

Electronic Supplementary Information

Ugi Four-Component Polymerization of Amino Acid Derivatives: A Combinatorial Tool for the Design of Polypeptoids.

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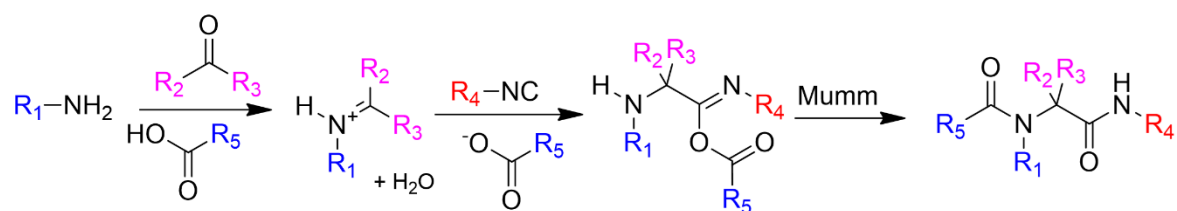
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A) Mechanism of Ugi-4CR



B) Intramolecular Ugi-4CR of α -amino acids

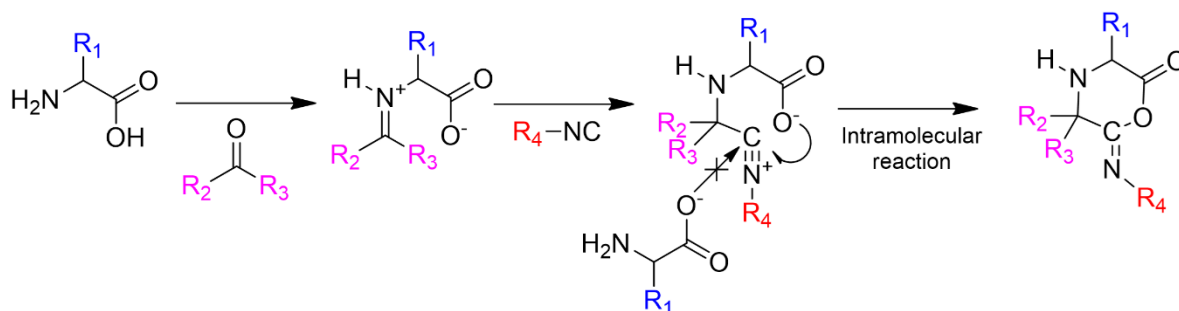


Figure S1. A) Mechanism of Ugi-4CR and B) Intramolecular Ugi-4CR of α -amino acids leading to six-membered ring intermediate.

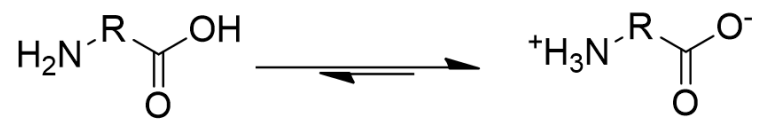


Figure S2. Displaced equilibrium between neutral and zwitterionic forms of amino acid around neutral pH.

Table S1. Ugi-4C polymerization of glygly : Effect of temperature, time and stoichiometry.

Entry	Temperature (°C)	Time (hours)	[glygly]/ [formaldehyde]/ [tBuNC]	M _n (g/mol) ^a	M _p (g/mol) ^a	Đ ^a
1	20	24	1/1.3/1.3	5400	11800	2.09
2	50	24	1/1.3/1.3	3100	6100	2.04
3	20	120	1/1.3/1.3	5600	10000	1.77
4	20	24	1/1/1	1400	4200	2.54

Conditions: polymerization in 0.62 mL H₂O/MeOH (1:1 v:v). ^a determined by SEC in DMF using a PS calibration.

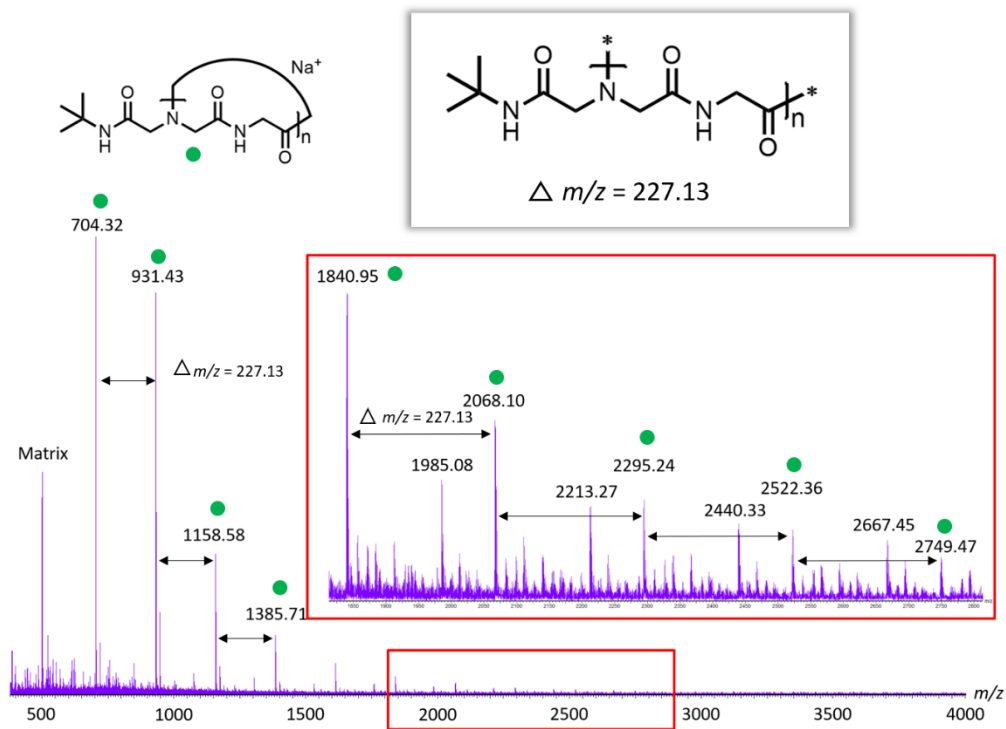
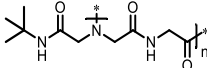
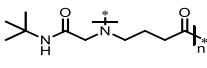
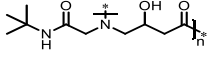
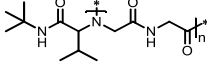
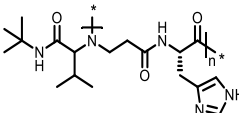
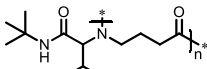
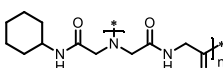
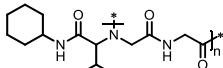
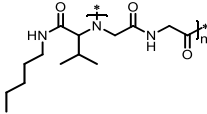
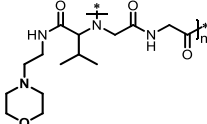


Figure S3. MALDI-ToF spectrum and magnification between m/z 1800 – 2800 of the polypeptoid obtained from glygly/tBuNC/formaldehyde (entry 3, Table 1).

Table S2. Synthesis and purification of polymers P₁-P₁₀.

Entry	Polymer	Before Dialysis		After dialysis		Yield ^b (%)
		<i>M_w</i> ^a (g.mol ⁻¹)	<i>M_n</i> ^a (g.mol ⁻¹)	<i>M_w</i> ^a (g.mol ⁻¹)	<i>M_n</i> ^a (g.mol ⁻¹)	
P ₁		9600	4900	10500	5900	83
P ₂		6500	3500	7100	4200	72
P ₃		6600	3800	7100	4600	70
P ₄		7400	3100	11600	7900	54
P ₅		3900	2600	5000	3500	70
P ₆		5400	1800	11600	8000	33
P ₇		5500	3200	6000	4000	35
P ₈		4600	2700	5100	3400	45
P ₉		2000	1600	4200	3200	24
P ₁₀		3300	2200	5700	3600	42

polymerization at r.t. in water/MeOH (1:1 v:v) mixture (P₁, P₂, P₃, P₆ and P₇) or in MeOH (P₄, P₅, P₈, P₉ and P₁₀). [H₂N-R-CO₂H]/[aldehyde]/[isocyanide] = 1/1.3/1.3, 24 hours. Purification by dialysis (cut-off of 1kD). ^a determined by SEC in DMF using a PS calibration. ^b Isolated yields were determined by gravimetry after dialysis.

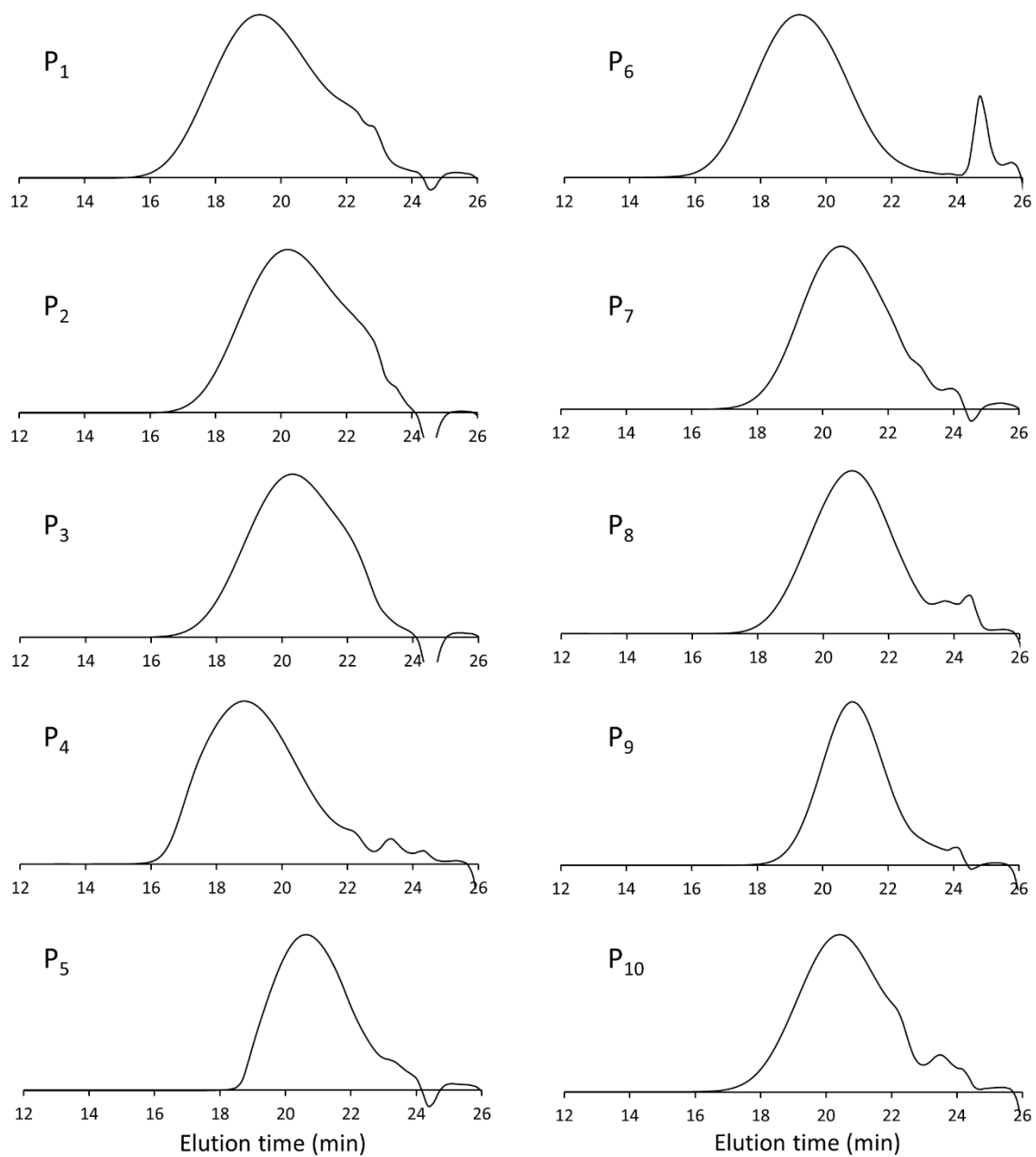


Figure S4. Size exclusion chromatography of polymers P₁-P₁₀ after purification by dialysis.

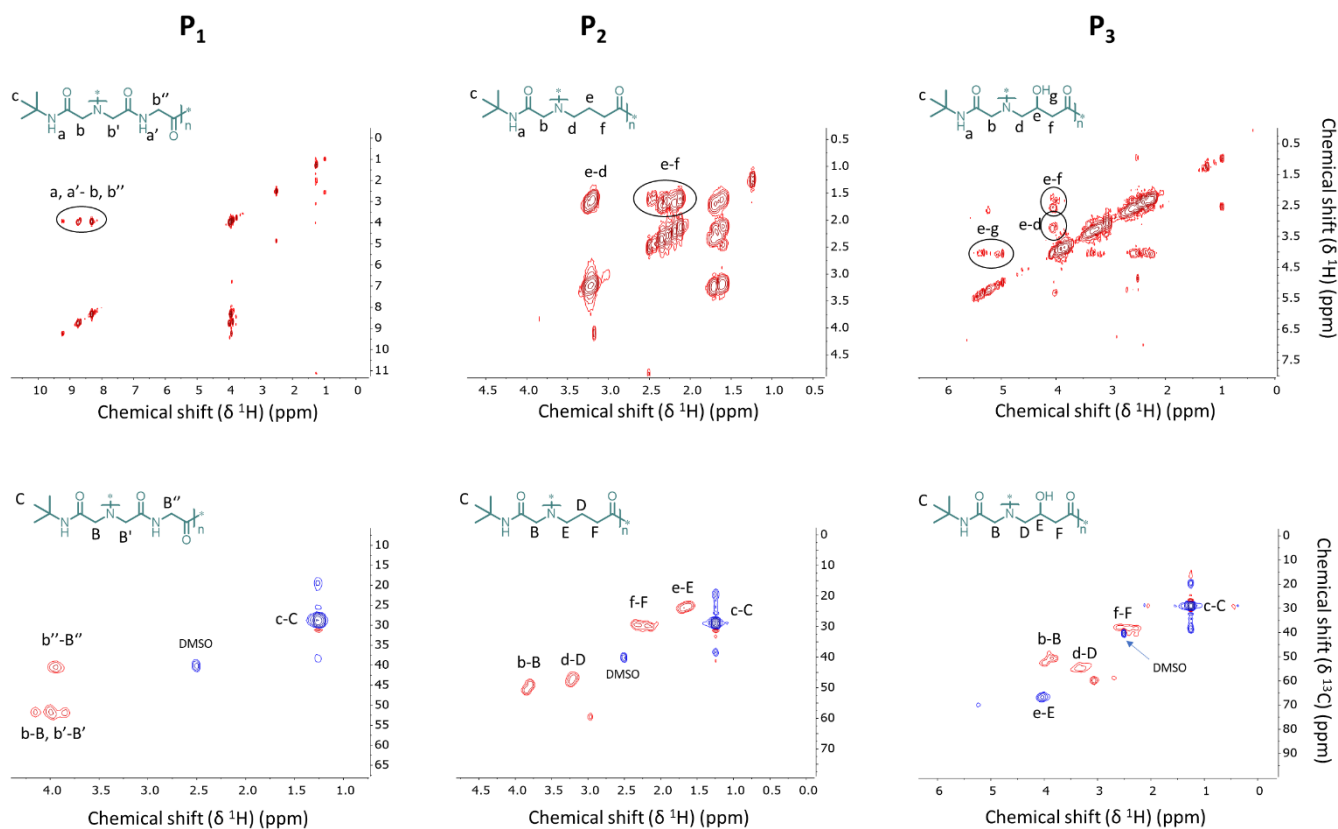


Figure S5. COSY and HSQC NMR spectra of P₁, P₂ and P₃ presented in Table S1. The lowercase letters and capital letters design protons and carbon respectively.

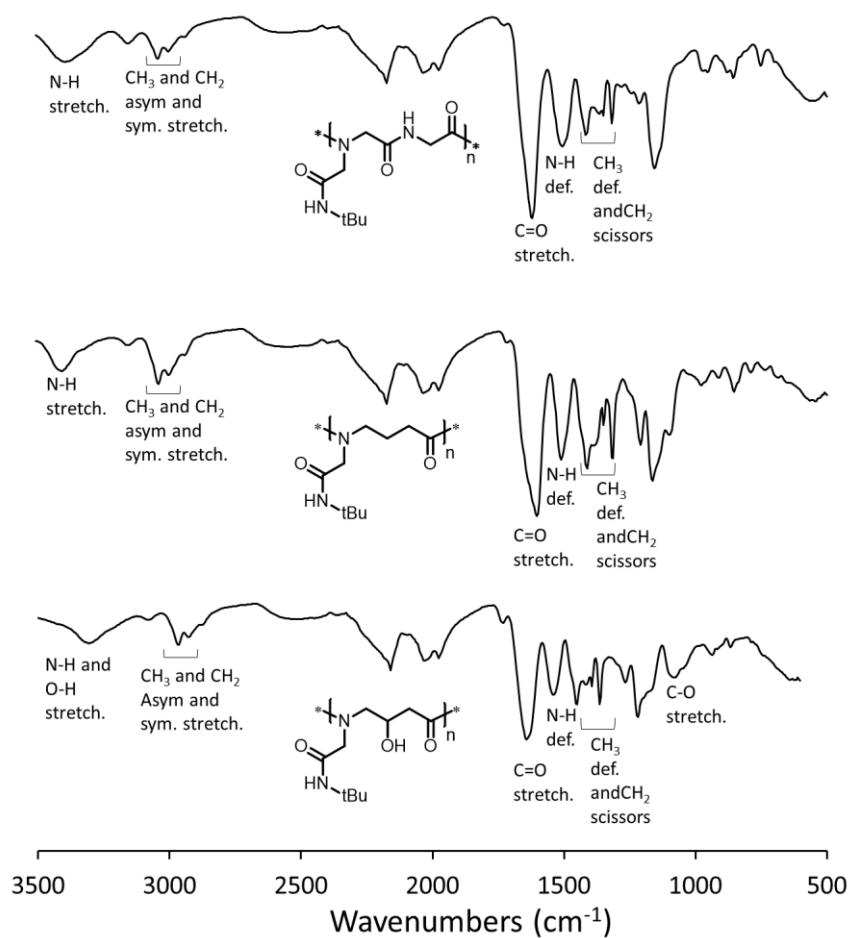


Figure S6. ATR spectra of P₁, P₂ and P₃ presented in Table S1. Peaks between 1900 and 2500 cm⁻¹ corresponds to the signal of diamond phonon band.

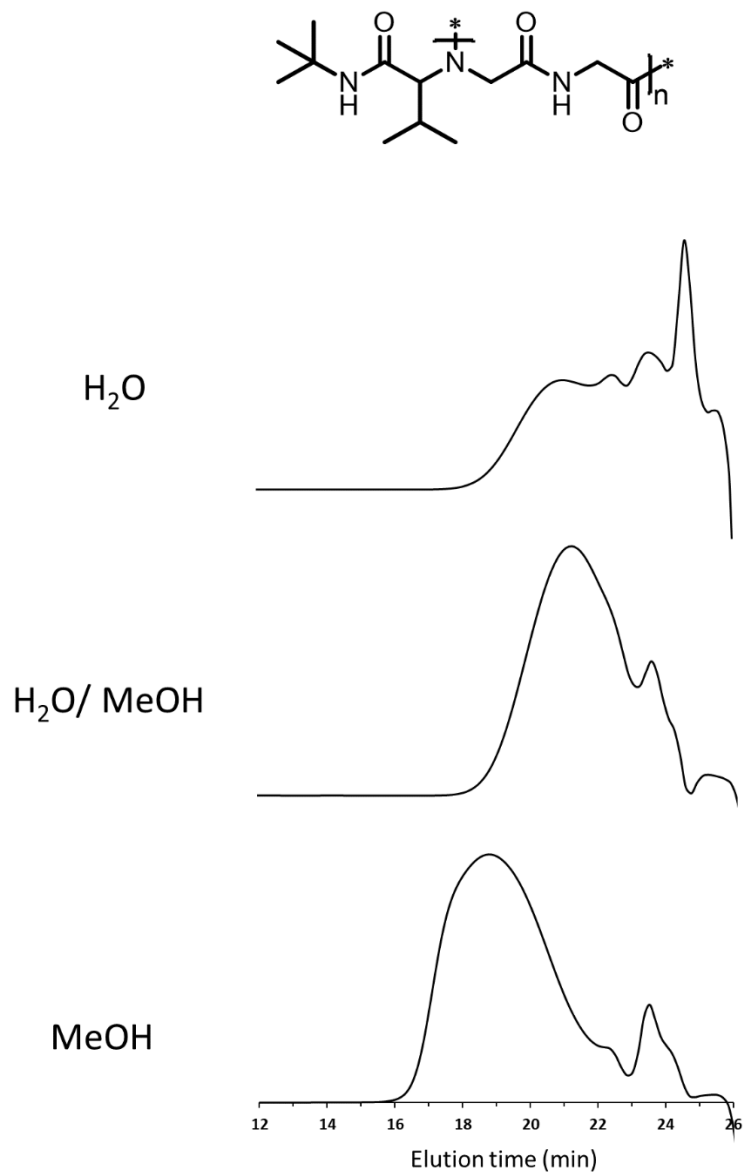


Figure S7. SEC chromatograms for the polymerizations of Gly-Gly with isobutyraldehyde and *tert*-butyl isocyanide in different solvents. Macromolecular parameters (M_n , M_w and \mathcal{D}) are presented in Table 2.

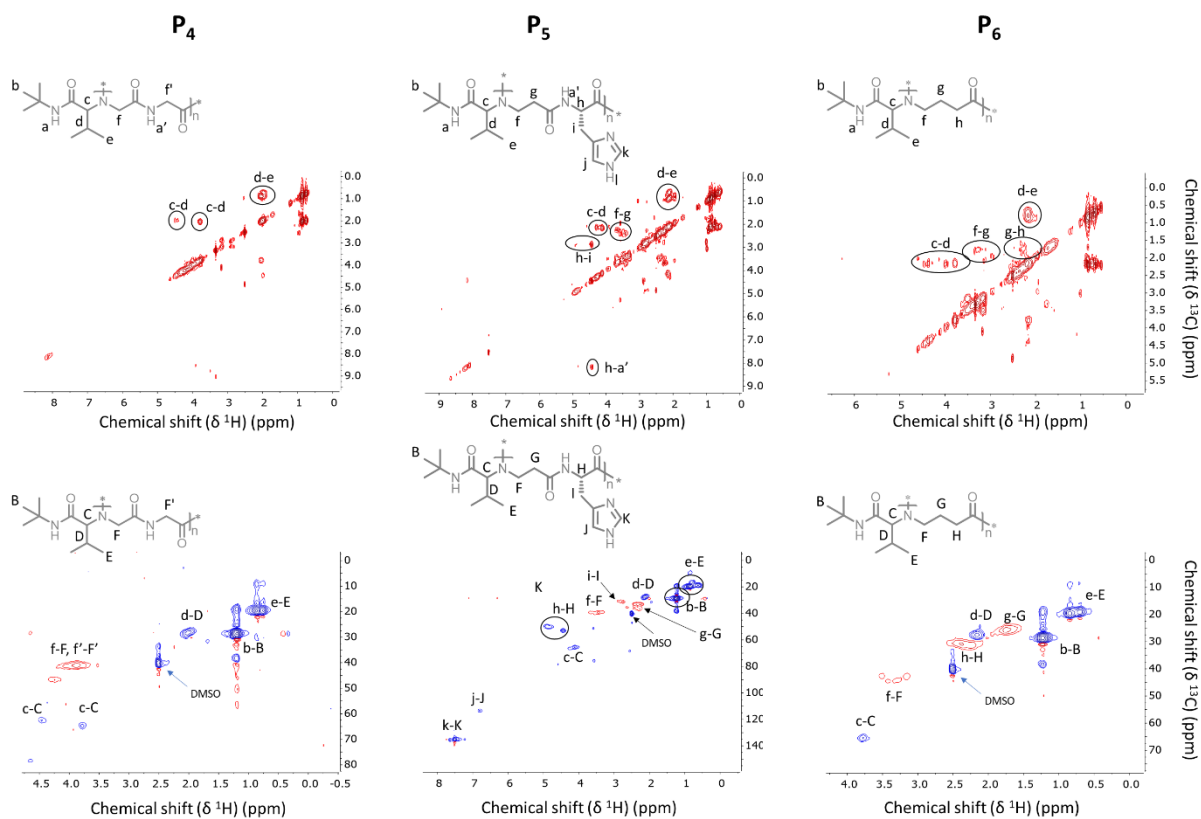


Figure S9. COSY and HSQC NMR spectra of P₄, P₅ and P₆ presented in Table S1. The lowercase letters and capital letters design protons and carbon respectively.

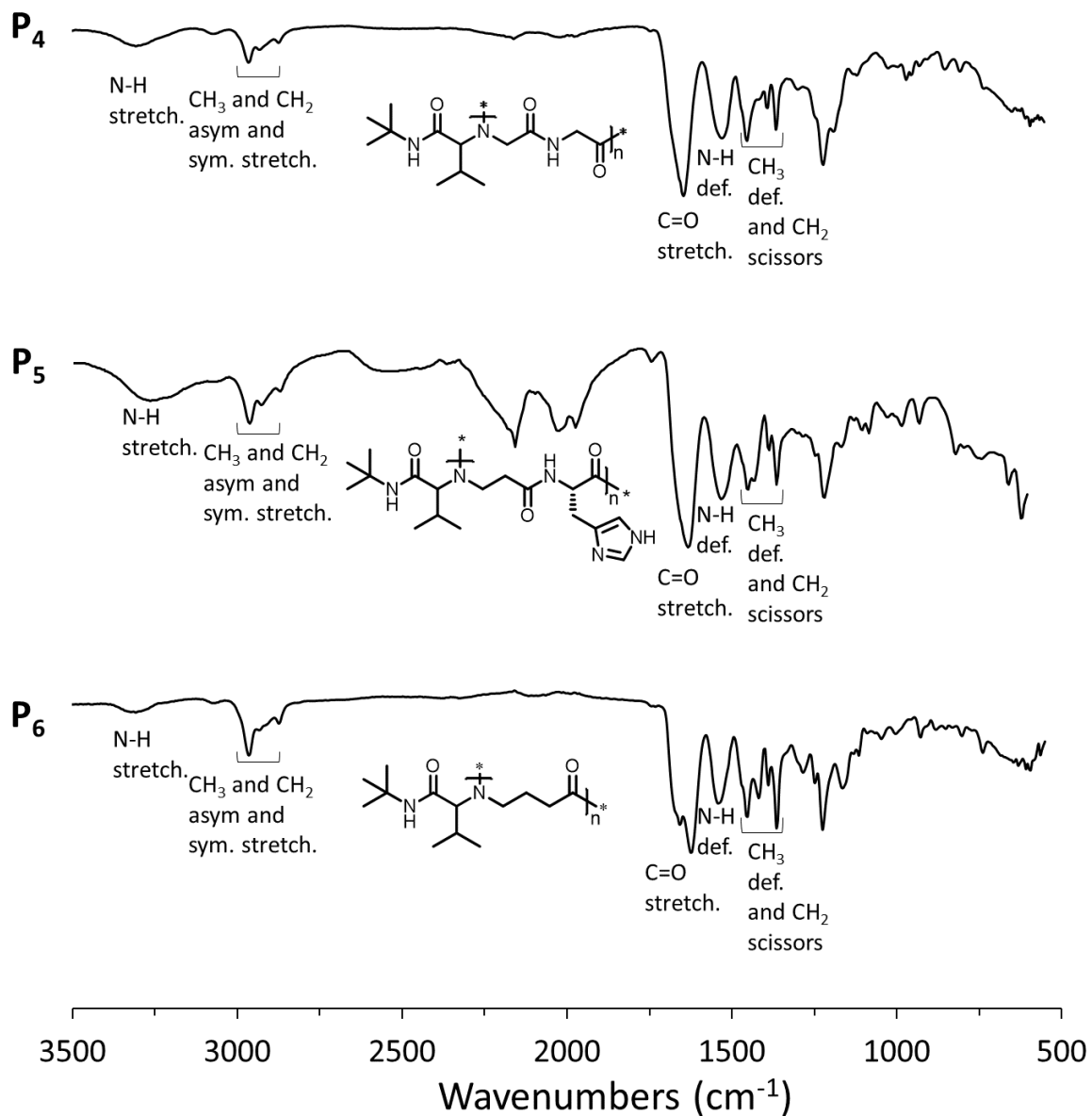


Figure S10. ATR spectra of P₄, P₅ and P₆ presented in table S1. Peaks between 1900 and 2500 cm⁻¹ corresponds to the signal of diamond phonon band.

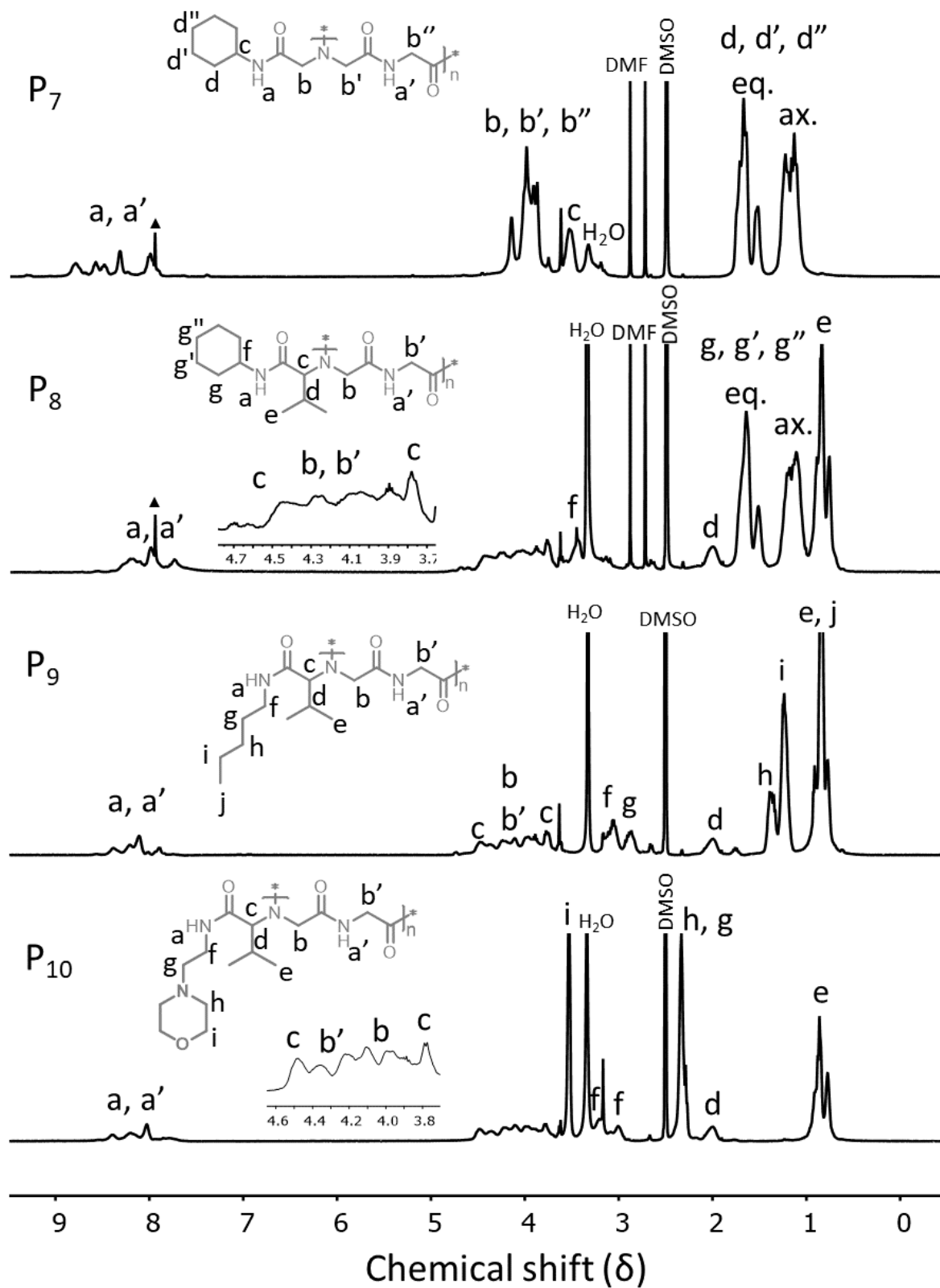


Figure S11. ^1H NMR spectra of P_7 , P_8 , P_9 and P_{10} presented in Table S1 in deuterated DMSO.

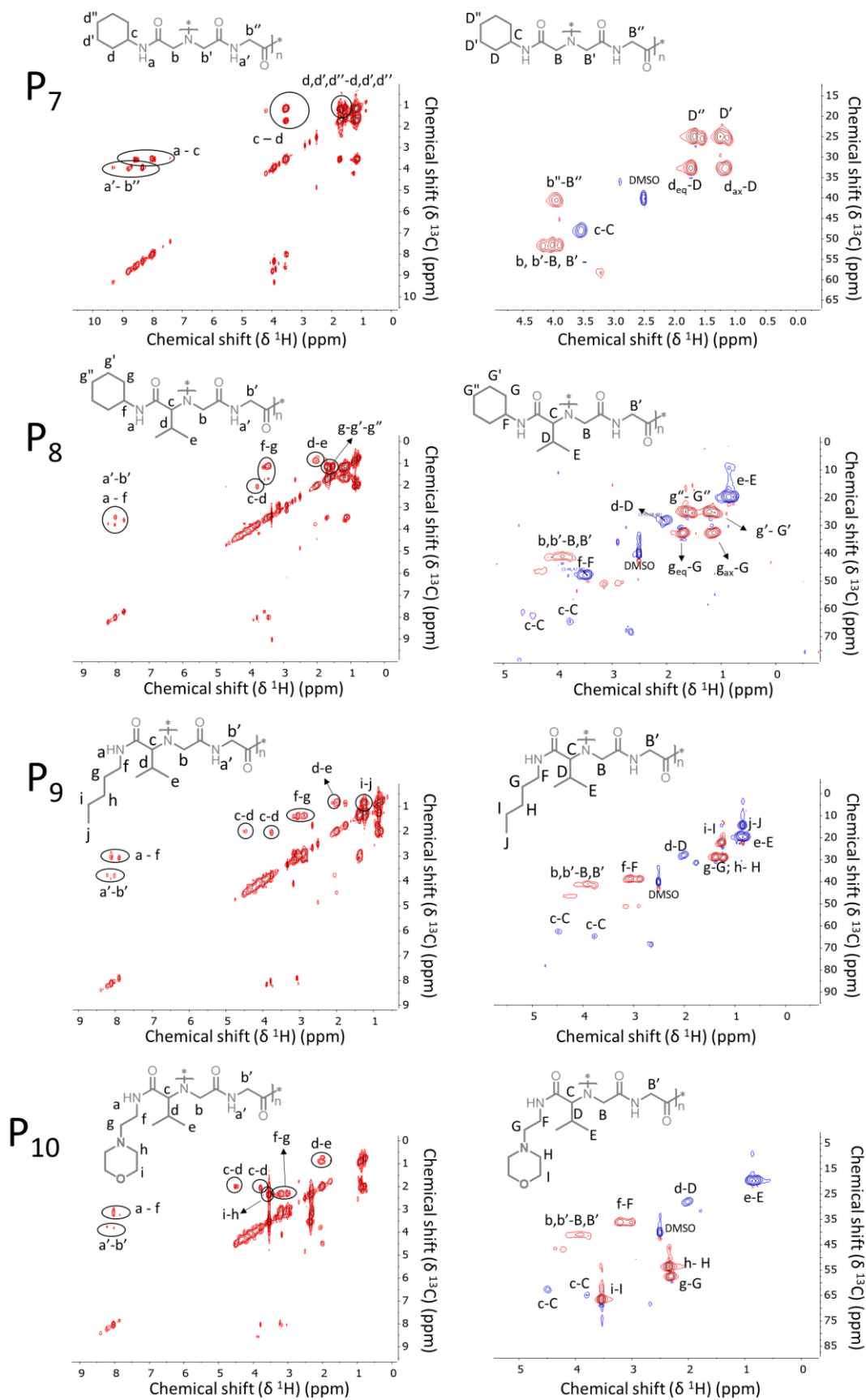


Figure S12. COSY and HSQC NMR spectra of P₇, P₈, P₉ and P₁₀ presented in Table S1 in deuterated DMSO. The lowercase letters and capital letters design protons and carbon respectively.

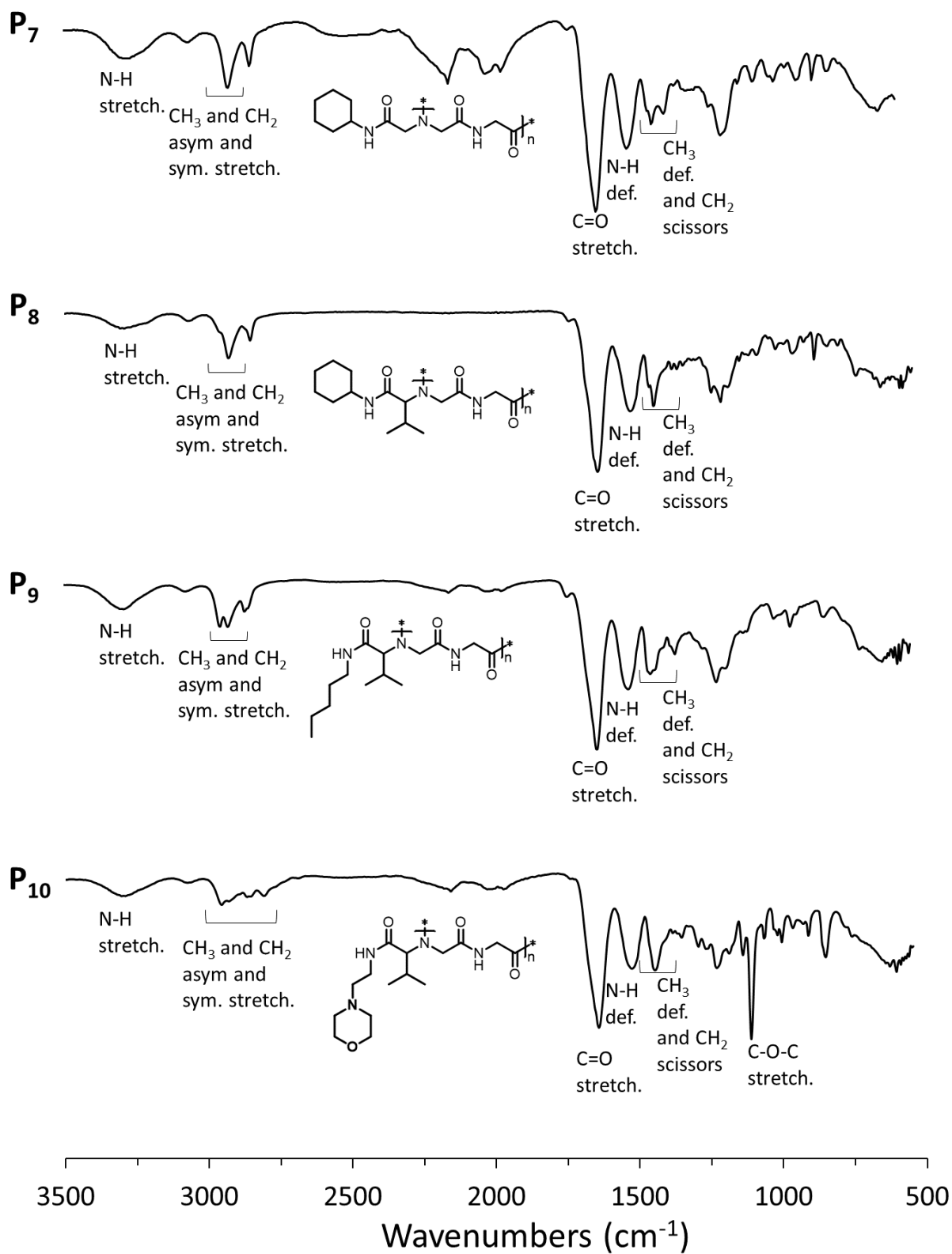


Figure S13. ATR spectra of P₄, P₅ and P₆ presented in Table S1. Peaks between 1900 and 2500 cm⁻¹ corresponds to the signal of diamond phonon band.

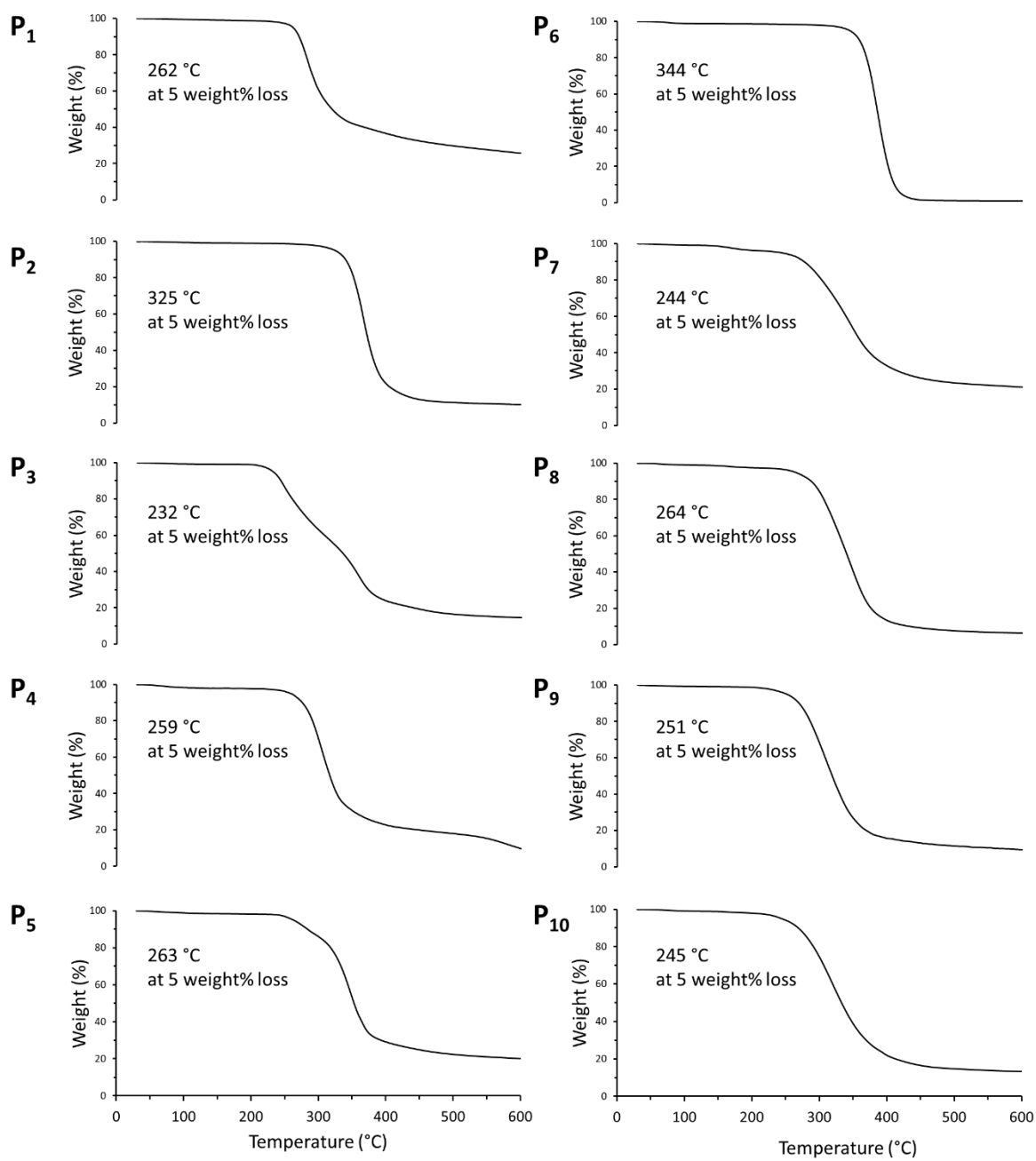


Figure S14. Thermogravimetric analysis of polymers P₁-P₁₀ presented in Table S1 recorded with a temperature ramp of 20 °C/min from 30 to 600 °C.

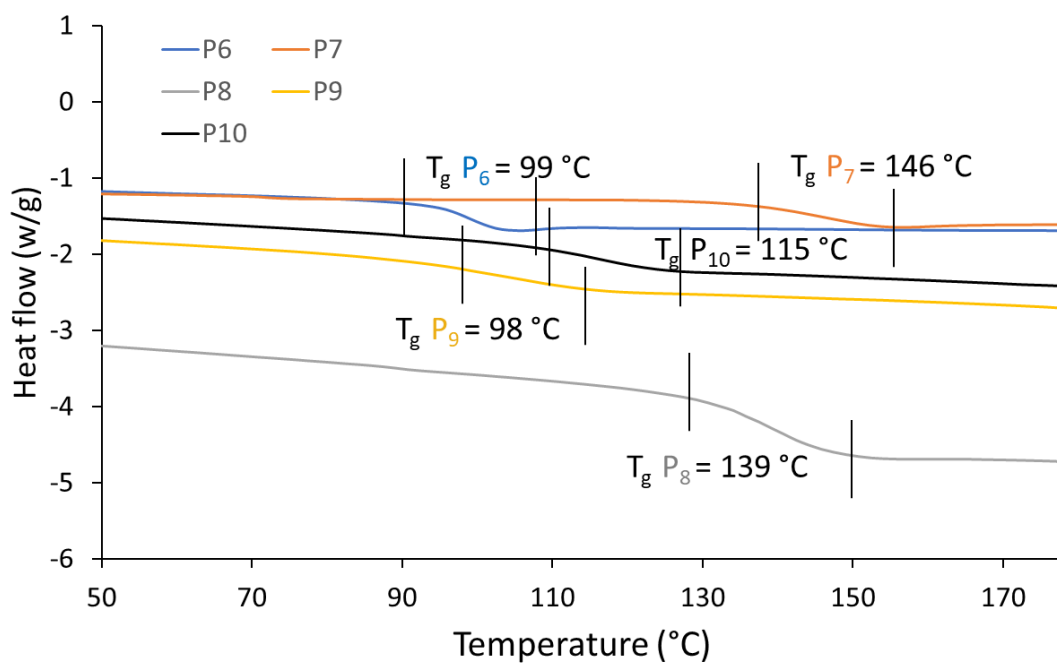
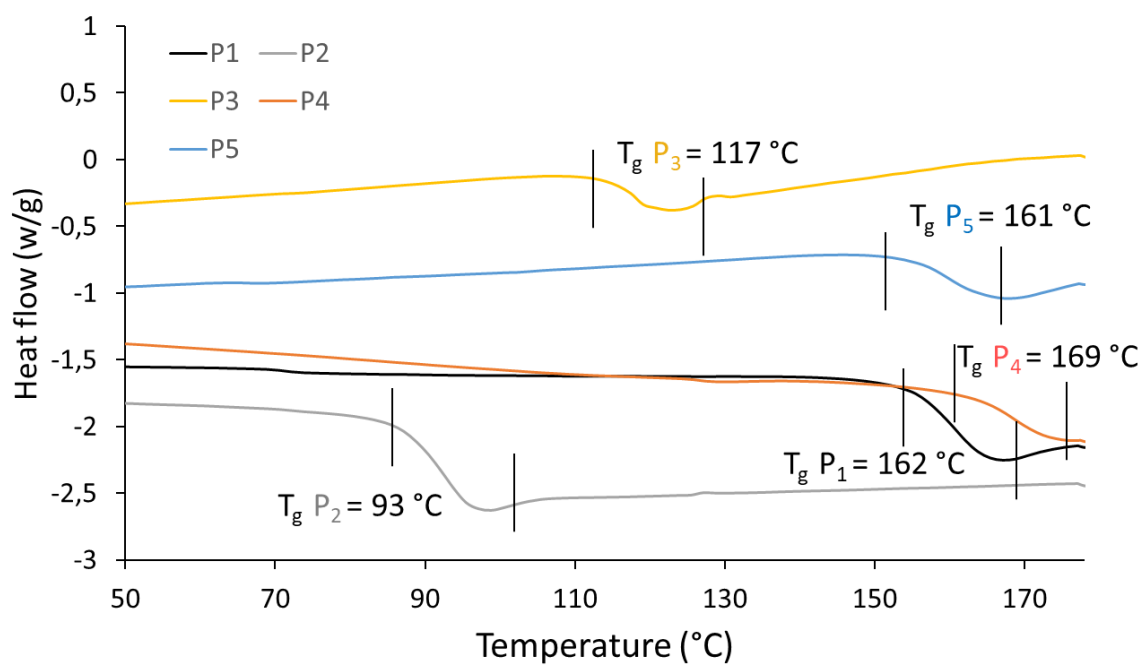
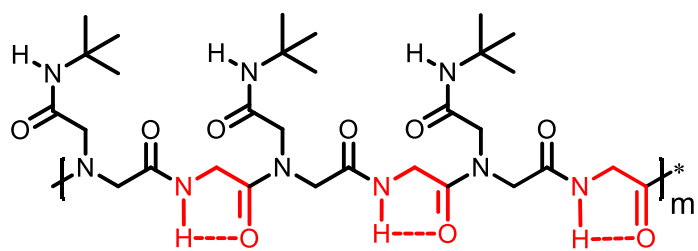
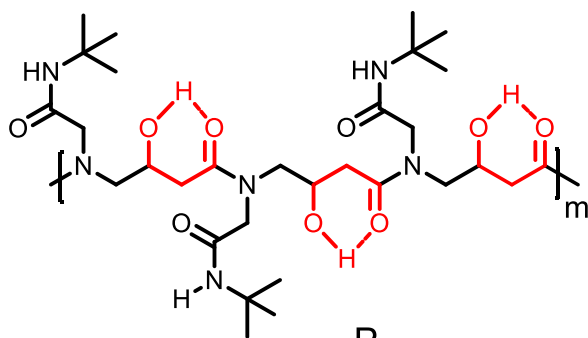


Figure S15. Differential scanning calorimetry analysis of polymers P₁-P₁₀ presented in Table S1.



P₁



P₃

Figure S16. Possible intramolecular hydrogen bonds in P₁ and P₃ leading to 6-membered and 5-membered rings, respectively.

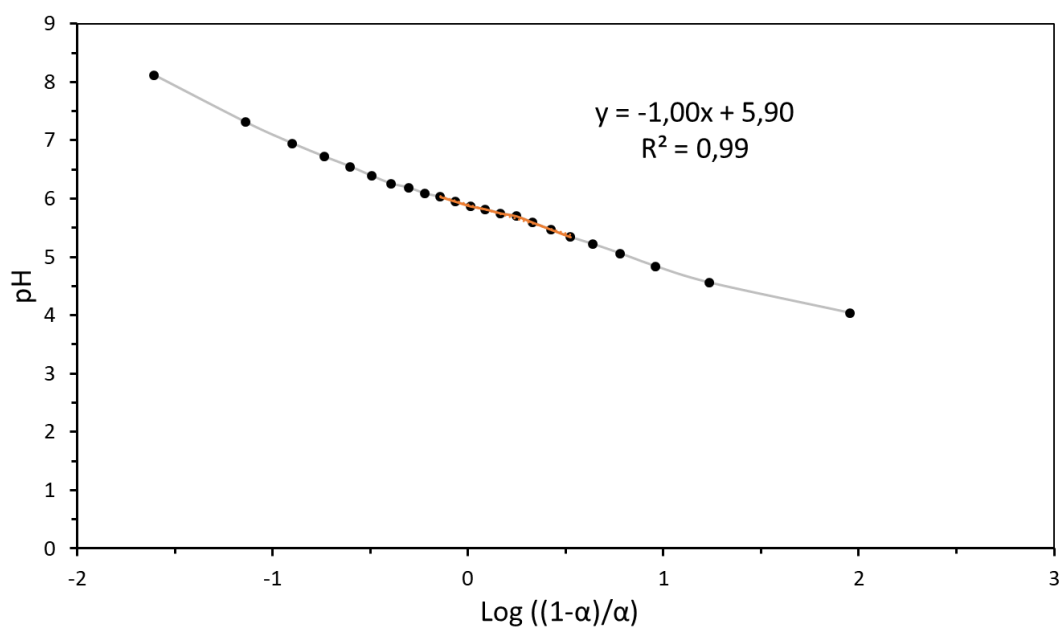
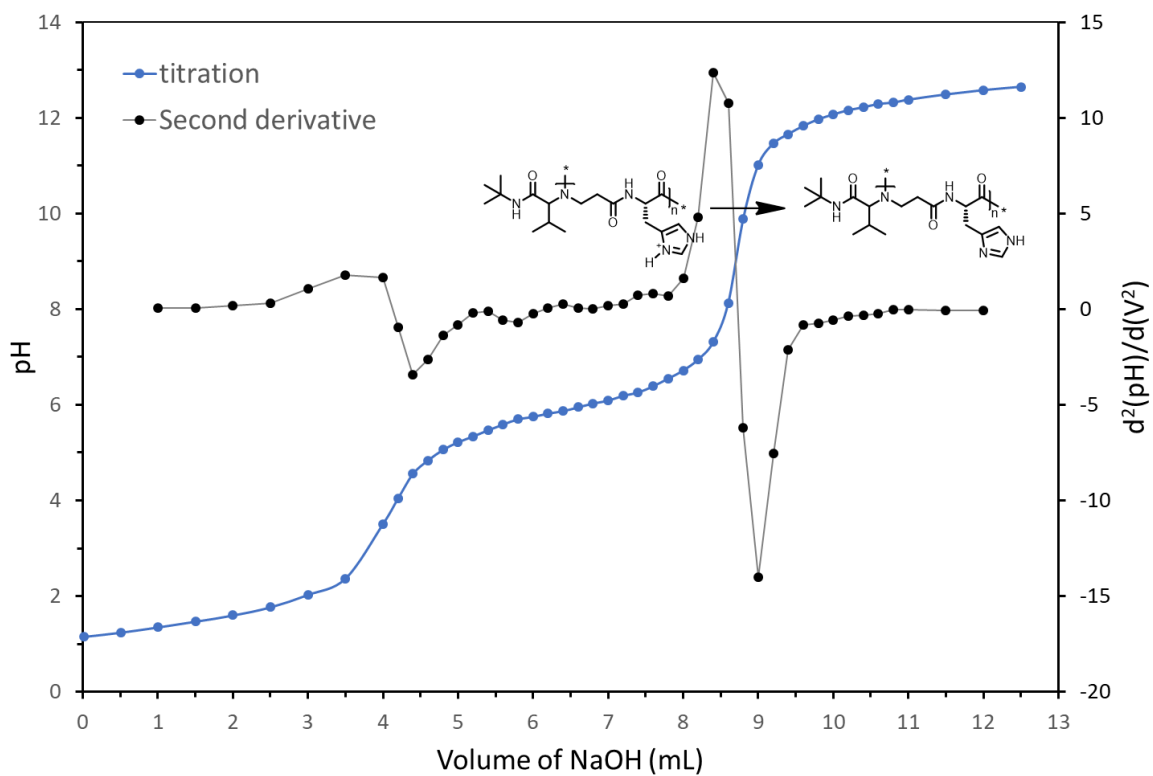


Figure S17. Upper plot: Titration curve of a solution 0.05 M of P₅ acidified with HCl, by NaOH 0.1 M. The second discrete derivative are represented on the curve and are obtained *via* the finite difference method. Lower plot: Henderson-Hasselbalch plot and linear regression on the region where α value ranges between 0.2 and 0.6.

Calculation:

The first and second derivatives were calculated via the finite difference method.

$$\text{Second derivative: } \frac{\Delta\left(\frac{\Delta pH_n}{\Delta V_n}\right)}{\Delta V_n} = \frac{\left(\frac{\Delta pH_n}{\Delta V_n}\right)_{n+1} - \left(\frac{\Delta pH_n}{\Delta V_n}\right)_{n-1}}{V_{n+1} - V_{n-1}}$$

The second derivative allows to find the inflection points that are located at $f''(x) = 0$. The equivalence points and the half-equivalence correspond to inflection points. They are located at 4.15, 6.1 and 8.71 mL of NaOH.

The Henderson-Hasselbalch plot is calculated from the data from the titration. The degree of neutralization is fixed at 0 and 1 for volumes of NaOH of 4.15 and 8.71 respectively. It corresponds to the titration of the histidine moiety of P₅. Before 4.15 mL of NaOH, it was the excess of HCl which was titrated.

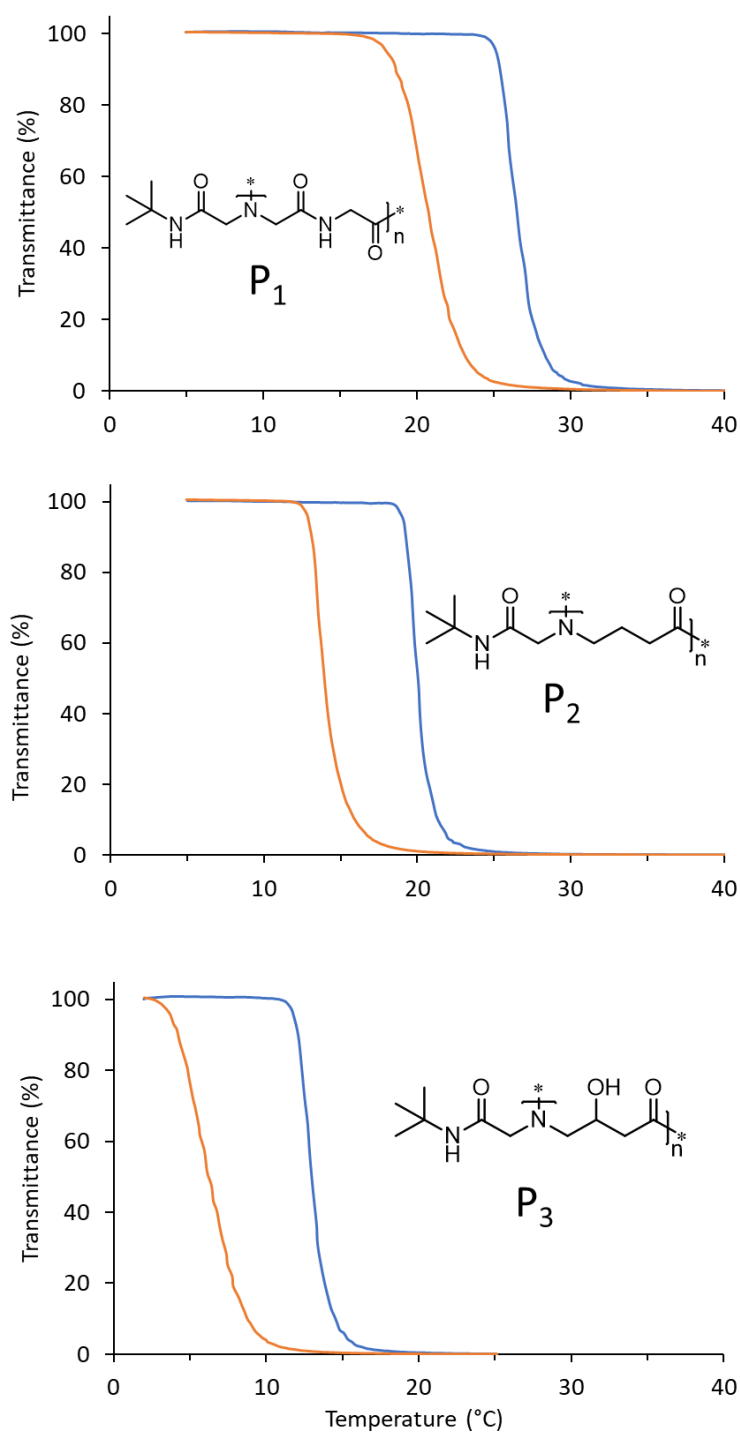


Figure S18. Turbidimetry measurements of aqueous solution of P₁, P₂ and P₃ at a concentration of 2 mg mL⁻¹ subjected to heating-cooling cycle at a constant rate of 2 °C/min. The blue and orange curves represent the heating and cooling steps, respectively.

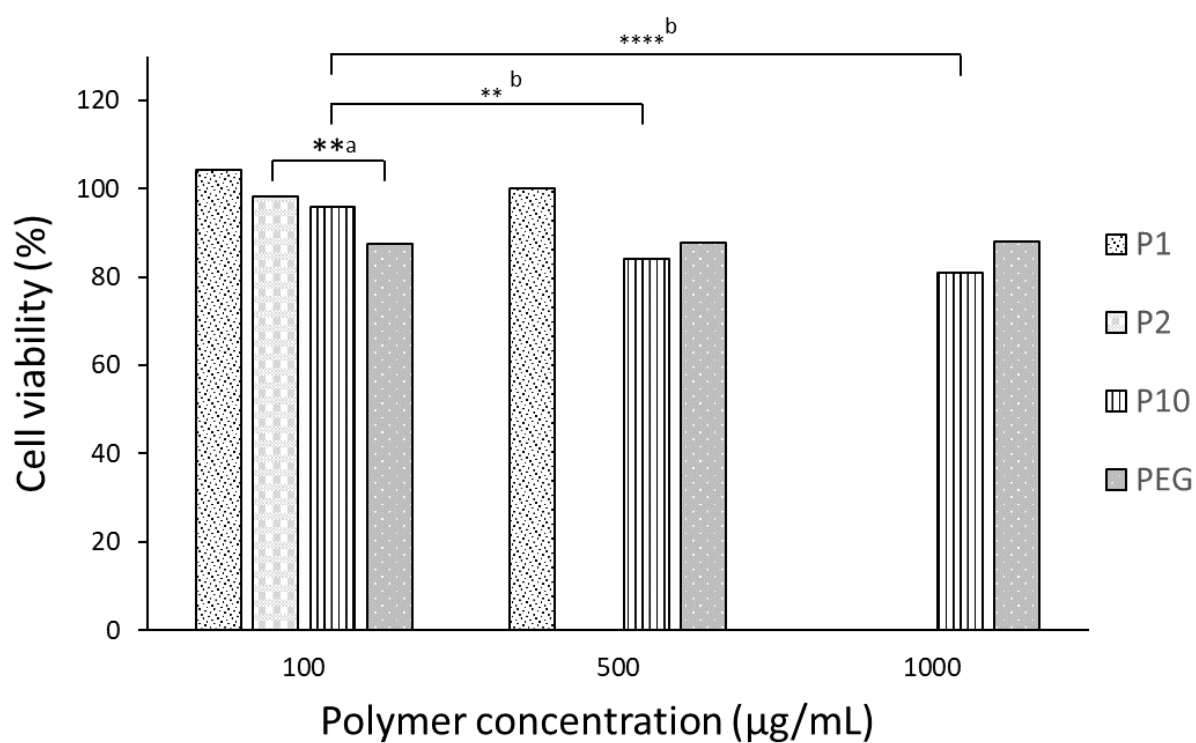


Figure S19. Cell viability of P₁, P₂ and P₁₀ compared with PEG_{5k} evaluated by MTS method after 72 h of incubation with HeLa cells at 37 °C. The stars represent the summary of the statistical difference (* = p value < 0.05, ** = p value < 0.01, *** = p value < 0.001 ****p value < 0.0001). ^a Unpaired t test. ^b Ordinary One-way ANOVA test followed by Tukey's multiple comparisons test.