Supporting information

Reversible p*K*a Modulation of Carboxylic Acids in Temperature-Responsive Nanoparticles through Imprinted Electrostatic Interactions

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Scheme S1 and S2

Table S1. Polymerization conditions and yields of AxDy NPs.

	Polymerization pH	NIPAm (mol%)/(mg)	BIS (mol%)/(mg)	AAc (mol%)/(μL)	DMA (mol%)/(μL)	Reaction scale of polymerization (mL)	Yield of NPs (%)
A2.0D0.0	3.1	96.0 / 1694.7	2.0 / 48.1	2.0 / 21.4	0.0 / 0.0	50	74
A1.5D3.5	3.1	93.0 / 3283.5	2.0 / 96.2	1.5 / 32.1	3.5 / 179.2	100	79
A1.5D5.0	3.1	91.5 / 3230.5	2.0 / 96.2	1.5 / 32.1	5.0 / 256.0	100	83
A3.0D0.0	3.0	95.0 / 3354.1	2.0 / 96.2	3.0 / 64.2	0.0 / 0.0	100	79
A2.5D3.5	3.1	92.0 / 3248.7	2.0/ 96.2	2.5 / 53.5	3.5 / 179.2	100	78
A2.5D5.0	3.1	90.5 / 3195.2	2.0 / 96.2	2.5 / 53.5	5.0 / 256.0	100	86
A2.5D7.0	3.1	88.5 / 3124.6	2.0 / 96.2	2.5 / 53.5	7.0 / 358.4	100	79
A5.0D0.0	3.1	95.0 / 3354.0	2.0 / 96.2	5.0 / 107.0	0.0 / 0.0	100	76
A5.0D3.5	3.1	94.0 / 3318.8	2.0 / 96.2	5.0 / 107.0	3.5 / 179.2	100	80

Table S2. Incorporation of ionic groups and pK_a values of AAc in AxDy NPs.

	Incorporation of AAc (mol%)	Incorporation of DMA (mol%)	pK_a of AAc (10ºC)	pK_a of AAc (75ºC)
A2.0D0.0	1.9	0.0	4.8	7.1
A1.5D3.5	2.0	1.8	4.9	5.6
A1.5D5.0	1.5	3.5	4.7	5.4
A3.0D0.0	3.1	0.0	5.2	7.3
A2.5D3.5	3.3	2.3	4.9	5.4
A2.5D5.0	2.8	3.7	4.9	5.5
A2.5D7.0	2.6	5.9	4.7	5.4
A5.0D0.0	5.5	0.0	4.9	7.2
A5.0D3.5	5.7	2.0	4.8	6.7

Table S3. Polymerization conditions and yields of pDMAAm.

	Polymerization pH	DMAAm (mol%)/(mg)	AAc (mol%)/(μL)	DMA (mol%)/(μL)	Reaction scale of polymerization (mL)	Yield of NPs (%)
pDMAAm (AAc)	3.0	98.0 / 1575.3	2.0 / 21.3	-	50	67
pDMAAm (AAc+DMA)	3.0	94.5 / 1519.1	2.0 / 21.3	3.5 / 89.6	50	53

Table S4. Incorporation of ionic groups and pK_a values of AAc in pDMAAm.

	Incorporation of AAc (mol%)	Incorporation of DMA (mol%)	pK_a of AAc (10ºC)	pK_a of AAc (75ºC)
pDMAAm (AAc)	2.9	0.0	4.8	5.2
pDMAAm (AAc+DMA)	2.5	3.9	4.6	4.8

Table S5. Polymerization conditions and yields of (AAc + cations) NPs.

	Polymerization pH	NIPAm (mol%)/(mg)	BIS (mol%)/(mg)	AAc (mol%)/(μL)	Cationic monomer (mol%)/(mg)	Cationic monomer species	Reaction scale of polymerization (mL)	Yield of NPs (%)
AAc	3.0	95.0 / 3354.1	2.0 / 96.2	3.0 / 64.2	-	-	100	79
AAc+ATA	3.0	90.5 / 3195.2	2.0 / 96.2	2.5 / 53.5	5.0 / 322.5	ATA	100	68
AAc+DMA	3.1	90.5 / 3195.2	2.0 / 96.2	2.5 / 53.5	5.0 / 243.7	DMA	100	86
AAc+APM	3.0	90.5 / 3195.2	2.0 / 96.2	2.5 / 53.5	5.0 / 278.8	APM	100	72
AAc+GUA	3.0	90.5 / 3195.2	2.0 / 96.2	2.5 / 53.5	5.0 / 344.1	GUA	100	71

Table S6. Incorporation of ionic groups and pK_a values of AAc in (AAc + cations) NPs.

	Incorporation of AAc (mol%)	Incorporation of Cationic group (mol%)	Cationic monomer species	pK_a of AAc (10ºC)	pK_a of AAc (75ºC)
AAc	3.1	0.0	-	5.2	7.3
AAc+ATA	2.6	3.4	ATA	4.8	5.7
AAc+DMA	2.8	3.7	DMA	4.9	5.5
AAc+APM	2.7	3.9	APM	4.9	5.1
AAc+GUA	2.5	3.5	GUA	4.9	5.0

Table S7. Polymerization conditions and yields of (AAc + BGUA) NPs.

	Polymerization pH	NIPAm (mol%)/(mg)	TBAm (mol%)/(mg)	BIS (mol%)/(mg)	AAc (mol%)/(μL)	BGUA (mol%)/(mg)	Reaction scale of polymerization (mL)	Yield of NPs (%)
AAc+BGUA	4.0	90.5 / 2715.9	0.0 / 0.0	2.0 / 81.8	2.5 / 45.5	5.0 / 510.5	170	75
AAc+BGUA+TBAAm	4.0	70.5 / 1866.8	20.0 / 595.3	2.0 / 72.2	2.5 / 40.1	5.0 / 450.5	150	77
AAc+BGUA+BIS	4.0	50.5 / 1783.0	0.0 / 0.0	5.0 / 240.5	2.5 / 53.5	5.0 / 600.0	200	44

Table S8. Incorporation of ionic groups and pK_a values of AAc in (AAc + BGUA) NPs.

	Incorporation of AAc (mol%)	Incorporation of GUA (mol%)	pK_a of AAc (10ºC)	pK_a of AAc (75ºC)
AAc+BGUA	2.7	3.9	4.7	4.4
AAc+BGUA+TBAAm	3.3	4.8	4.6	4.0
AAc+BGUA+BIS	2.9	4.2	4.4	4.0

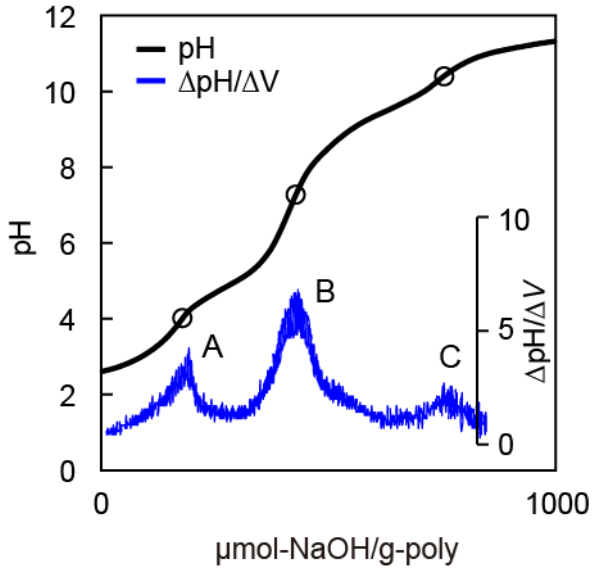


Figure S0. Acid–base titration curves for A2.5D5.0 NPs (black), and changes in pH (ΔpH) versus volume of NaOH added (ΔV) (blue). The three peaks in the blue line indicate neutralization of (A) HCl (HCl + NaOH ⇄ NaCl + H_2O), (B) AAc (R-COOH + NaOH ⇄ R-COONa + H_2O), and (C) DMA (R-NR_2HCl + NaOH ⇄ R-NR_2 + NaCl + H_2O).

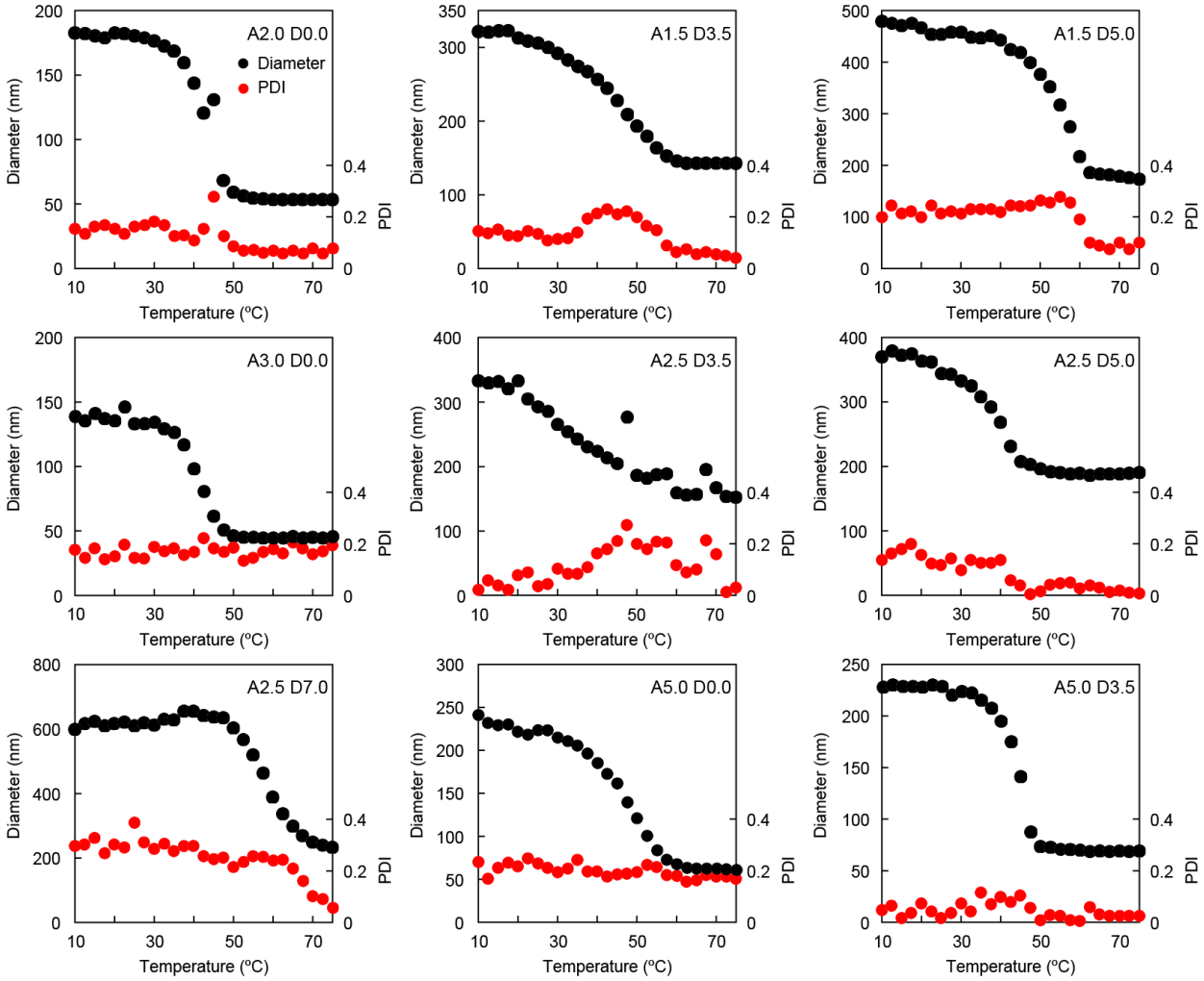


Figure S1. Hydrodynamic diameters (black) and PDI (red) of AxDy NPs at 10–75 °C.

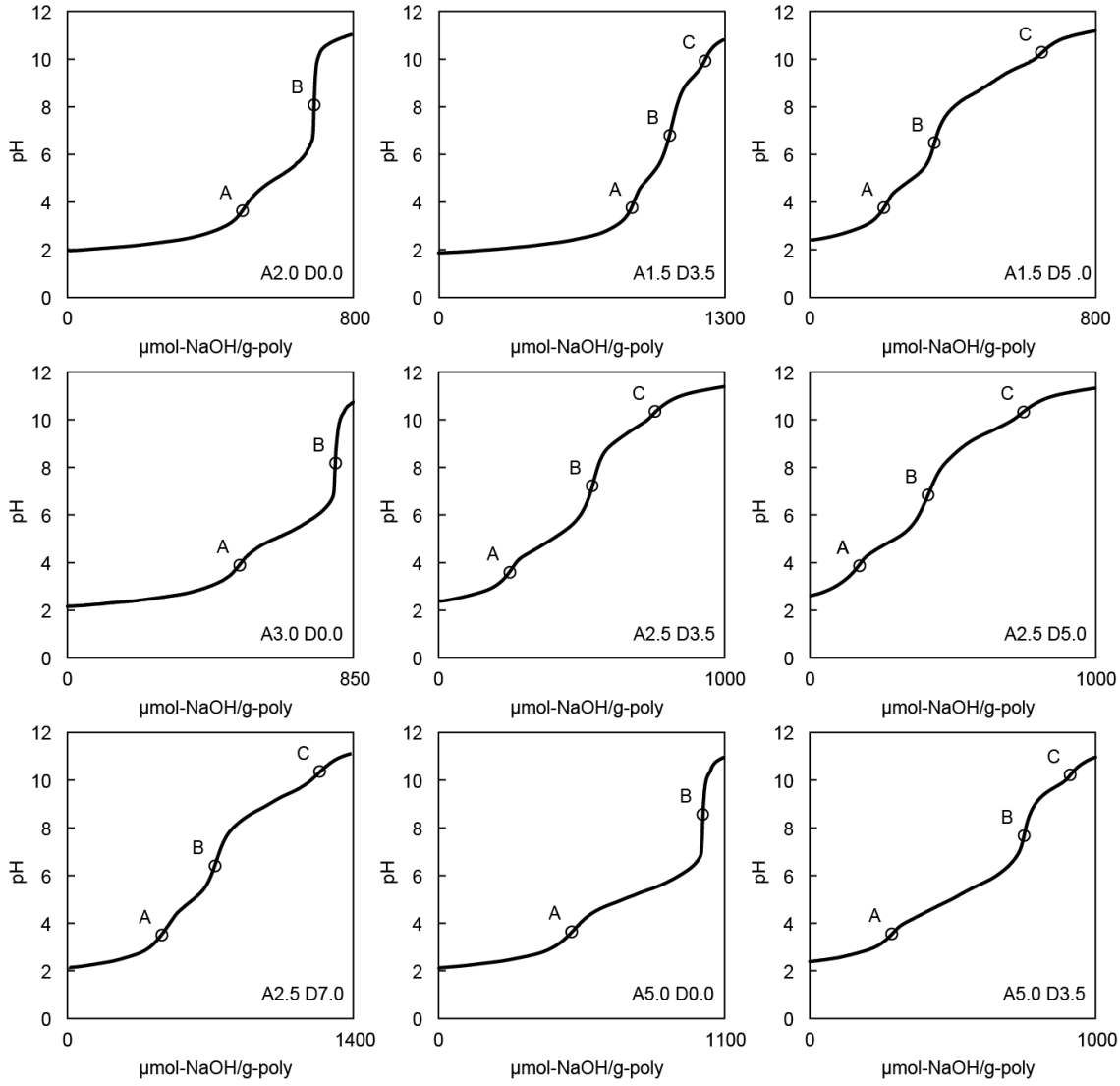


Figure S2. Acid–base titration curves for AxDy NPs. Plots A, B and C indicate neutralization point of HCl, carboxylic acids and ammonium ions, respectively.

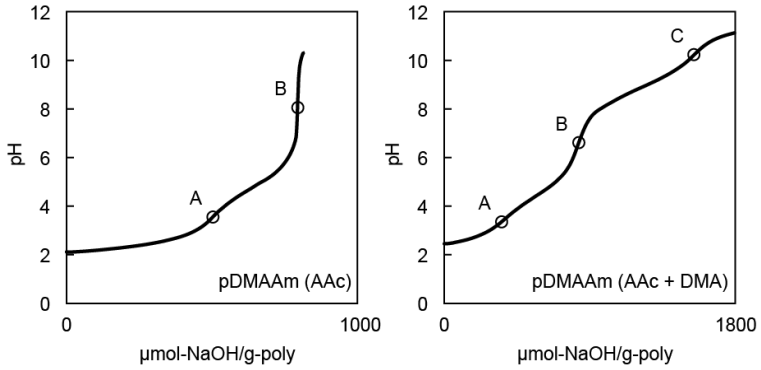


Figure S3. Acid–base titration curves for pDMAAm. Plots A, B and C indicate neutralization point of HCl, carboxylic acids and ammonium ions, respectively.

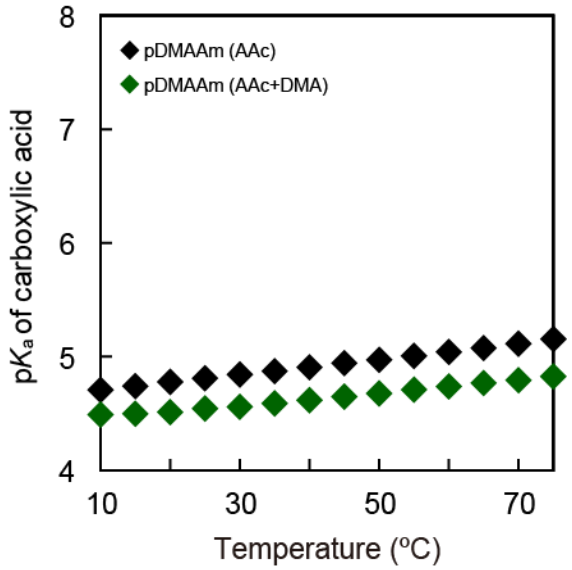


Figure S4. The pK_a values of carboxylic acids in pDMAAm (AAc) (black) and pDMAAm (AAc + DMA) (green) as a function of temperature.

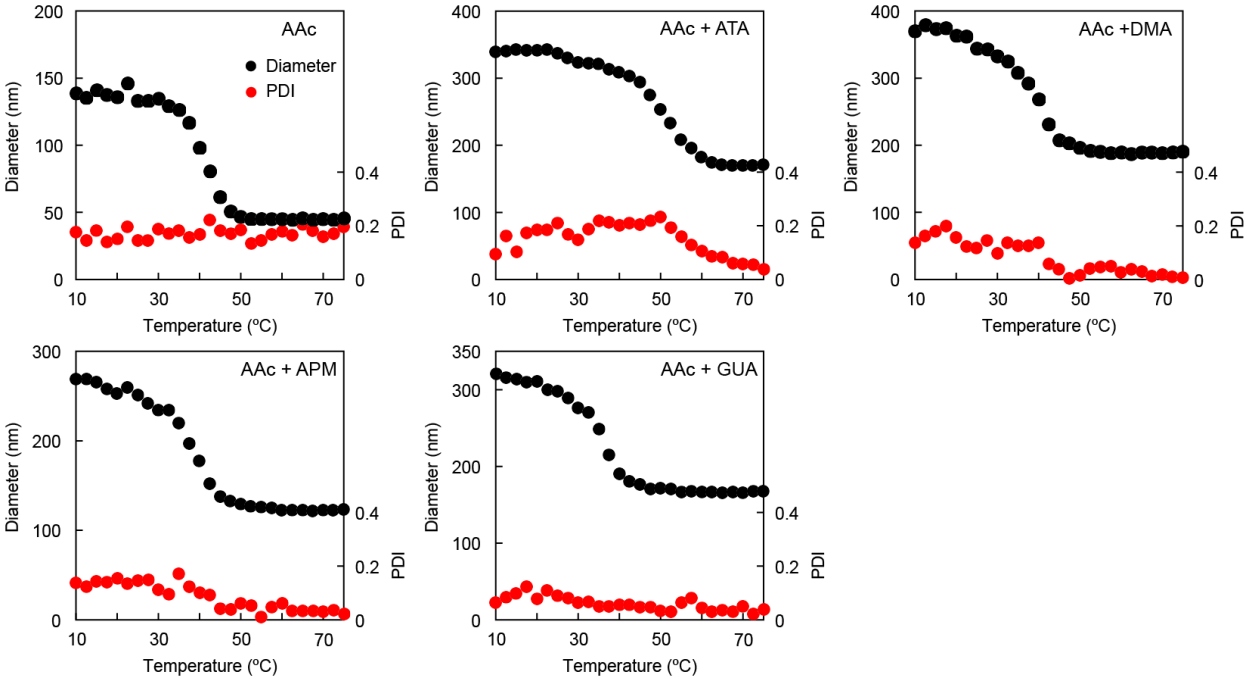


Figure S5. Hydrodynamic diameters (black) and PDI (red) of (AAc + cations) NPs at 10–75 °C.

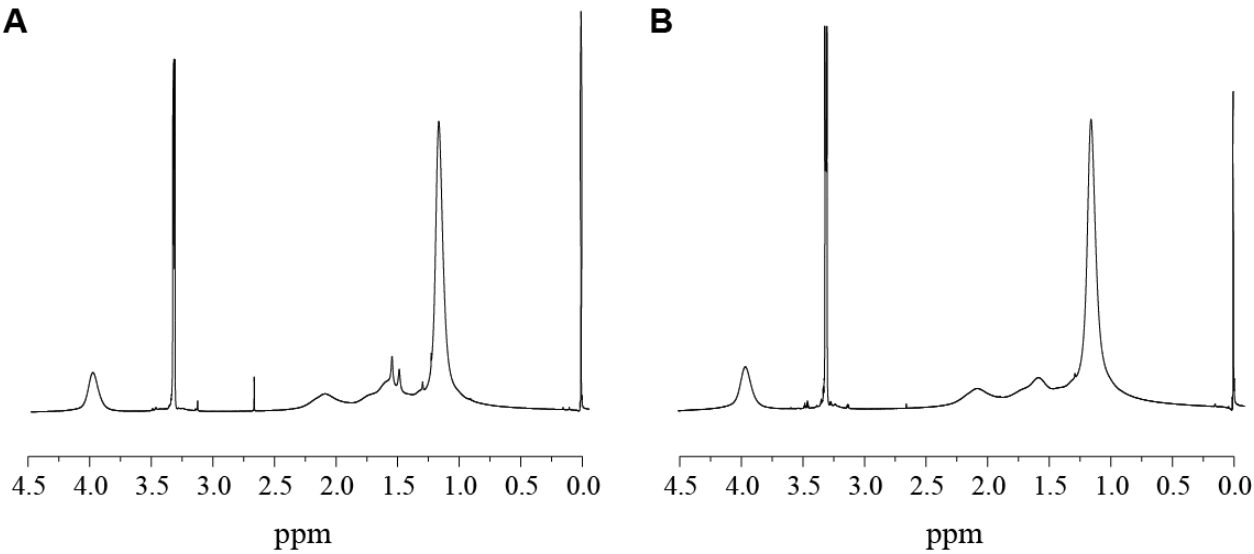


Figure S6. ^{1}H NMR spectrum of (AAc + BGUA) NPs (**A**) after and (**B**) before deprotection in MeOD at room temperature. After deprotection, the two Boc peaks at around 1.5 ppm disappeared.

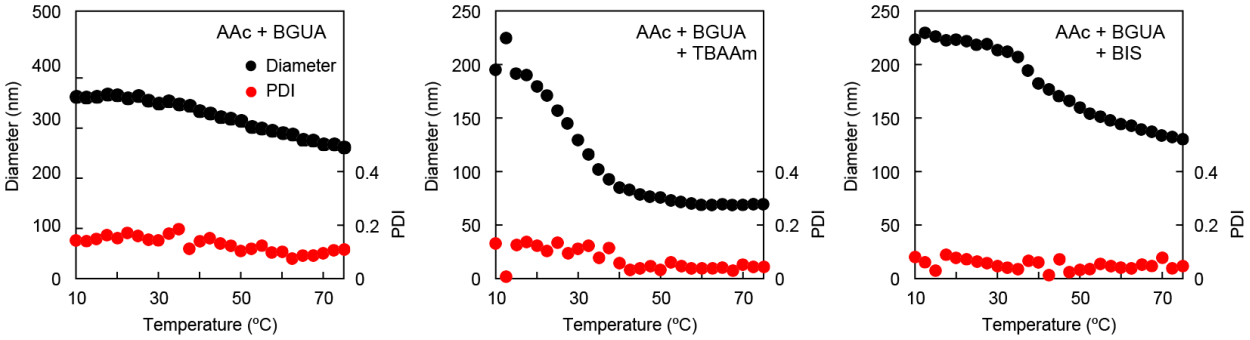


Figure S7. Hydrodynamic diameters (black) and PDI (red) of (AAc + BGUA) NPs at 10–75 °C.

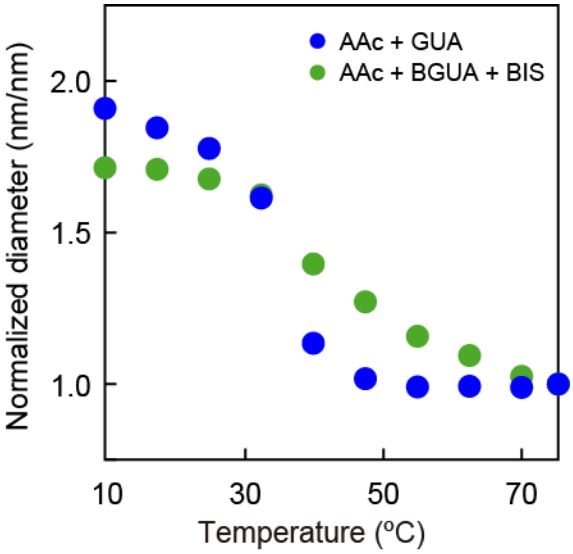


Figure S8. Hydrodynamic diameters of (AAc + GUA) NPs (blue) and (AAc + BGUA + BIS) NPs (light green), normalized by the diameter of each NP type at 75 °C, as a function of temperature.

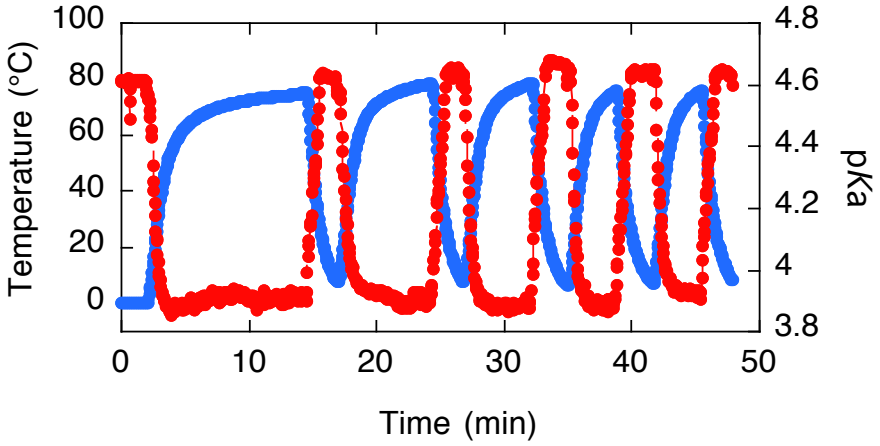
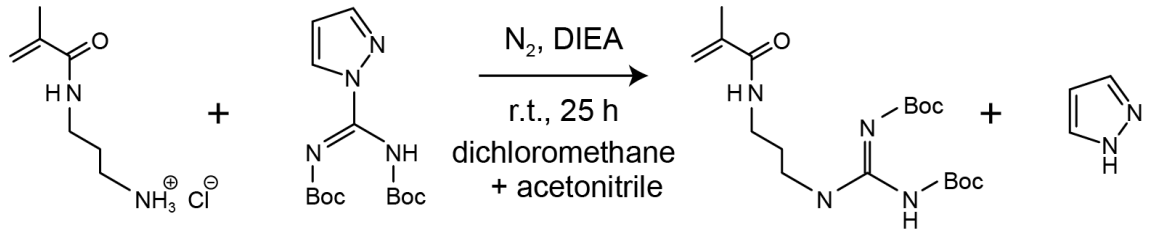


Figure S9. pK_a profile of carboxylic acids in (AAc + BGUA + TBAAm) NPs (red plots). Temperature of the solution (blue plots) was heated and cooled by hot water bath and ice bath respectively, and monitored by thermometer in the pH probe.



Scheme S1. Synthesis of BGUA.

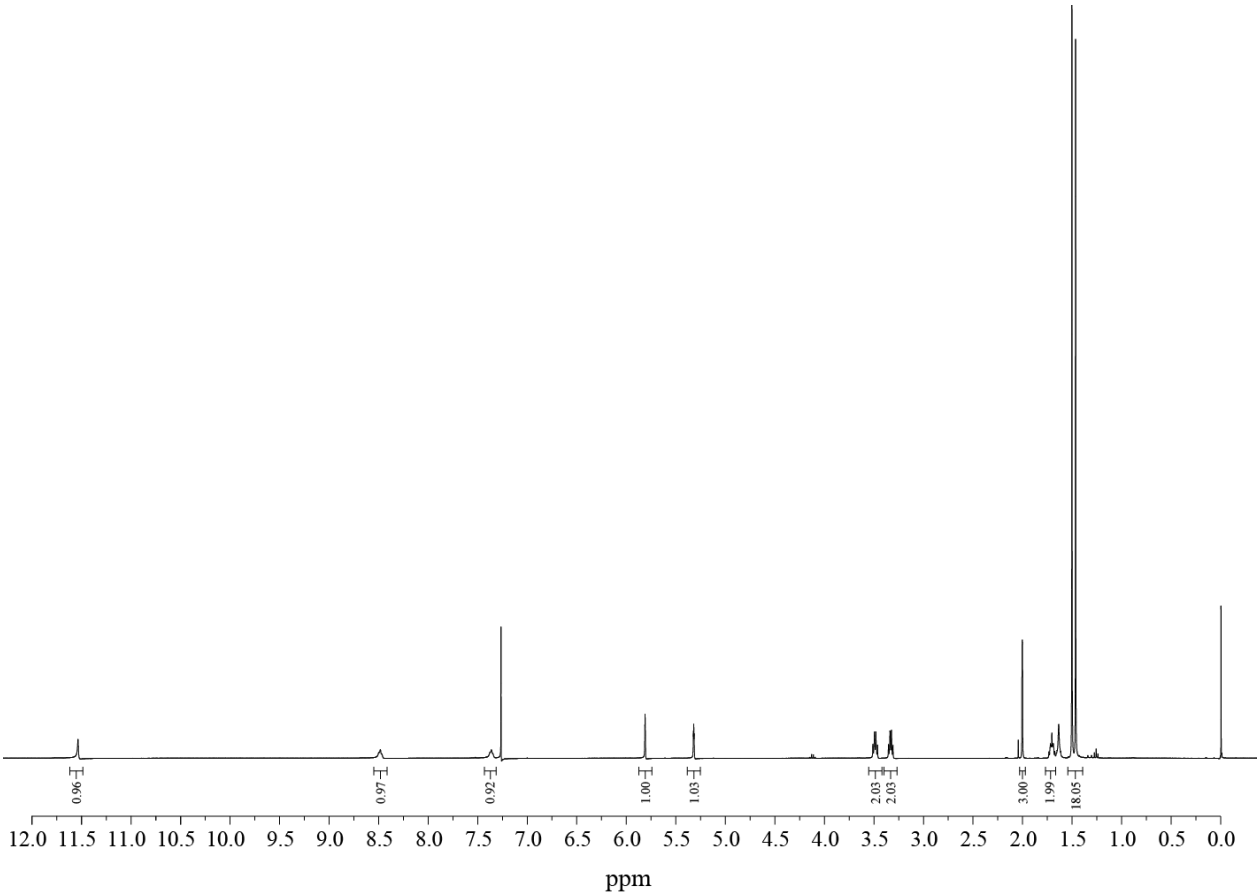
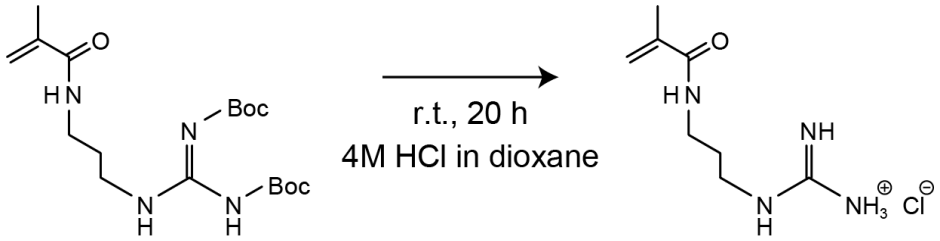


Figure S10. ^{1}H NMR spectrum of BGUA in $CDCl_3$ at room temperature.



Scheme S2. Synthesis of GUA.

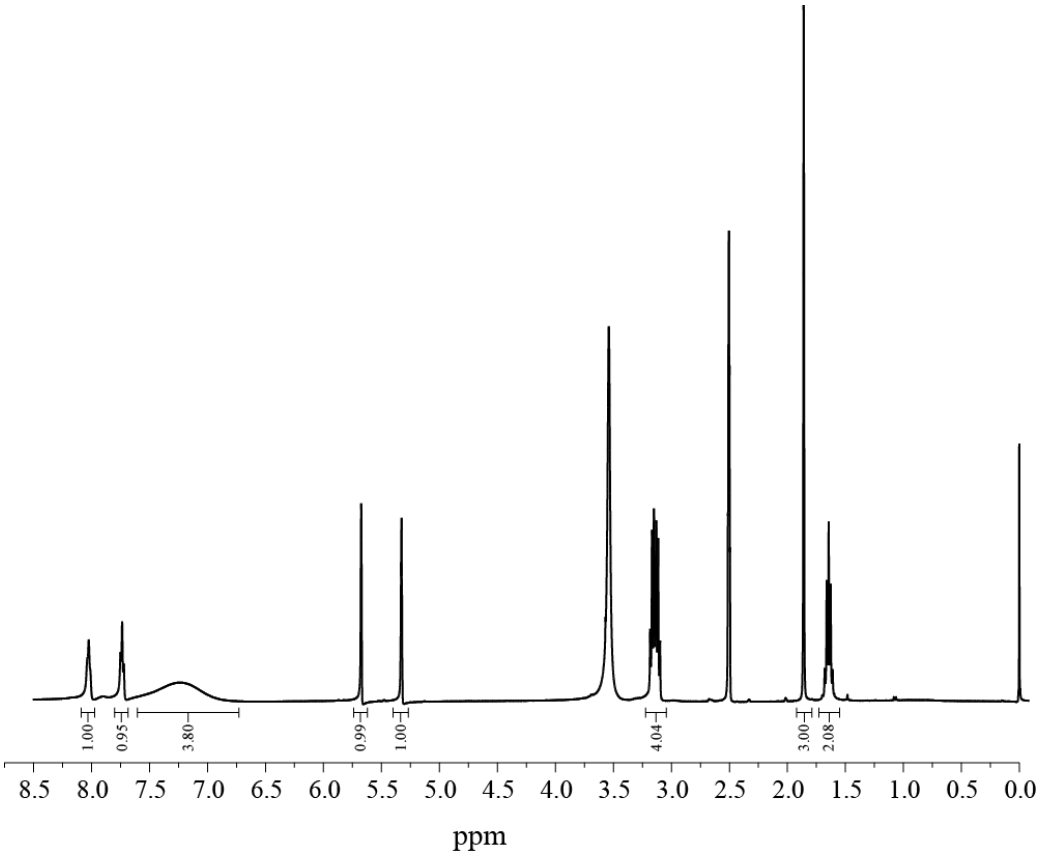


Figure S11. ^{1}H NMR spectrum of GUA in DMSO-d_6 at room temperature.

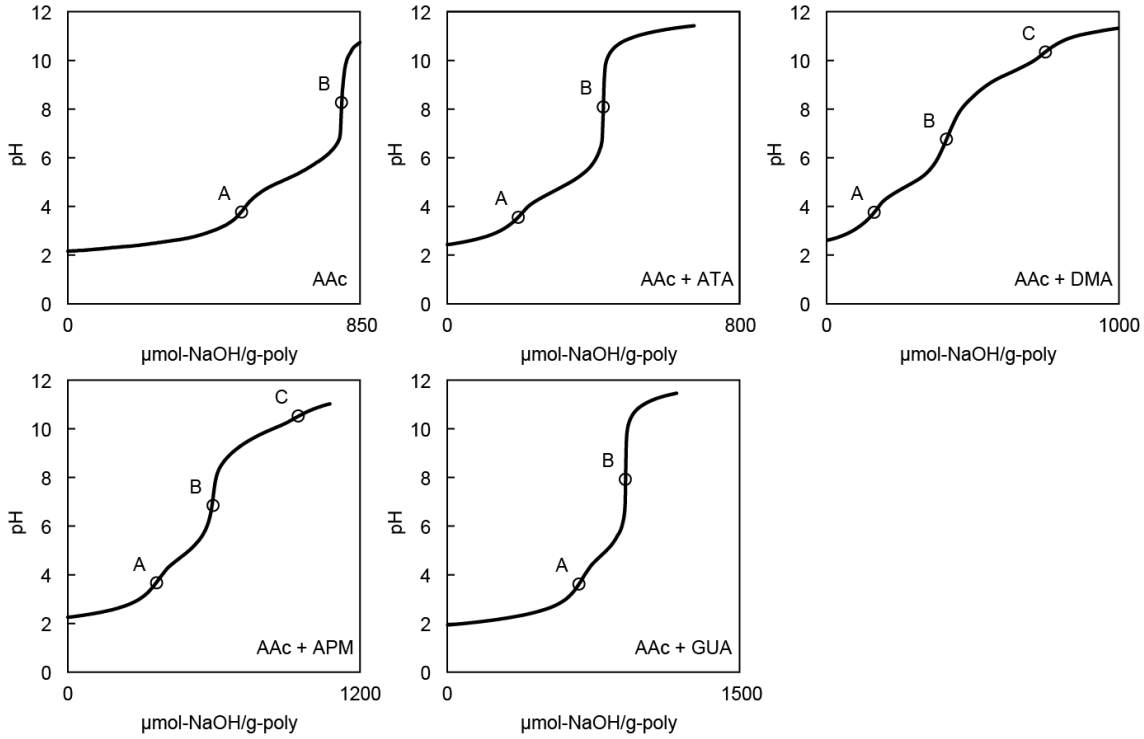


Figure S12. Acid–base titration curves for (AAc + cations) NPs. Plots A, B and C indicate neutralization point of HCl, carboxylic acids and cations, respectively. ATA and GUA have high pK_a values, so their neutralization points were not observed by this titration. Instead, the amounts of ATA and GUA introduced were determined by a back-titration method.

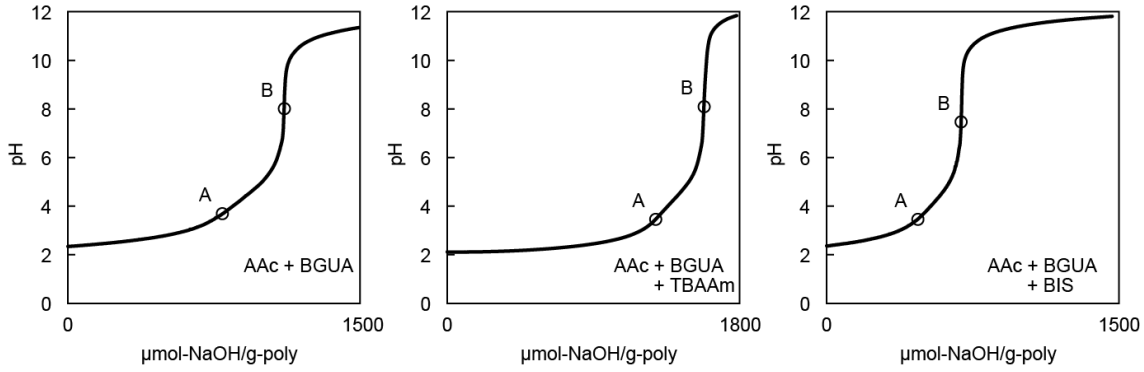


Figure S13. Acid–base titration curves for (AAc + BGUA) NPs. Plots A and B indicate neutralization point of HCl, carboxylic and acids, respectively. The amounts of GUA introduced were determined by a back-titration method.