Supporting Information

A Facile Synthesis of pH Stimuli Biocompatible Block Copolymer Poly(methacrylic acid)-*block*-Poly(*N*-vinylpyrrolidone) Utilizing Switchable RAFT Agents

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Synthesis of statistical copolymer P(MAA-*co*-NVP)

P(MAA-*co*-NVP) statistical copolymer was synthesised with the use of 4-((((2-carboxyethyl)thio)carbonothioyl)thio)-4-cyanopentanoic acid as RAFT agent. To a reaction flask, the monomers MAA and NVP were added at a 1:1 molar ratio to a 1:1 (w/w) deionized water and ethanol solution to yield a 1:3 (w/w) total monomer to solvent ratio. 2,2'-Azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-044) was added at 10% with respect to RAFT agent molar ratio. The mixture was homogenised and then the flask was sealed. The polymerisation solution was degassed three times, then put into an oil bath at 45°C for 16 hours. The statistical copolymer was purified by the addition of 1 N hydrochloric acid (HCl) to precipitate polymer, centrifugation, and resuspension in deionized water. After three wash cycles, the polymer solution was neutralised, frozen in liquid nitrogen, and lyophilised.

Self-assembly of statistical copolymer P(MAA-*co*-NVP)

The above statistical copolymer PMAA-*co*-PNVP (5 mg) was dissolved in DMSO (1 mL) and 1M sodium hydrogen carbonate (3 mL), then hydrochloric acid (pH 2.5) (6 mL) was added dropwise under stirring. The statistical copolymer immediately precipitated out from the solution, hence the statistical copolymer failed to self-assemble into micelle.

Characterisation of P(*t*-BMA) macro-RAFT agent

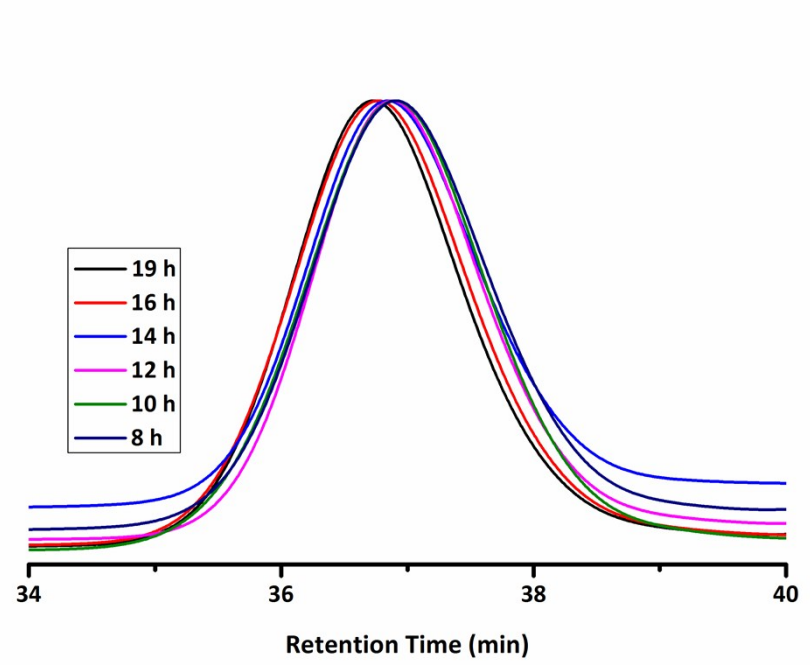


Fig. S1. GPC traces of kinetic polymerization of *t*-BMA in THF ([M]:[CTA]:[I] 80:1:0.1)

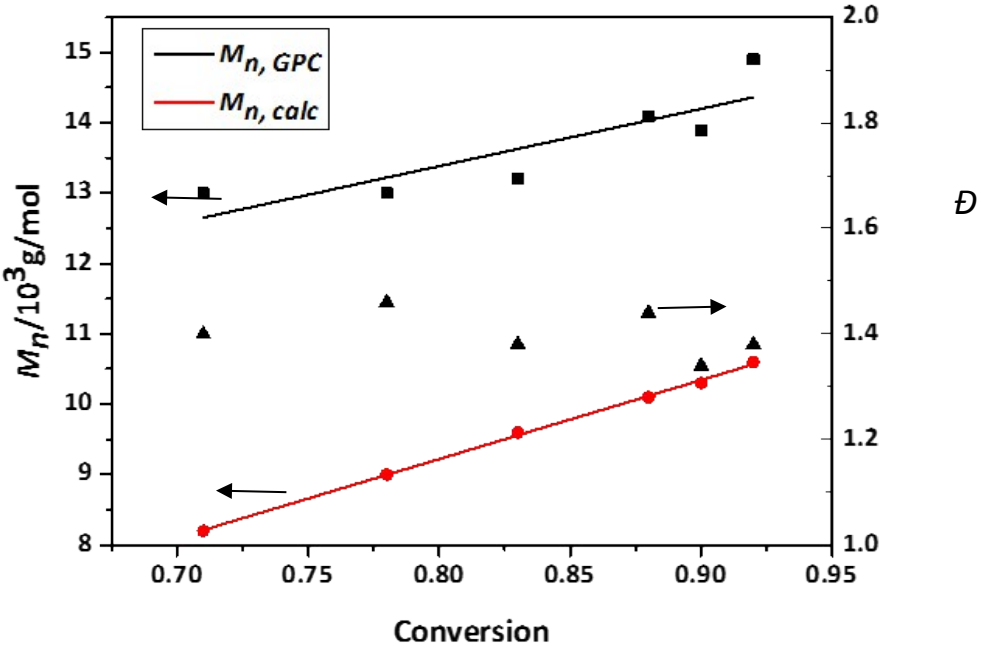


Fig. S2. Number average molecular weight (M_n) and dispersity vs monomer conversion for the RAFT polymerization of *t*-BMA with 2-cyanopropan-2-yl *N*-methyl-*N*-(pyridine-4-yl)carbanodithioate (SRA 1)

Results of P(*t*-BMA) synthesised using different switchable RAFT agents

Table S1. Polymerisation results of P(*t*-BMA) synthesised using SRA 1 and SRA 2

Polymer sample P(*t*-BMA)[#]	RAFT [10^{-2} M]	TfOH [10^{-2}M]	Monomer [M]	$M_n/10^3$	$M_{n,calc}/10^3$	*Đ*	Conv. (%)
P1	5.59	4.59	5.03	15.0	11.0	1.38	83
P2	6.12	5.03	2.98	9.0	3.7	1.44	50
P3	4.14	4.18	2.43	9.4	6.8	1.25	75

[#] P1, P2 are P(*t*-BMA) made with SRA 1**;** and P3 is P(*t*-BMA) made with SRA 2.

Table S2. GPC results of P(*t*-BMA) obtained in different solvents

Polymers[#]	$M_{n,cal}/10^3$	solvent	$M_{n1}/10^3$	*Đ*	solvent	$M_{n2}/10^3$	*Đ*
P1	11.0	THF	15.0	1.38	DMAC	16.5	1.34
P2	3.7	THF	9.0	1.44	DMAC	8.0	1.37
P3	6.8	THF	9.4	1.25	DMAC	8.1	1.26

[#] P1, P2 are P(*t*-BMA) made with SRA 1**;** and P3 is P(*t*-BMA) made with SRA 2.

Kinetic of NVP polymerization by RAFT agent 1

Table S3. Polymerisation results of PNVP synthesised using SRA 1

Entry	Time (h)	$M_n/10^3$	$M_{n,calc}/10^3$	*Đ*[#]	Conv. (%)
1	2	6.2	6.2	1.26	26
2	4	15.8	12.9	1.16	65
3	6	23.9	15.3	1.18	85
4	8	26.2	15.1	1.29	93

[#]Determined by DMAC eluent GPC;[M]=4.47mol/L, [RAFT]=0.02mol/L, [M]:[CTA]:[I]=215:1:0.1.

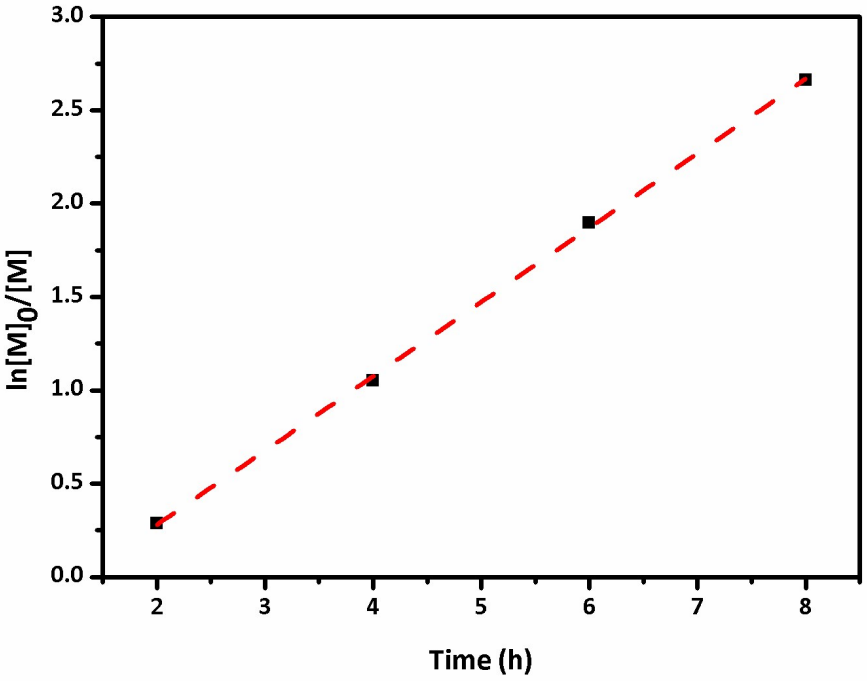


Fig. S3. Pseudo-first-order kinetics plot for the RAFT polymerisation of NVP using SRA 1 [M]:[CTA]:[I] 215:1:0.1

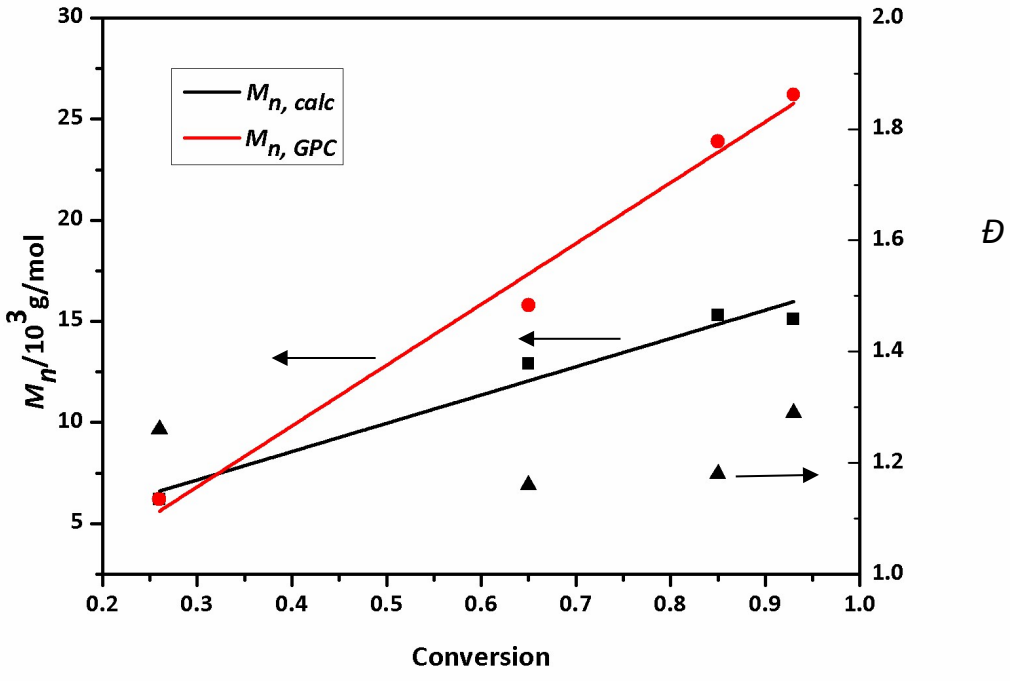


Fig. S4. Number average molecular weight (M_n) and dispersity vs monomer conversion for the RAFT polymerization of NVP with SRA 1

Results of P(*t*-BMA)-*b*-PNVP

Table S4: Molecular weight data of block copolymers P(*t*-BMA)-*b*-PNVP determined by GPC in different solvents

Polymers[#]	$M_{n,cal}/10^3$	solvent	$M_{n1}/10^3$	Đ	solvent	$M_{n2}/10^3$	Đ
P1a	32.0	THF	21.4	1.29	DMAC	32.1	1.51
P2a	19.0	THF	19.2	1.34	DMAC	26.9	1.67
P3a	10.7	THF	14.5	1.25	DMAC	20.7	1.57

[#] P1a and P2a are block copolymers P(*t*-BMA)-*b*-PNVP where the first block P(*t*-BMA) made with SRA 1, P3a is block copolymer P(*t*-BMA)-*b*-PNVP where the first block P(*t*-BMA) made with SRA 2.

Table S5. Polymerisation results of P(*t*-BMA) and P(*t*-BMA)-*b*-PNVP

Polymers[#]	RAFT $[10^{-2}$ M]	Monomer [M]	Time (h)	Conv.[a] (%)	$M^a_{n,calc}/10^3$	$M^b_n/10^3$	$Đ^b$
P1	5.59	5.03	16	83	11.0	15.0	1.38
P2	6.12	2.98	16	50	3.7	9.0	1.44
P3	4.14	2.43	16	75	6.8	9.4	1.25
P1a	0.93	1.89	10	71	32.0	21.4	1.29
P2a	1.81	1.96	8	67	19.0	19.2	1.34
P3a	2.00	2.01	4	36	10.7	14.5	1.25

[#] P1a and P2a are block copolymers P(*t*-BMA)-*b*-PNVP where the first block P(*t*-BMA) made with SRA 1, P3a is block copolymer P(*t*-BMA)-*b*-PNVP where the first block P(*t*-BMA) made with SRA 2. P1a, P2a and P3a are synthesized by macro RAFT agent P1, P1 and P3 respectively. [a] Determined by ^{1}H NMR; [b] Determined by GPC (THF eluent).

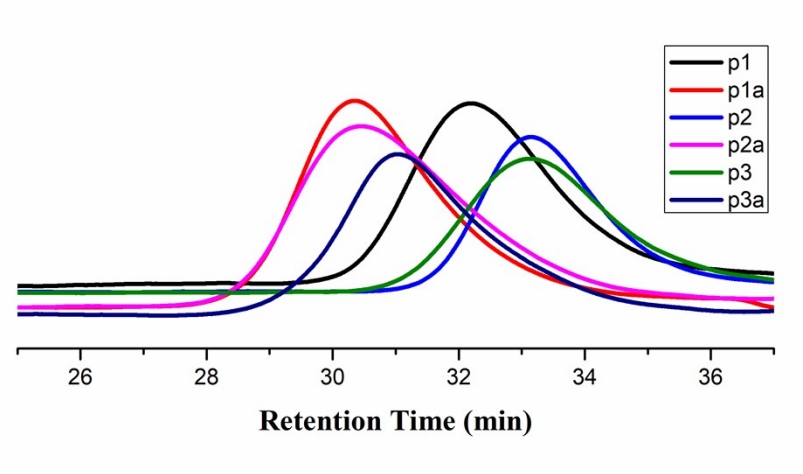


Fig. S5. GPC traces of homopolymer P(*t*-BMA) and block copolymer P(*t*-BMA)-*b*-PNVP

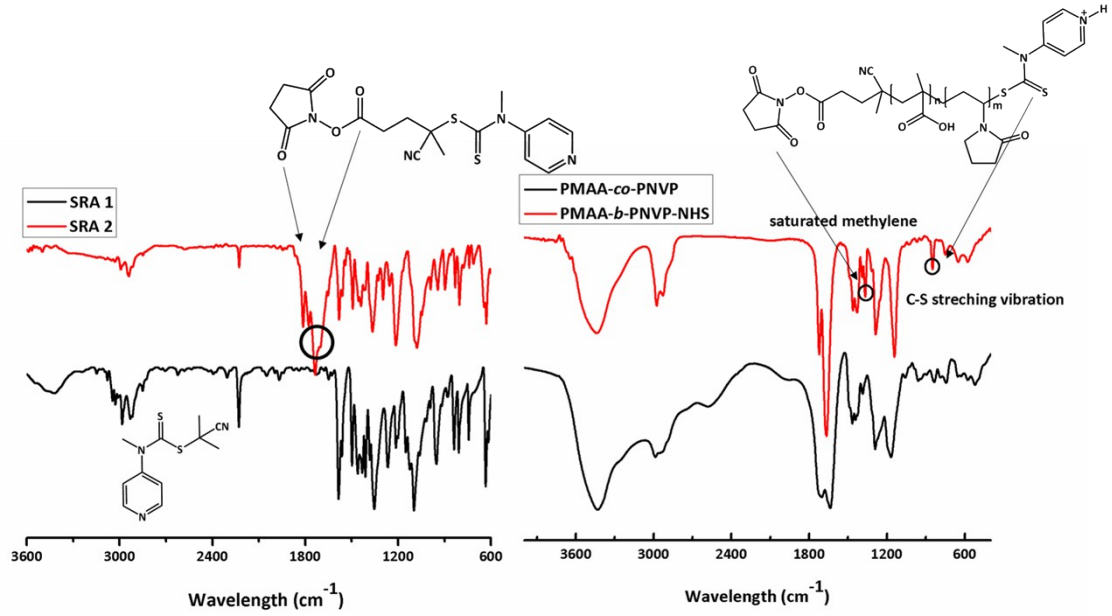


Fig. S6. FT-IR spectra of PMAA-*b*-PNVP-NHS, PMAA-*co*-PNVP, SRA 1 and SRA 2

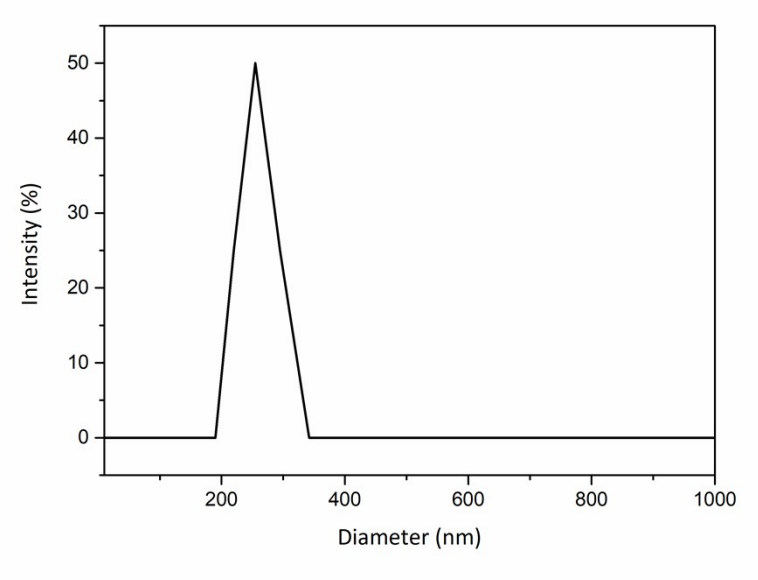


Fig. S7. DLS particle size distribution obtained for a (M_n = 31.7×10^3 g/mol, DP_1 = 75, DP_2 = 188) micelle in hydrochloric acid (pH = 2.0, 0.1mg/ml) dispersion

The conversion (%) of P(*t*-BMA) polymers (Table 1) were determined by ^{1}H NMR analysis. Based on the ratio of integration between the residual vinyl proton peaks of monomer (at δ5.5 and 6.0 ppm) and *t*-butyl protons of polymer at δ 1.4 ppm, **Fig. S8** is one such NMR analysis of P(*t*-BMA) conversion.

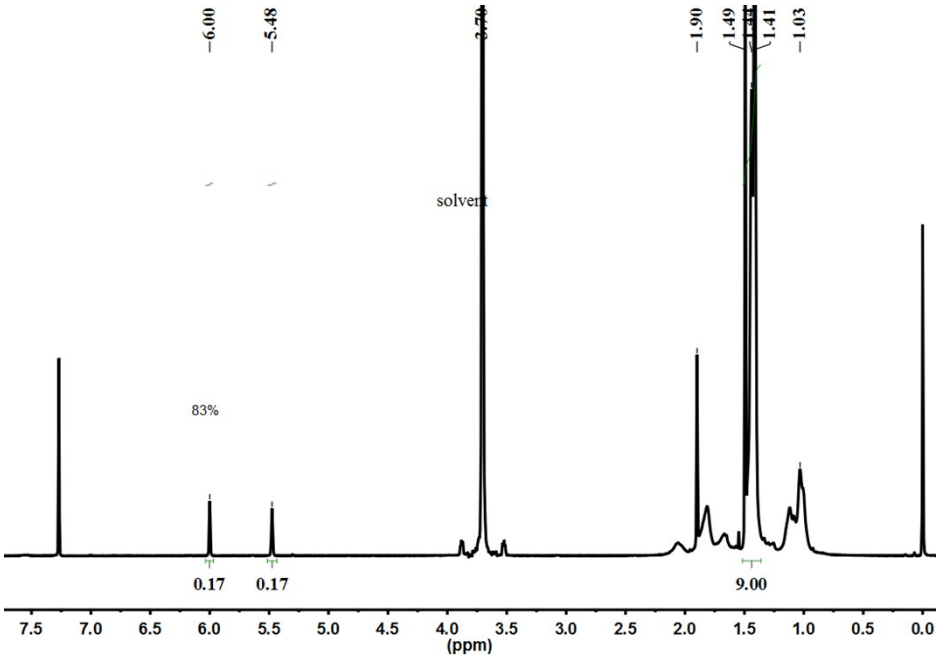


Fig. S8. ^{1}H-NMR spectrum of P(*t*-BMA) in $CDCl_3$

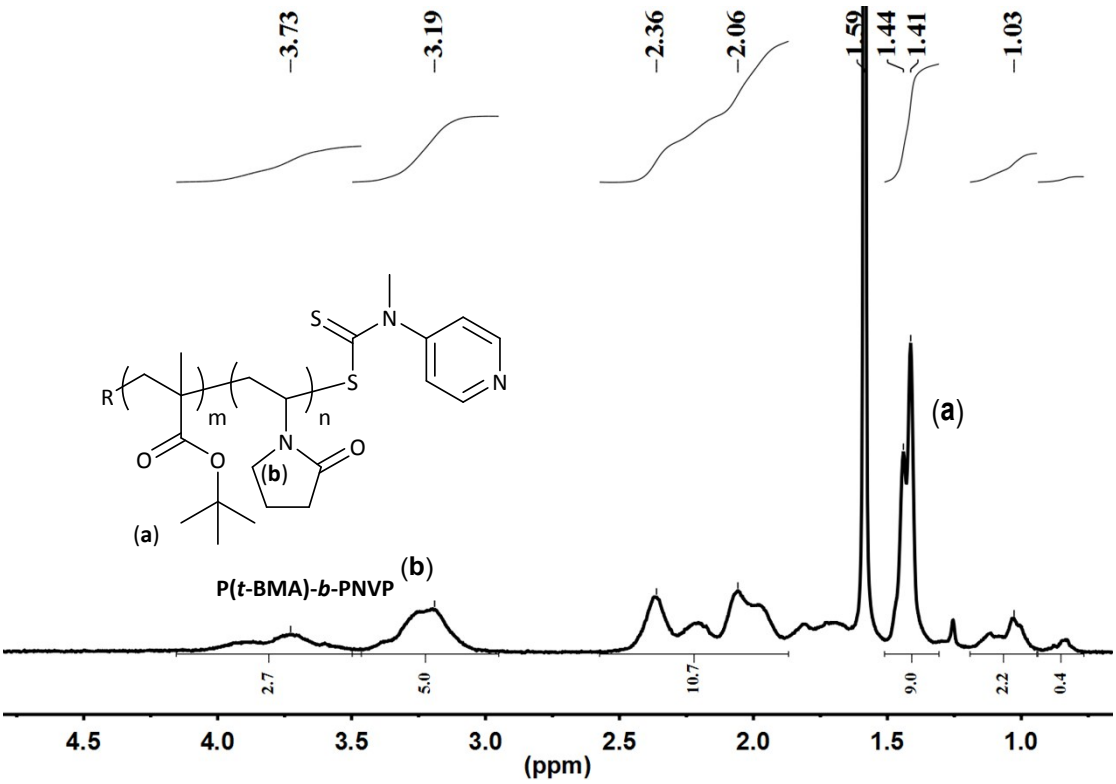


Fig. S9. ^{1}H-NMR spectrum of a block copolymer P(*t*-BMA)-*b*-PNVP in $CDCl_3$

The composition and the $M_{n,cal\ (block)}$ of a block copolymer can be estimated and calculated based on the integration values from the indicative polymer peaks. **Fig. S9** shows a ^{1}H NMR spectrum of a block copolymer P(*t*-BMA)-*b*-PNVP and integration values $I_{(PNVP)}$ for signal at δ3.2 ppm (2H, **b** of PNVP) and $I_{P(t\text{-}BMA)}$ for signal at δ1.4 ppm (9H, **a** of P(*t*-BMA)), and that the $M_{n,cal\ (block)}$ can be determined by the following equation. Table S5 summarizes the results of the block copolymer. The molecular weight of P1, P2 and P3 determined by GPC are higher than the molecular weight calculated by ^{1}H NMR. However, the molecular weight of P1a determined by GPC is lower than the molecular weight calculated by ^{1}H NMR. This is consistent with the phenomenon we observed from PNVP. The block copolymer presents the nature of PNVP due to the composition of P1a is P(*t*-BMA)$_{75}$-*b*-PNVP$_{144.}$ P2a is P(*t*-BMA)$_{75}$-*b*-PNVP$_{73,}$ P3a is P(*t*-BMA)$_{44}$-*b*-PNVP$_{36,}$ therefore, the molecular weight determined by GPC is higher than by ^{1}H NMR.

$$M_{n,cal\ (block)} = \frac{9 \times M_{n,cal\ P(t\text{-}BMA)} \times I_{PNVP}}{2 \times I_{P(t\text{-}BMA)}} + M_{n,cal\ P(t\text{-}BMA)}$$

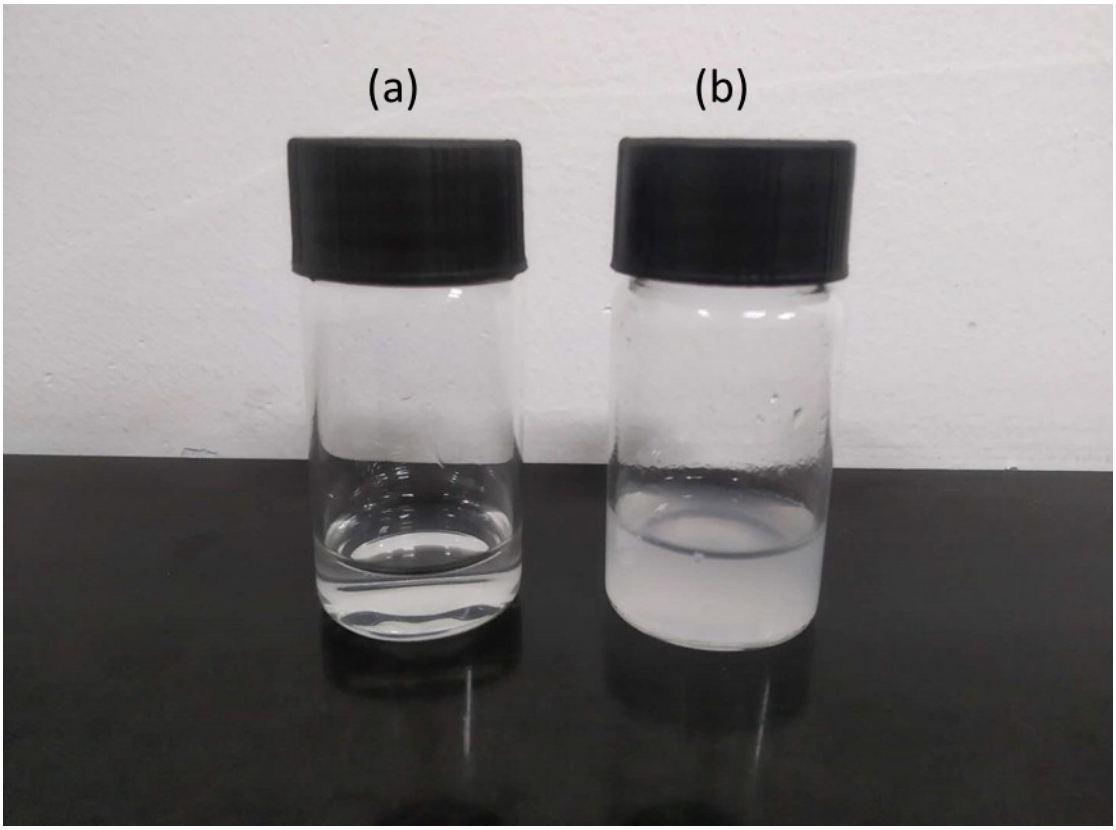
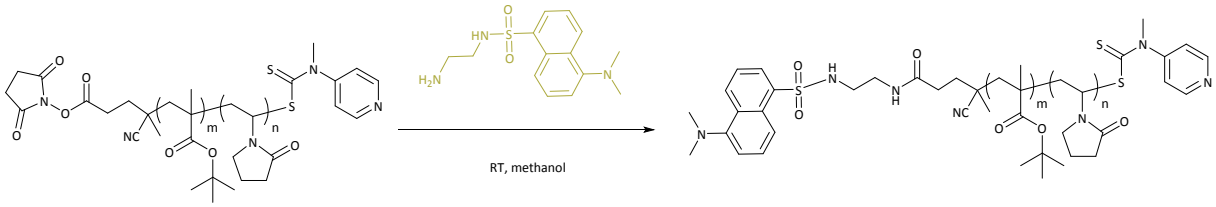


Fig. S10. (a) Disassemble of PMAA-*b*-PNVP under pH 7.4 (b) self-assemble of PMAA-*b*-PNVP in pH 2.5



Scheme S1. Dansylethylenediamine reaction with NHS ester