Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supporting Information

Exploring the role of polymer hydrophobicity in polymer–metal binding thermodynamics

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Materials:

Trace metals grade $EuCl_3 \cdot 6H_2O$, AIBN, 1,4-dioxane, and 1,3,5-trioxane were purchased from Sigma Aldrich. 2,3,4,5-Tetrafluorophenol was purchased from Synquest. Acryloyl chloride was purchased from Alfa Aesar. Glycine, DL-alanine, DL-valine, and DL-leucine were purchased from Oakwood Chemical. Dialysis bags (pre-treated regenerated cellulose tubing, 1 kDa molecular weight cut-off) were purchased from Spectrum Labs. AIBN was recrystallized from MeOH prior to use. All other chemicals were used as-is.

Characterization:

NMR: ^{1}H NMR, ^{19}F, and ^{13}C NMR spectra were acquired on an Agilent MR4 400 MHz spectrometer. Chemical shifts in the ^{1}H NMR and ^{13}C NMR spectra were referenced to the residual solvent resonance signals.

Size Exclusion Chromatography: Size exclusion chromatography (SEC) was performed in tetrahydrofuran (THF) at 1 mL min^{-1} at 30 °C on two MIXED-B Agilent PLgel 10 μm columns connected in series with a Wyatt Optilab Rex refractive index detector and a Wyatt Dawn Heleos 2 light scattering detector. Data analysis was performed using Astra version 7.2.2.10 software (Wyatt Technologies). Molecular weights were calculated relative to the dn/dc of polystyrene standards (30 and 200 kDa).

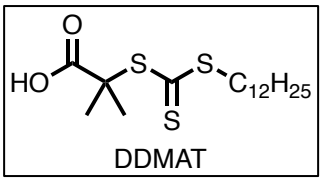
Isothermal titration calorimetry experimental procedure:

The ITC instrument used was an Affinity-ITC (TA Instruments, New Castle, DE), which operated at constant temperature (278–308 K). To carry out a binding experiment, a sample solution was prepared by dissolving the polymer and $EuCl_3$ in a pH 5, 100-mM NaOAc–HOAc buffer.

Before the ITC experiment, each solution was degassed for 15 min. The polymer solution (350 μL) was placed in the sample cell and the reference cell was filled with deionized H_2O (300 μL). Both cells were mounted in an adiabatic chamber at a constant temperature during the measurement. A long-needle syringe with a twisted paddle fastened to its end, was filled with the metal-ion solution. The syringe was placed inside the sample cell, and the entire syringe assembly was rotated continuously (185 RPM) to provide proper mixing of the contents of the sample cell within a few seconds after an injection. After reaching thermal equilibrium, the injection of the metal ion solution was automatically conducted stepwise until the polymer was saturated with metal ion. Due to the possible dilution of the first measurement, the first injection was ignored in the data analysis, which is standard practice for ITC experiments.[1-2] The first 1.0-μL injection was followed by a series of 2.0-μL injections. The chosen time interval between two consecutive injections was 300 sec to ensure that the equilibrium was reached before the next injection.

Nonlinear least-squares curve fitting was conducted with TA Instruments Nano Analyze and TA Instruments Independent model. Heats of dilution from control titrations (metal ion into buffer (*no polymer present*), and buffer into polymer (*without metal ion present*)) were subtracted before curve fitting.

Synthesis of 2-(Dodecylthiocarbonothioylthio)-2-methylpropionic acid (DDMAT):



DDMAT

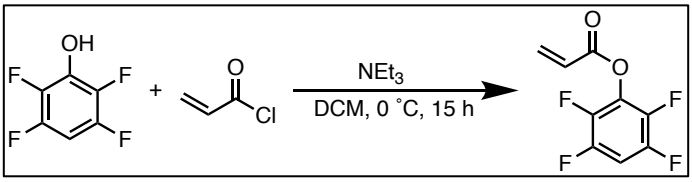
DDMAT was prepared according to the previously reported procedure.[3] Dodecanethiol (5.0 mL, 20.9 mmol, 1.3 equiv) and K_3PO_4 (3.60 g, 16.9 mmol, 1.1 equiv) was combined in a 100 mL round bottomed flak with 70 mL of acetone. After stirring for 20 minutes, CS_2 (3.0 mL, 49.6 mmol, 3.1 equiv) was added dropwise, during which the reaction solution turned yellow. 2-bromo-2-methylpropionic acid (2.64 g, 15.8 mmol, 1.0 equiv) was added to the stirring solution in one portion; stirring continued overnight at room temperature. To the reaction mixture, 1M HCl (aq, 200 mL) was added; the solution was then poured into a separatory funnel. The mixture was extracted with DCM (2 $\times$ 150 mL). The combined organic layers were dried over $MgSO_4$; the solvent was removed under reduced pressure. The crude product was recrystallized from hexanes to afford DDMAT as yellow crystals (65 % recovery).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.28 (t, 2H), 1.73 (s, 6H), 1.68 (m, 2H), 1.38 (m, 2H), 1.28 (s, 16H), 0.87 (t, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, δ): 221.3, 178.2, 55.9, 37.5, 32.4, 30.1, 30.0, 29.9, 29.8, 29.6, 29.4, 28.3, 25.7, 23.2, 14.6 ppm.

Synthesis of 2,4,5,6-tetrafluorophenyl acrylate (TFPA):

Scheme S1. Synthesis of 2,4,5,6-tetrafluorophenyl acrylate.



TFPA was prepared according to the previously reported procedure.[4] In general, 2,4,5,6-tetrafluorophenol (134.6 mmol, 1.0 equiv) was dissolved in approximately 50 mL of DCM under nitrogen at 0 ˚C. Triethylamine (208 mmol, 1.5 equiv) was added to the reaction flask and stirred for 20 min. Acryloyl chloride (148.5 mmol, 1.1 equiv) was added dropwise over 45 min. The reaction continued to stir overnight. The reaction mixture was filtered into a separatory funnel, extracted with 3 M HCl (3 × 25 mL), and brine (3 × 25 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vaccuo*. The resulting oil was purified by vacuum distillation at 78 ˚C to provide a clear liquid in 73 % yield.

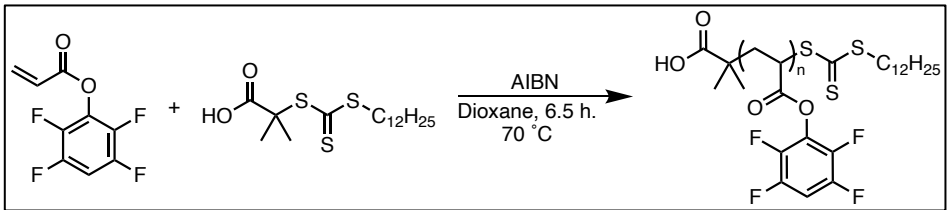
^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.0 (tt, 1H), 6.8 (dd, 1H), 6.4 (dd, 1H), 6.2 (dd, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, δ): 161.6, 147.3, 144.8, 139.5, 135.1, 125.5, 103.1 ppm.

^{19}F NMR (375 MHz, $CDCl_3$, δ): –139.1, –153.0 ppm.

Synthesis of poly(2,4,5,6-tetrafluorophenyl acrylate) *via* RAFT polymerization:

Scheme S2. Synthesis of poly(TFPA).



TFPA (22.9 mmol, 100.0 equiv), DDMAT (0.23 mmol, 1.0 equiv), and AIBN (3.6 mg, 0.1 equiv) were combined in a 20 mL glass vial with 1,4-dioxane (3.5 mL). 1,3,5-trioxane was added as an internal standard. The vial was subsequently sealed with a septum and parafilm, and purged with N_2 for 30 min. The vial was then placed in a heating block equilibrated at 70 ˚C. After 6.5 h, the vial was removed from the heating block and exposed to air. ^{1}H NMR of the crude reaction solution confirmed that the monomer conversion was 94%. The solution was precipitated into cold MeOH resulting in an off-white solid. The solid was re-dissolved in THF and reprecipitated into MeOH; this process was repeated twice more. SEC (PS standards, THF): M_n = 12.5 kDa, M_w = 14.8 kDa, Đ = 1.18.

Figure S1: ^{1}H NMR of poly(TFPA)

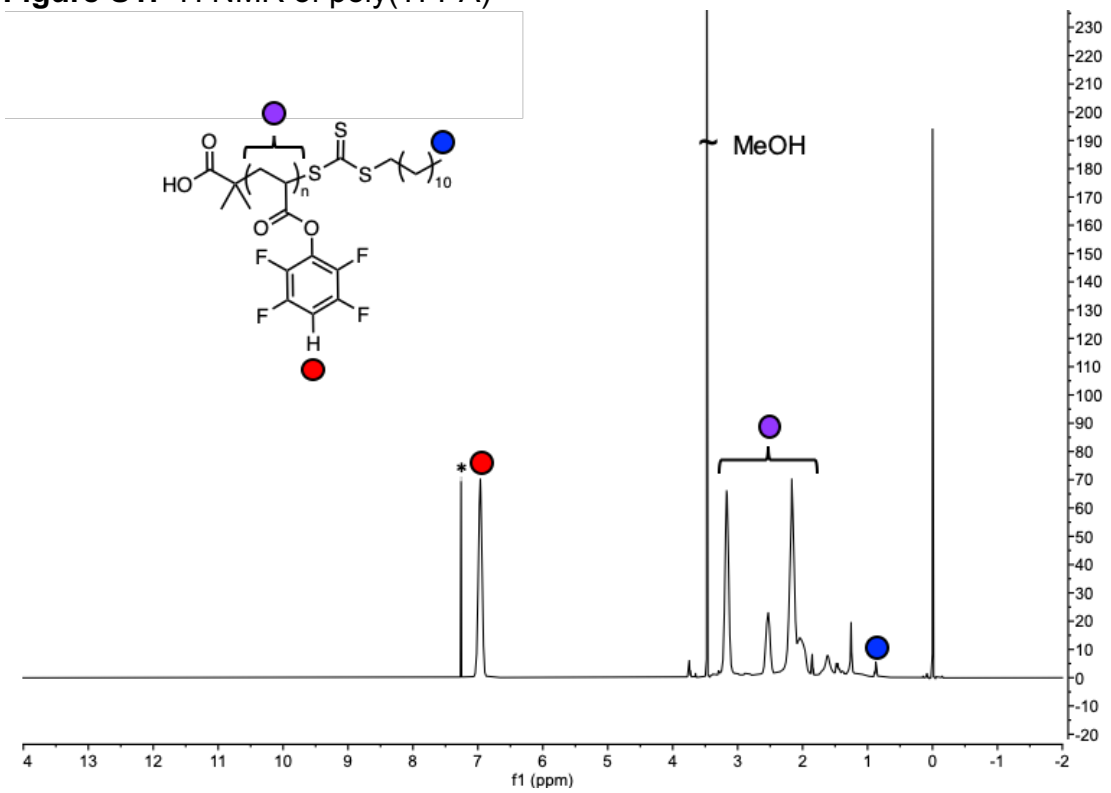


Figure S2: ^{19}F NMR of poly(TFPA)

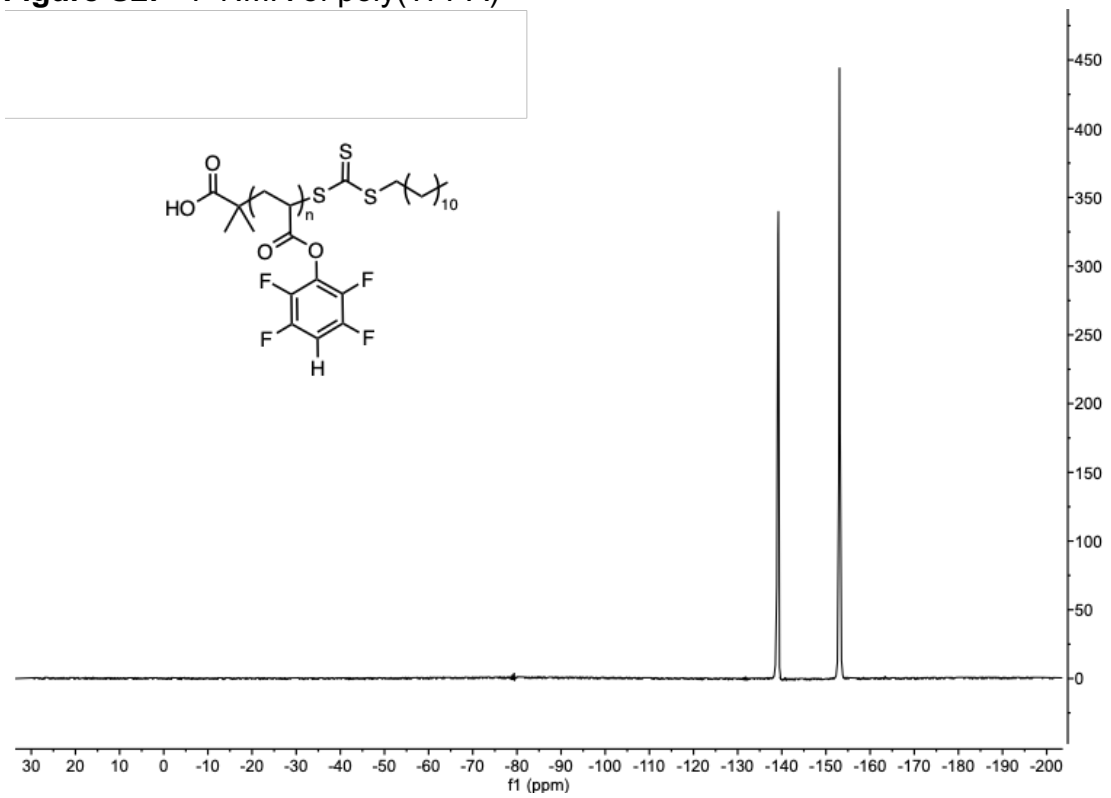
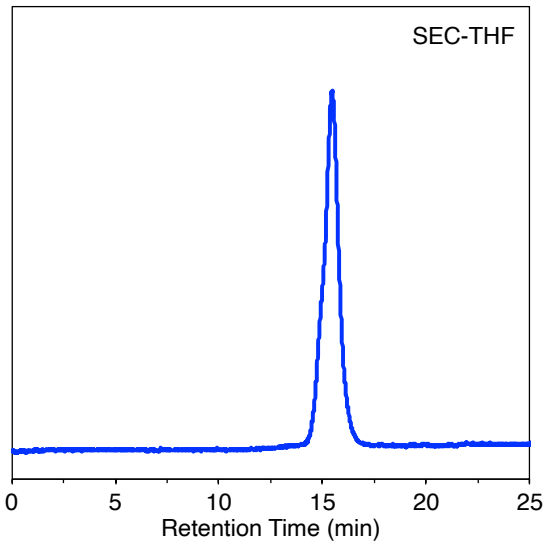


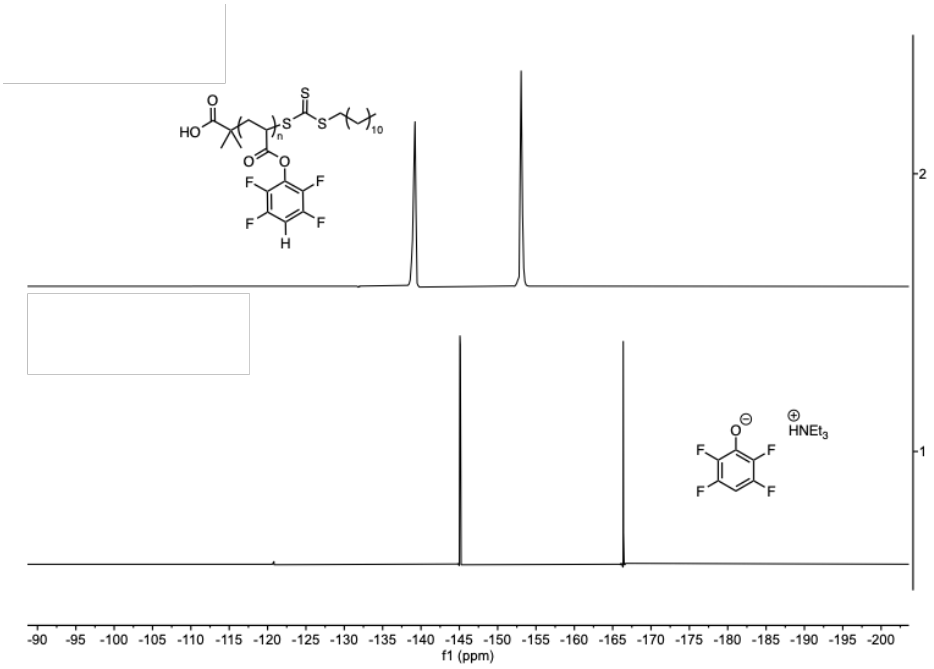
Figure S3: SEC trace of poly(TFPA)



Representative post-polymerization modification procedure to synthesize poly(glycine acrylamide):

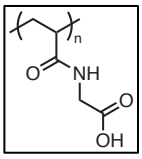
Poly(TFPA) (499.5 mg, 2.3 mmol, 1.0 equiv with respect to the mass of the repeat unit) was dissolved in DMSO (4 mL). Glycine (216.2 mg, 2.9 mmol, 1.3 equiv) was dissolved separately in a vial with triethylamine (0.5 mL, 1.6 equiv) and DI H_2O (5 mL). The resulting solution was added to the dissolved polymer solution in one portion and heated at 70 ˚C. After a few min, complete dissolution of the reaction solution occurred. The reaction mixture continued to stir for 10 h at 70 ˚C, after which the reaction mixture was cooled to rt and the solvent was removed under reduced pressure. ^{19}F NMR of the crude reaction mixture showed only signals for 2,4,5,6-tetrafluorophenoxide (**Fig. S4**). The reaction mixture was redissolved in of DI H_2O (5 mL), placed in a dialysis bag, and exhaustively dialyzed in DI H_2O for 3 d.

Figure S4: Representative ^{19}F NMR of reaction solution following post-polymerization modification



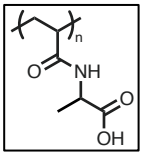
Characterization of poly(amino acid acrylamides) following post-polymerization modification:

Poly(glycine acrylamide): Brown crystalline solid purified from dialysis from DI H_2O.



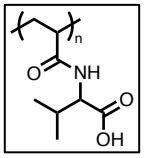
(84 mg = 32 % isolated yield); ^{1}H NMR (400 MHz, D_2O, δ): 3.9 (br, 2H), 2.3 (br, 1H), 1.6 (br, 2H) ppm.

Poly(DL-alanine acrylamide): Brown solid purified from dialysis from DI H_2O (47.5 mg



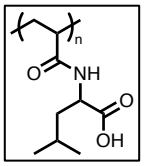
= 17 % isolated yield); ^{1}H NMR (400 MHz, D_2O, δ): 4.2 (br, 1H), 2.2 (br, 1H), 1.5 (br, 2H), 1.3 (br, 3H) ppm.

Poly(DL-valine acrylamide): White solid purified from dialysis from DI H_2O (138 mg =



40 % isolated yield); ^{1}H NMR (400 MHz, DMSO-d6, δ): ppm: 3.9 (br, 1H), 2.0 (br, 3H), 0.8 (br, 6H) ppm.

Poly(DL-leucine acrylamide): Brown solid purified from dialysis from DI H_2O (75 mg =



19 % isolated yield); ^{1}H NMR (400 MHz, DMSO-d6, δ): ppm: 4.1 (br,1H), 2.2 (br, 1H), 1.6 (br, 2H), 1.4 (br, 3H), 0.8 (br, 6H) ppm.

Figure S5: ^{1}H NMR of poly(glycine acrylamide)

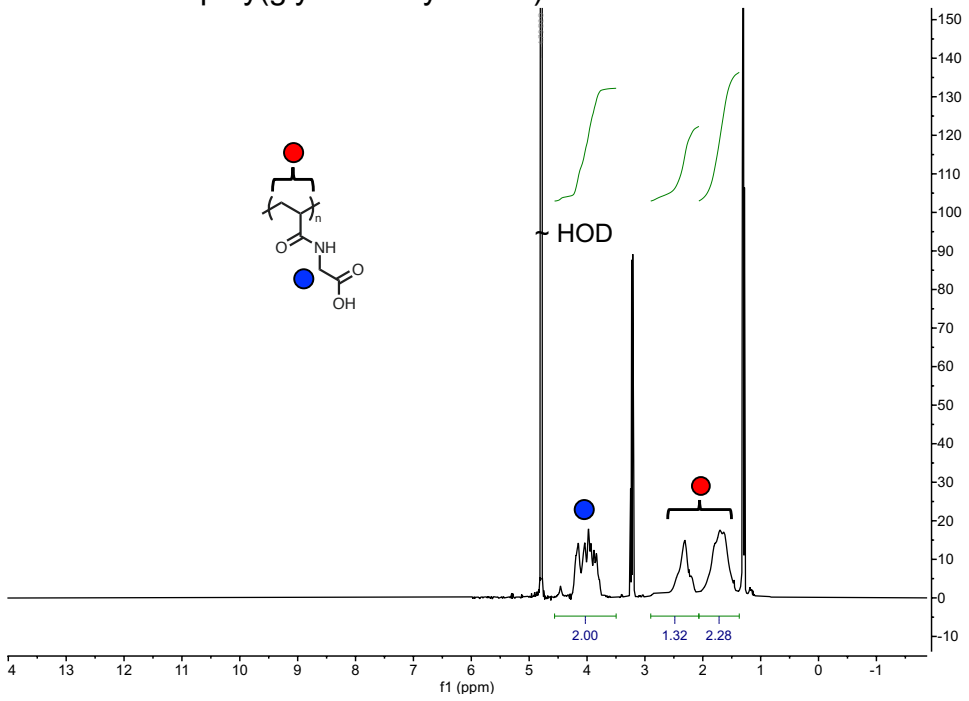


Figure S6: ^{1}H NMR of poly(DL-alanine acrylamide)

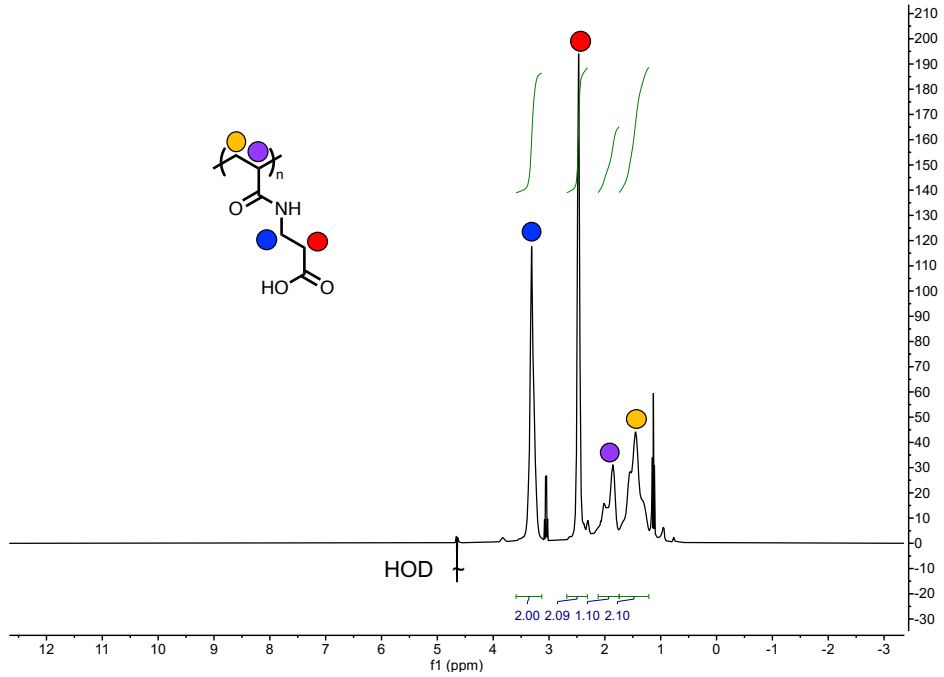


Figure S7: ^{1}H NMR of poly(DL-valine acrylamide)

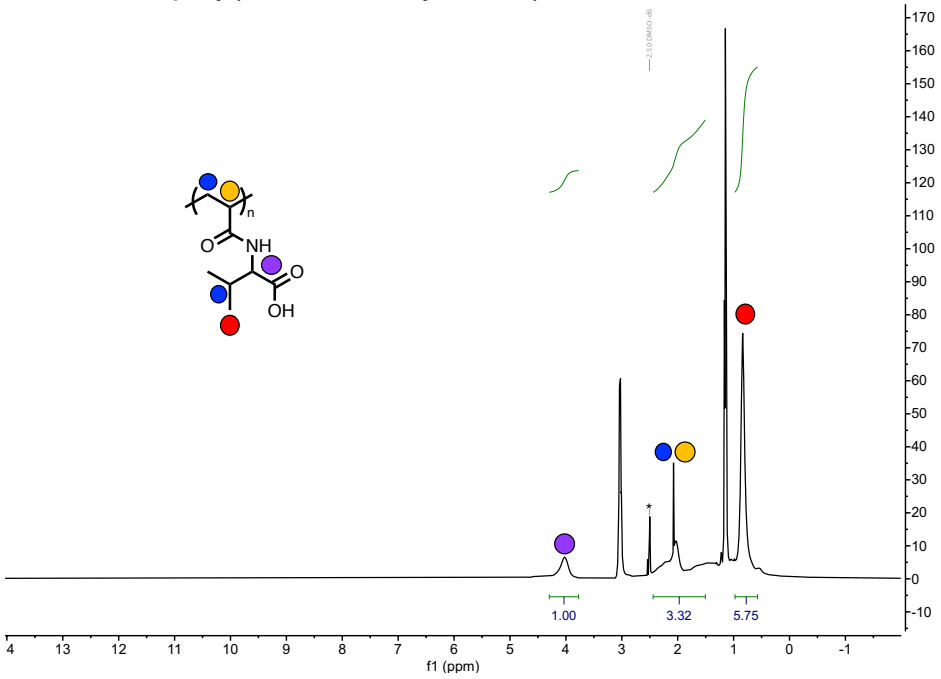


Figure S8: ^{1}H NMR of poly(DL-leucine acrylamide)

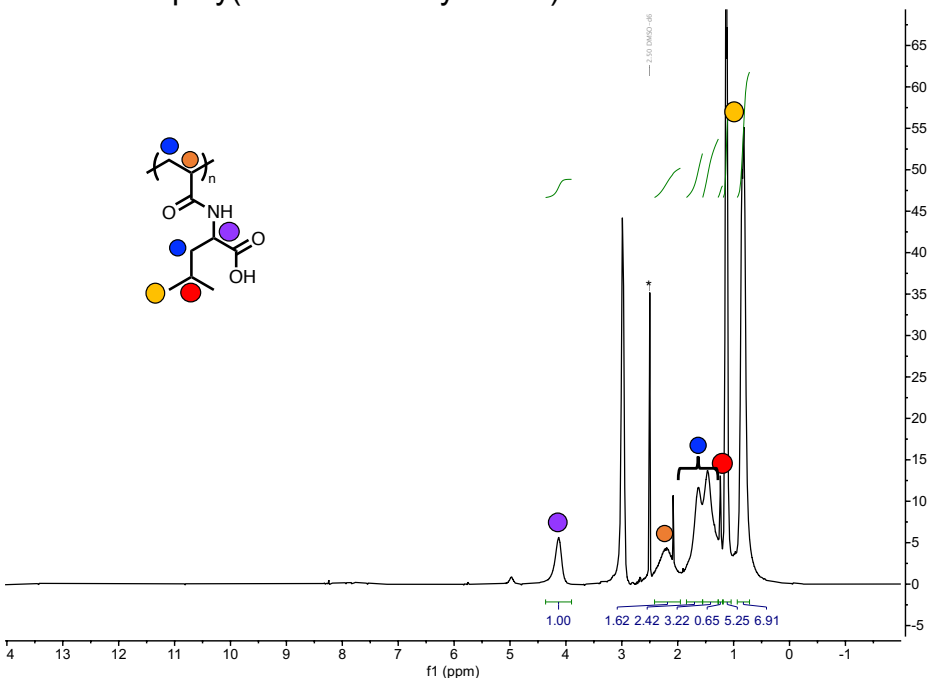


Table S1: Metal and polymer concentrations used for ITC experiments

Sample	Concentration (mM)	
Polymer Side Chain	**Poly(amino acid acrylamide)**	**Eu(III)**
Glycine	1.5	3.4
DL-Alanine	2.0	3.5
DL-Valine	1.5	3.5
DL-Leucine	2.0	2.3

Table S2: Thermodynamic properties of Eu(III) binding to amino acid acrylamide polymers in pH 5 acetate buffer. *N*, K_a, and ΔH are fitting parameters measured by ITC. ΔG and $-T\Delta S$ are calculated according to **Equations 2** and **3**. *N*, K_a, ΔH, ΔG, and $-T\Delta S$ are the reported as the average and standard deviations of duplicate measurements. ΔC_p is the linear dependence ΔH on temperature as shown in **Equation 1**. Error in ΔC_p was determined from the variance in the slope of the linear line of best fit.

Side Chain	T (K)	*N* (Repeat units per metal ion)	K_a (10^4 M^{-1})	ΔG (kJ mol^{-1})	ΔH (kJ mol^{-1})	$-T\Delta S$ (kJ mol^{-1})	ΔS (J mol^{-1} K^{-1})	ΔC_p (kJ mol^{-1} K^{-1})
Glycine 	278	3.2 ± 0.1	0.88 ± 0.02	–21.0 ± 0.4	8.7 ± 0.4	–29.7 ± 0.6	108.0 ± 0.7	0.04 ± 0.01
	288	2.4 ± 0.2	1.8 ± 0.1	–23.4 ± 0.2	9.5 ± 0.5	–32.9 ± 0.2	114.2 ± 0.8	
	298	2.5 ± 0.1	3.9 ± 0.1	–26.2 ± 0.1	9.6 ± 0.8	–35.9 ± 0.8	118.8 ± 1.4	
	308	2.6 ± 0.1	24.8 ± 2.6	–31.7 ± 0.3	9.9 ± 0.2	–41.7 ± 0.1	135.6 ± 0.1	
DL-Alanine 	278	5.6 ± 0.7	1.5 ± 0.2	–22.3 ± 0.3	13.1 ± 0.3	–35.4 ± 0.3	127.7 ± 1.2	0.08 ± 0.01
	288	4.5 ± 0.1	1.3 ± 0.04	–22.7 ± 0.1	14.1 ± 0.6	–36.8 ± 0.5	126.8 ± 1.7	
	298	4.1 ± 0.2	1.6 ± 0.2	–24.0 ± 0.2	15.0 ± 0.7	–39.1 ± 0.5	131.3 ± 2.1	
	308	4.7 ± 0.2	1.7 ± 0.2	–24.9 ± 0.3	15.4 ± 1.1	–40.4 ± 0.9	131.5 ± 4.5	
DL-Valine 	278	4.8 ± 0.1	1.7 ± 0.2	–22.5 ± 0.3	11.3 ± 0.6	–33.8 ± 0.3	121.4 ± 0.9	0.21 ± 0.04
	288	3.8 ± 0.1	3.2 ± 0.1	–24.8 ± 0.1	12.8 ± 0.4	–37.6 ± 0.5	130.8 ± 1.6	
	298	3.5 ± 0.1	8.4 ± 1.5	–28.1 ± 0.5	14.1 ± 0.2	–42.2 ± 0.3	141.5 ± 0.2	
	308	4.0 ± 0.1	26.9 ± 4.9	–32.0 ± 0.5	17.8 ± 0.1	–49.9 ± 0.6	161.9 ± 1.8	
DL-Leucine 	278	7.5 ± 0.5	20.8 ± 2.8	–28.3 ± 0.3	17.8 ± 0.9	–46.2 ± 0.7	166.1 ± 2.4	0.47 ± 0.05
	288	7.7 ± 0.4	12.1 ± 1.4	–28.0 ± 0.3	23.8 ± 0.7	–51.8 ± 0.5	186.4 ± 1.7	
	298	7.2 ± 0.3	4.3 ± 0.8	–26.4 ± 0.5	28.8 ± 0.1	–55.2 ± 0.4	198.7 ± 1.6	
	308	7.1 ± 0.6	3.7 ± 0.3	–26.9 ± 0.2	31.9 ± 0.2	–58.8 ± 0.3	211.6 ± 1.3	

Figure S9: Representative ITC titration curve showing independent model fit, raw area data, and standard deviations around curve fitting.

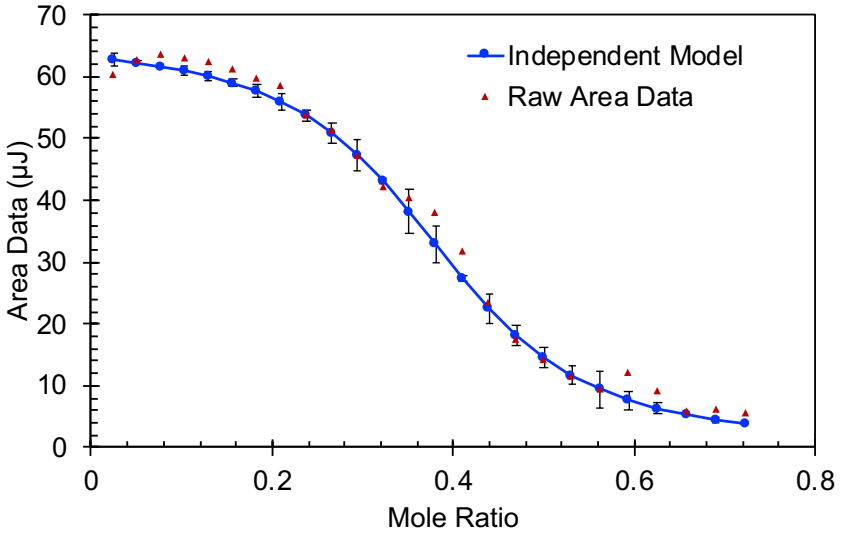


Figure S10: ITC Thermographs of Eu(III) titrations into poly(glycine acrylamide).

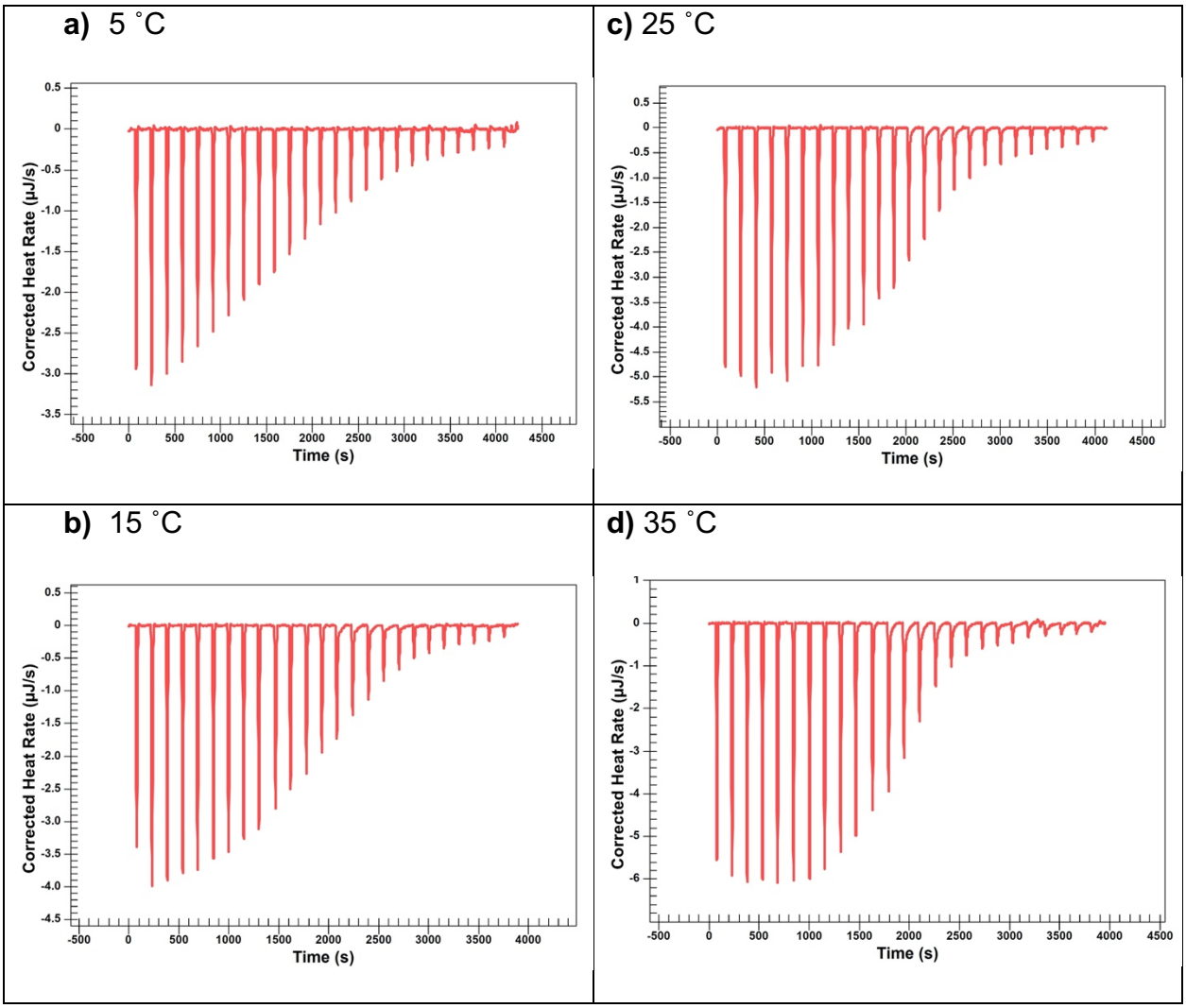


Figure S11: ITC Thermographs of Eu(III) titrations into poly(alanine acrylamide).

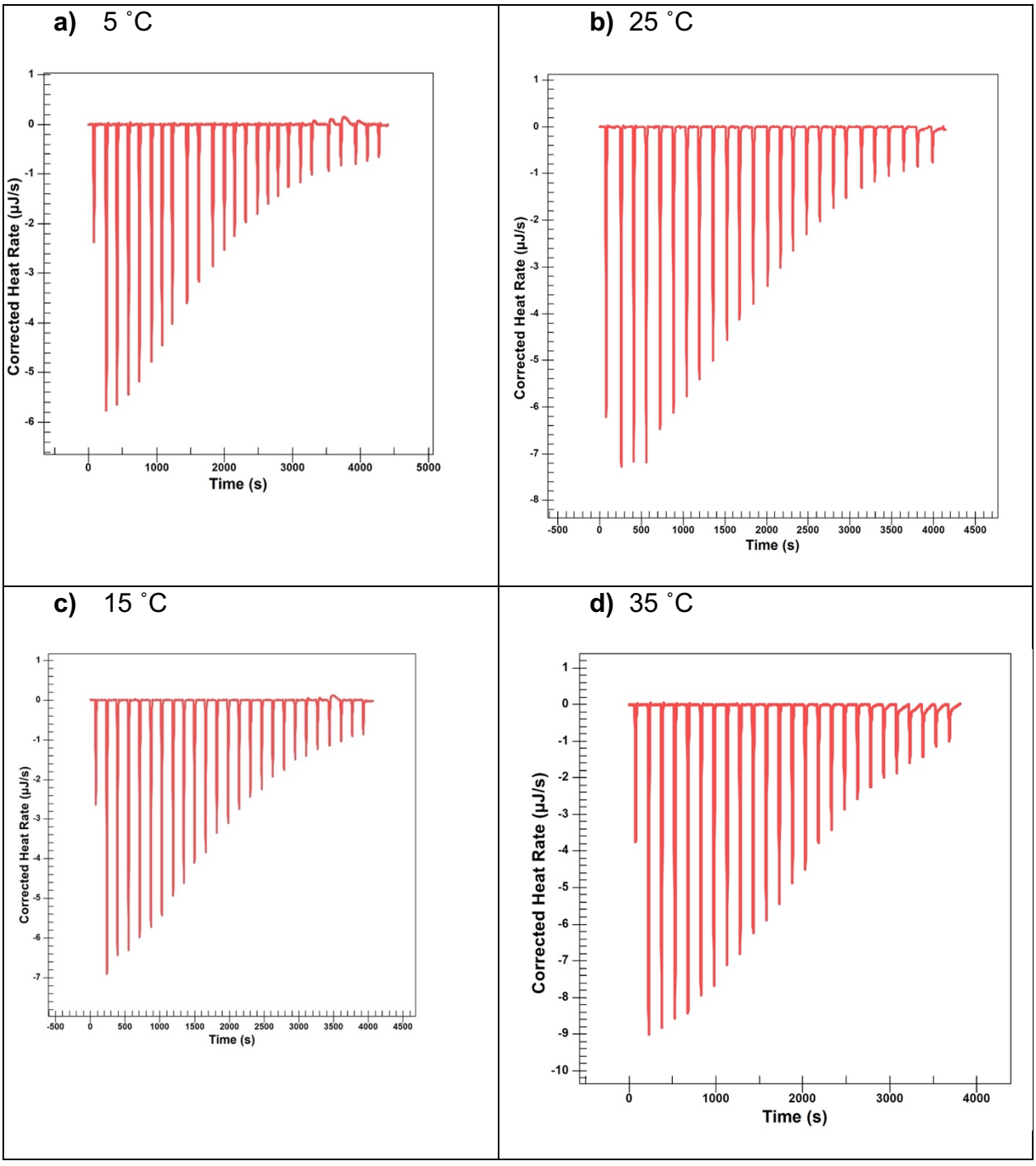


Figure S12: ITC Thermographs of Eu(III) titrations into poly(valine acrylamide).

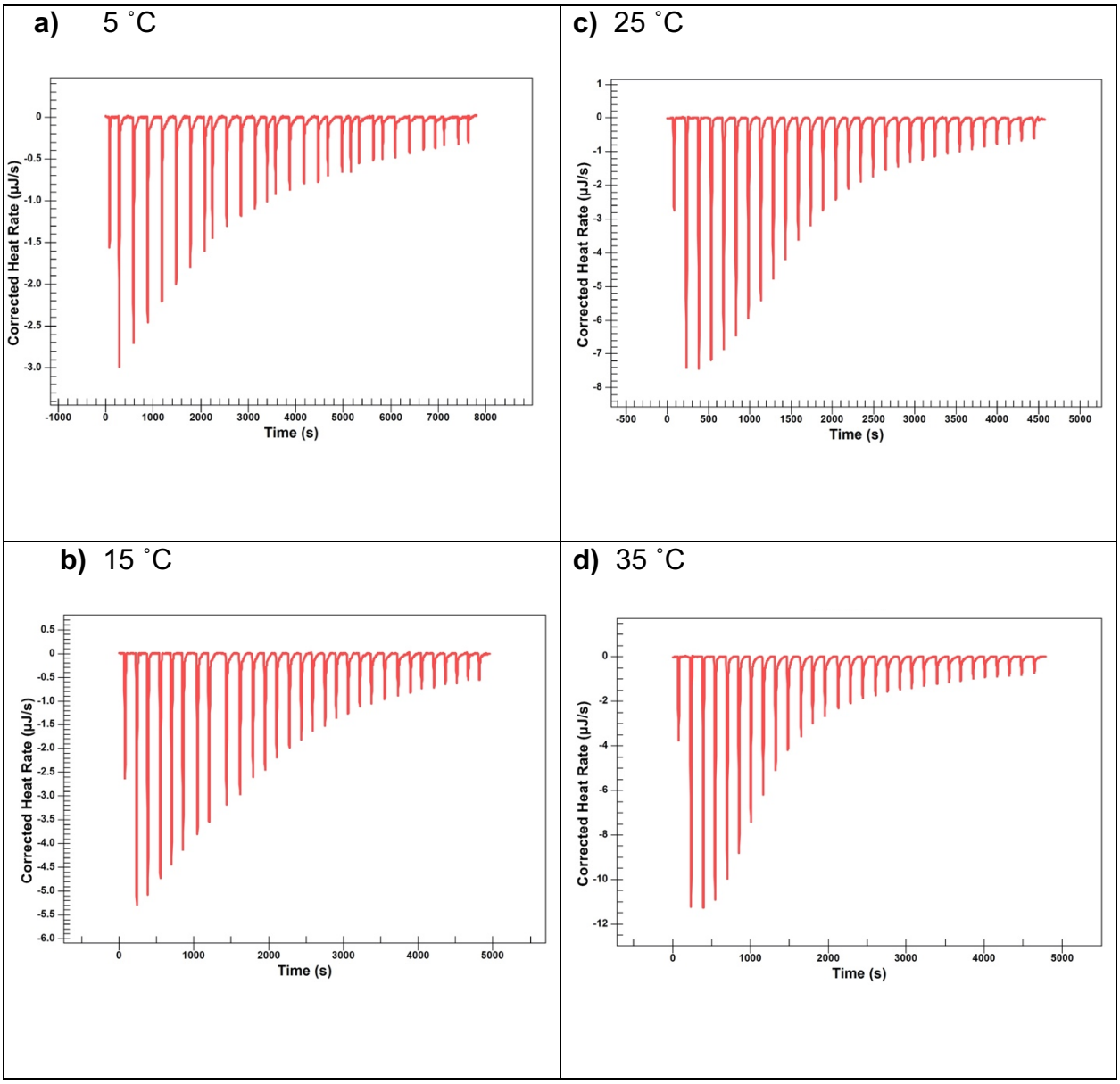
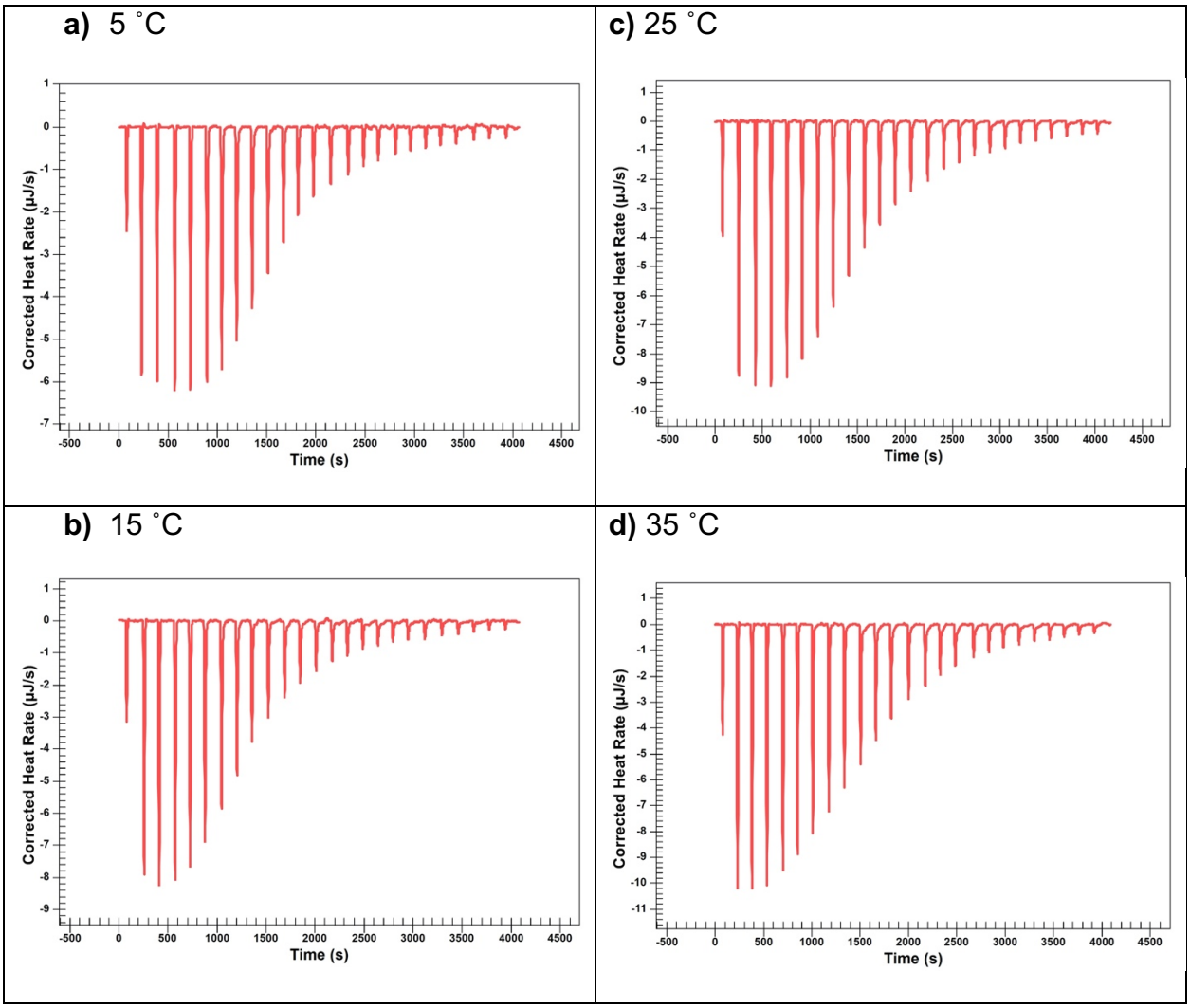


Figure S13: ITC Thermographs of Eu(III) titrations into poly(leucine acrylamide).



Computational Methods:

A 100 % functionalized, 20 unit-long polymer chain was created in Avogadro[5] for poly(DL-leucine acrylamide), poly(DL-alanine acrylamide), poly(DL-valine acrylamide) and poly(glycine acrylamide). Each chain was then explicitly solvated in a $70 \times 30 \times 50$ $Å^3$ H_2O box using Gromacs tools,[6] with Cl^- ions to neutralize the systems. This procedure was repeated adding 20 Eu(III) to each chain. NPT molecular dynamics simulations were then performed with the Tinker software package[7] by using the AMOEBA polarizable force field[8], already developed for amino acids. Parameters for Eu(III) were taken from Ref[9]. 400 ps production trajectories were acquired from a 1 femtosecond timestep and the radial distribution functions calculated from these trajectories with VMD.[10]

Table S3: Polymer structure and calculated solvent accessible surface area from molecular dynamics simulations.

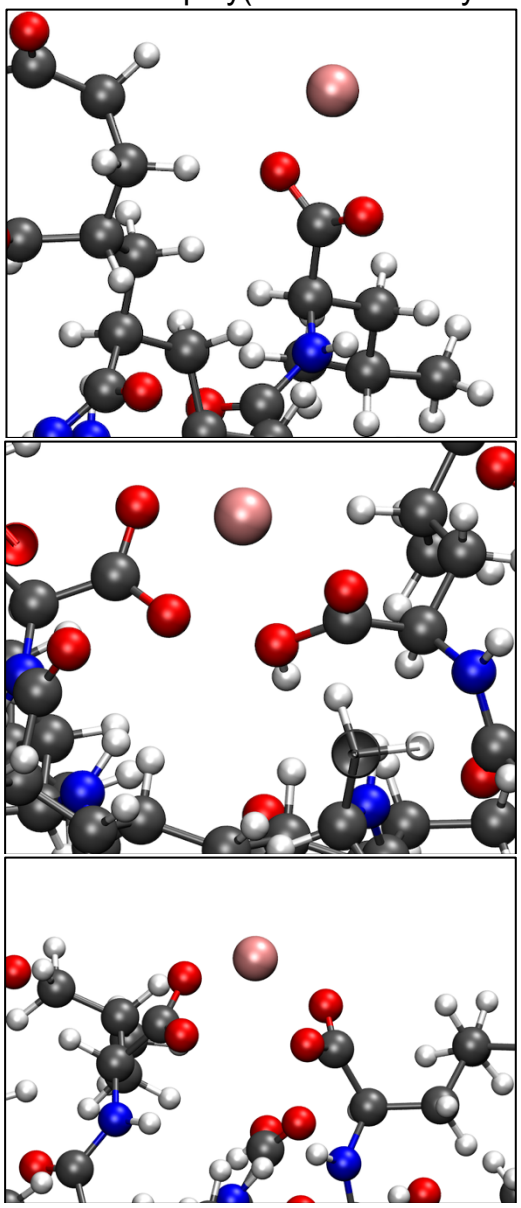
Polymer Side Chain	Solvent Accessible Surface Area ($Å^2$)
Glycine	3015.0
DL-Alanine	2930.8
DL-Valine	3470.7
DL-leucine	3777.0

Figure S14: Binding modes observed for poly(amino acid acrylamide)s

a)

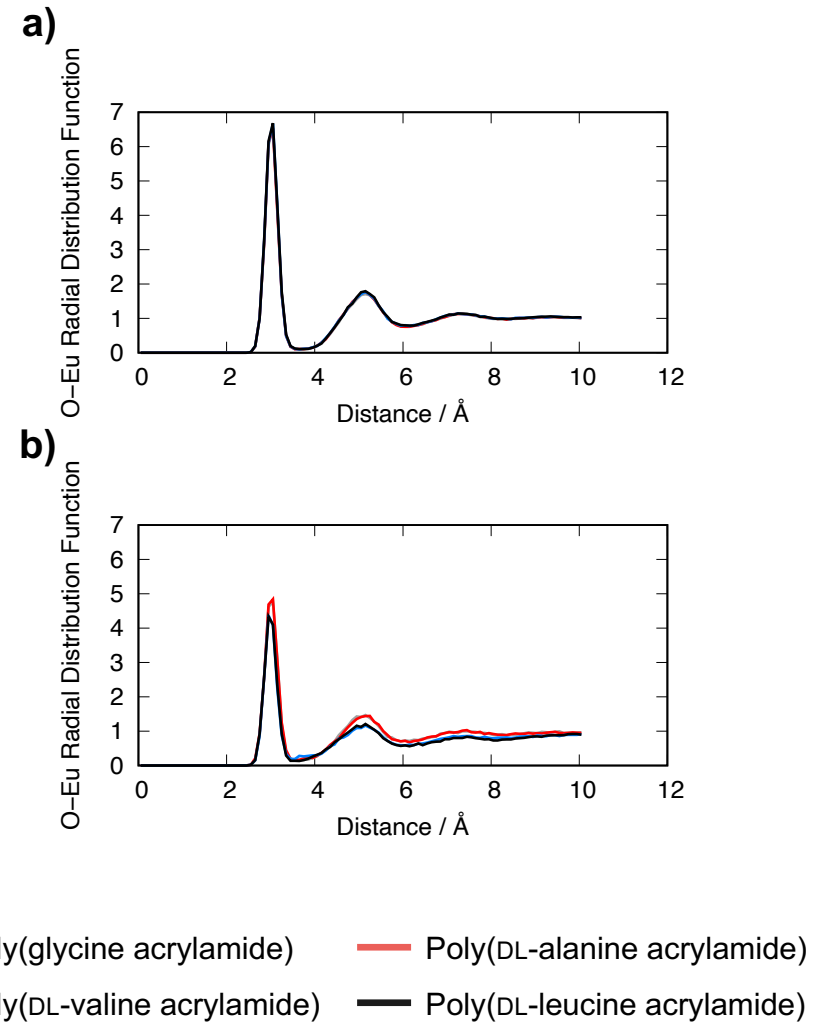
b)

c)



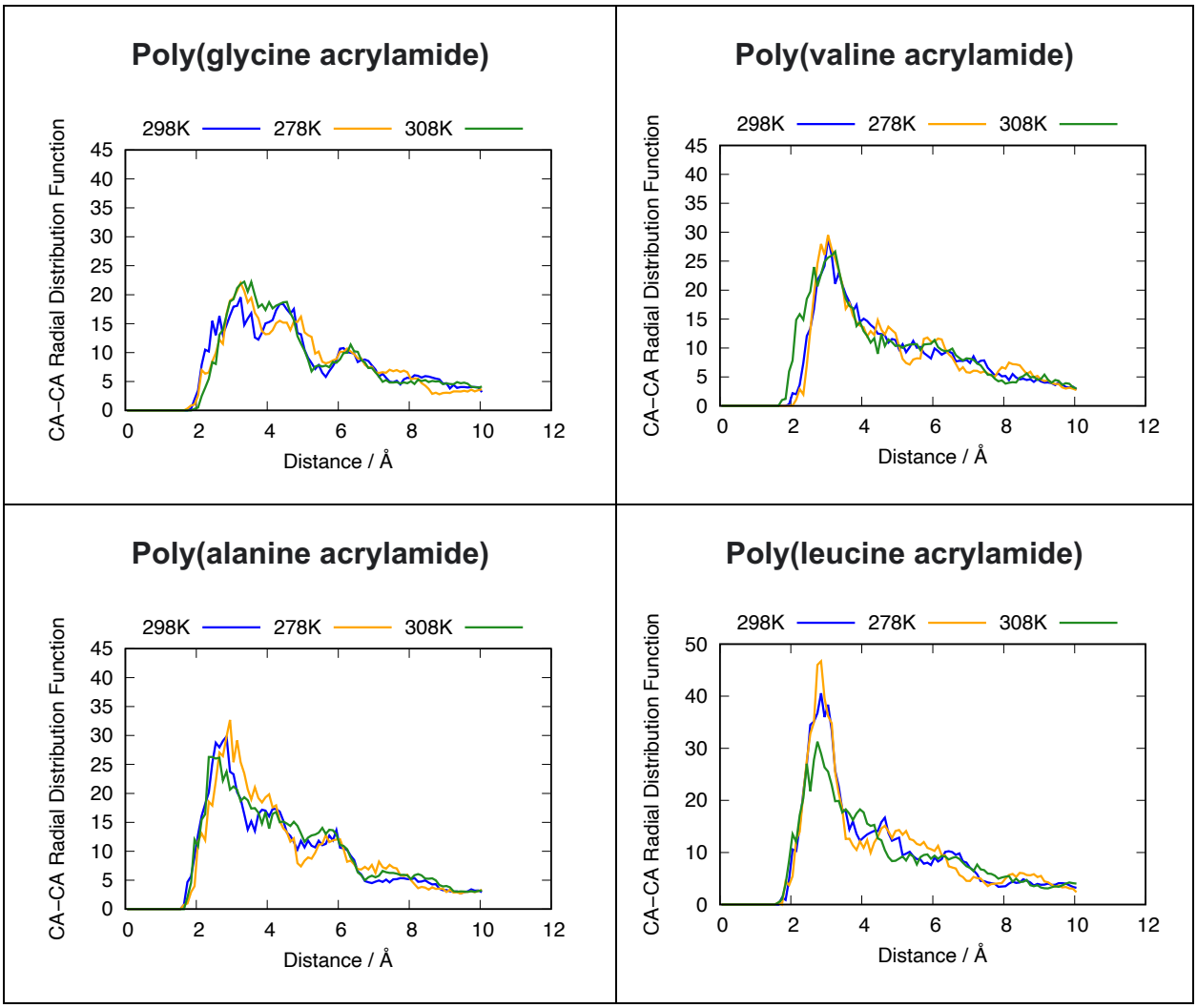
Three types of binding modes observed: **a)** Eu(III) binding to the COO^- of a single side chain, **b)** binding to a COO^--COOH pair across two side chains, and **c)** binding to a COO^--COO^- pair across two side chains.

Figure S15: Control radial distribution functions of Eu(III) with respect to water oxygens.



Control radial distribution function of Eu(III) with respect to water oxygens. **a)** Eu(III) in solution and **b)** polymer bound Eu(III). Bound Eu(III) has about 2 less coordinated water than Eu(III) in solution, consistent with gaining 2 oxygens from binding to COOH groups. Almost 3 less coordinated water in case of poly(DL-leucine acrylamide), consistent with multiple side chains being involved in the binding of one ion. Note that the binding process also disrupts the ordering of the second solvation shell of the ions: smaller and wider peaks, signature of disorder relative to a more structured network when the ion is in solution.

Figure S16: Variable temperature C_α–C_α radial distribution functions



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