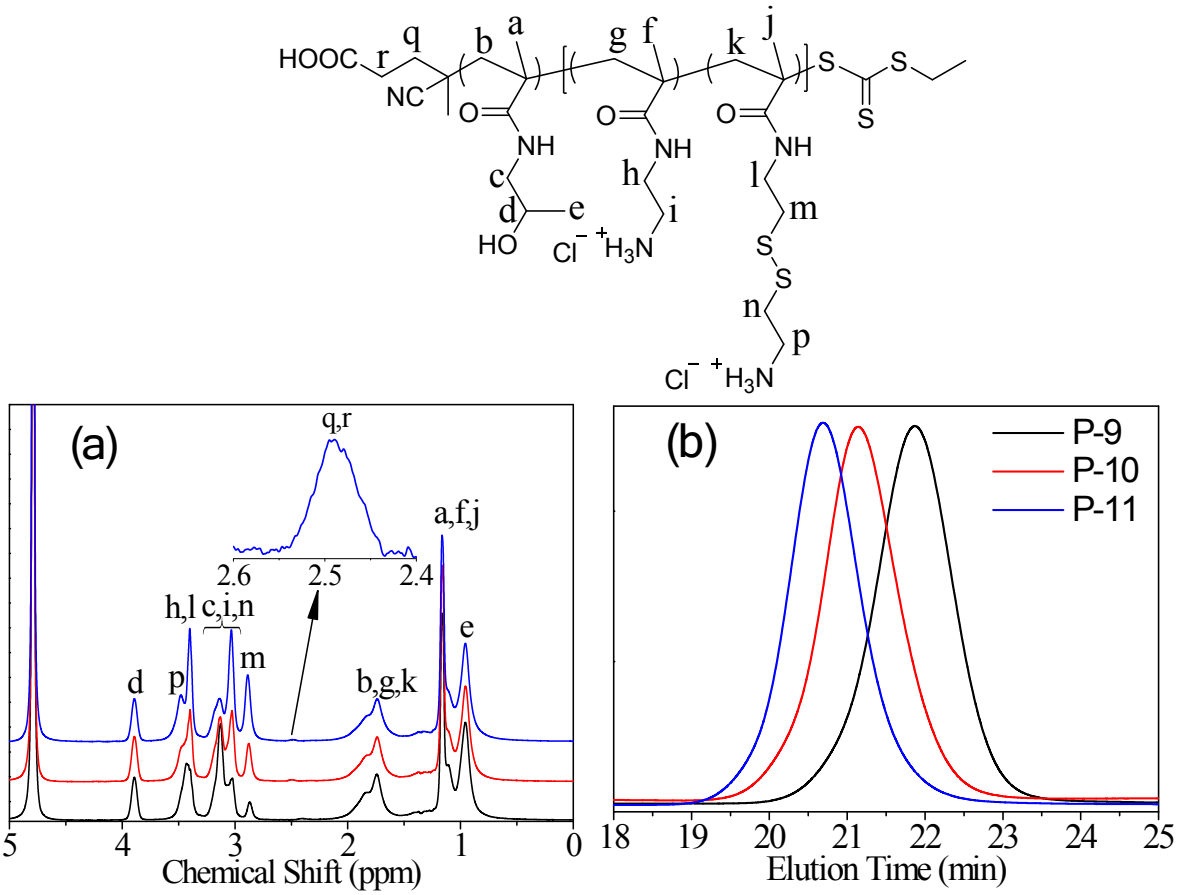


Fig. S10 ^{1}H NMR spectra (a) and SEC traces (b) of as-purified $PHPMA_{90}$-*b*-P($AEMA_{77}$-*stat*-$CysMA_{18}$) (P-9), $PHPMA_{90}$-*b*-P($AEMA_{51}$-*stat*-$CysMA_{47}$) (P-10) and $PHPMA_{90}$-*b*-P($AEMA_{16}$-*stat*-$CysMA_{78}$) (P-11).

The degrees of polymerization were assessed by ^{1}H NMR, according to Equations S1, S3 and S4. Their SEC traces are unimodal and symmetrical. Analysis results indicate the well-defined block-statistic copolymer with intact CysMA units: $PHPMA_{90}$-*b*-P($AEMA_{77}$-*stat*-$CysMA_{18}$) at M_n=30.8 kDa, M_w/M_n=1.17; $PHPMA_{90}$-*b*-P($AEMA_{51}$-*stat*-$CysMA_{47}$) at M_n=39.1 kDa, M_w/M_n=1.13; $PHPMA_{90}$-*b*-P($AEMA_{16}$-*stat*-$CysMA_{78}$) at M_n=44.0 kDa, M_w/M_n=1.18.

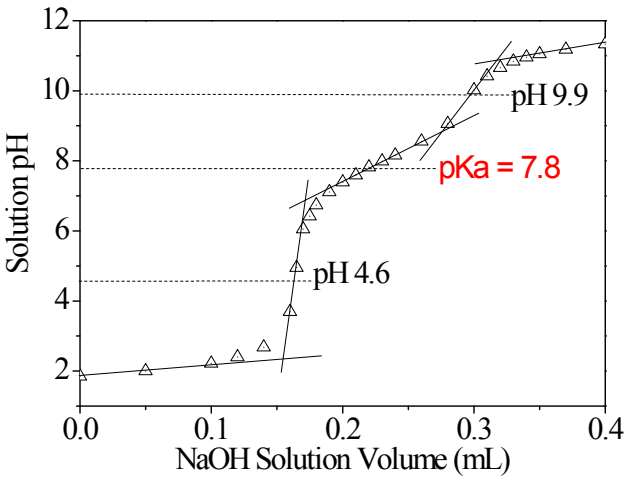


Fig. S11 Acid-base titration plots of $PHPMA_{90}$-*b*-$PCysMA_{70}$ block copolymer.