Regular Article

Synthesis and Thermoresponsive Property of End-Functionalized Poly(*N*-isopropylacrylamide) with Pyrenyl Group

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ABSTRACT: *N*–Isopropylacrylamide (NIPAM) was polymerized using 1-pyrenyl 2-chloropropionate (PyCP) as the initiator and CuCl/tris[2-(dimethylamino)ethyl]amine (Me_6TREN) as the catalyst system. The polymerizations were performed using the feed ratio of $[NIPAM]_0/[PyCP]_0/[CuCl]_0/[Me_6TREN]_0 = 50/1/1/1$ in DMF/water of 13/2 at 20 °C to afford an end-functionalized poly(*N*-isopropylacrylamide) with the pyrenyl group (Py–PNIPAM). The characterization of the Py–PNIPAM using matrix-assisted laser desorption ionization time-of-flight mass spectrometry provided the number average molecular weight ($M_{n,MS}$). The lower critical solution temperature (LCST) for the liquid–solid phase transition was 21.7 °C, 24.8 °C, 26.5 °C, and 29.3 °C for the Py–PNIPAMs with the $M_{n,MS}$'s of 3000, 3,400, 4200, and 5000, respectively; hence, the LCST was dramatically lowered with the decreasing $M_{n,MS}$. The aqueous Py–PNIPAM solution below the LCST was characterized using a static laser light scattering (SLS) measurement to determine its molar mass, $M_{w,SLS}$. The aqueous solutions of the Py–PNIPAMs with the $M_{n,MS}$'s of 3000, 3400, 4200, and 5000 showed the $M_{w,SLS}$ of 586,000, 386,000, 223,000, and 170,000, respectively. Thus, lowering the LCST for Py–PNIPAM should be attributable to the formation of the PNIPAM–aggregates. The LCST of 21.7 °C for Py–PNIPAM with the $M_{n,MS}$ of 3000 was effectively raised by adding β-cyclodextrin (β-CD) and reached the constant value of ca. 26 °C above the molar ratio of [β-CD]/[Py–PNIPAM] = 2/1, suggesting that β-CD formed an inclusion complex with pyrene in the chain-end to disturb the formation of PNIPAM–aggregates, thus raising the LCST.

Keywords: poly(*N*-isopropylacrylamide), atom transfer radical polymerization (ATRP), aggregation, inclusion complex, cyclodextrin

INTRODUCTION

Poly(*N*-isopropylacrylamide) (PNIPAM) is a well-known thermoresponsive polymer, which exhibits a coil-globule transition in aqueous solution at the lower critical solution temperature (LCST) of ca. 32 °C.[1-5] A great deal of attention has been focused on the thermoresponsive property of various copolymers consisting of *N*-isopropylacrylamide (NIPAM) from the view point of advanced materials for their extensive applications,[6] such as a temperature-dependent controlled release system[7-11] and surface modification.[12-16] Although great interest has focused on the controlled synthesis of the NIPAM-based polymer, it has not been achieved because PNIPAM and its copolymers have been traditionally prepared using conventional free radical polymerization. However, in recent years, the PNIPAM with a well-defined molecular weight and polydipersity has been provided through living anionic polymerizations[17] and living radical polymerizations, such as the niroxide-mediated radical polymerization,[18-20] the reversible addition-fragmentation chain transfer polymerization,[21-26] and the atom transfer radical polymerization (ATRP).[27-32] In general, the living nature of polymerization affords well-defined macromolecular architectures, therefore, it is interesting to prepare PNIPAMs with specific structures and properties.

An end-functionalized polymer, one of the typical macromolecular architectures, is produced by the living polymerization method using appropriate initiating or terminating agents, and thus there are various studies for the design of functional end-groups. Especially, the end-functionalized polymers having an amphiphilic property, such as a hydrophilic polymer with a hydrophobic end-functional group or a

hydrophobic polymer with a hydrophilic end-functional group, are interesting materials leading to polymeric aggregates. For PNIPAM, Okano et al. reported that alkyl chains were incorporated into the chain-end of the PNIPAMs, which formed a micellar structure by hydrophobic association.[33]

We now report that the end-functionalized PNIPAM with the pyrenyl group (Py-PNIPAM) is synthesized by the living polymerization method such as ATRP using 1-pyreneyl 2-chloropropionate (PyCP) as an initiator and CuCl/ tris(2-(dimethylamino)ethyl)amine (Me_6TREN) as the catalyst system (Scheme 1). It is well-known that a coil-globule transition in aqueous PNIPAM solution is caused by the hydrophobicity of the *N*-isopropyl group,[1-5] and thus there are many studies on the design, synthesis, and characterization of PNIPAMs containing hydrophobic groups, such as the pyrenyl group. For example, Winnik et al. reported the synthesis and coil-globule transition property of various types of pyrene-modified PNIPAMs and their derivatives.[34-41] In this article, the LCST of an aqueous Py-PNIPAM solution is described in relation to the hydrophobic chain-end and formation of PNIPAM–aggregates. Finally, we report the effect of an additive such as a β–cyclodextrin (β–CD), which is known to form an inclusion complex with pyrene,[42] on the LCST of aqueous Py-PNIPAM solutions.

EXPERIMENTAL

Materials

1-Hydroxypyrene (> 99 %, Acros Organics Company), 2-chloropropionyl chloride (> 95 %, Tokyo Kasei Kogyo Co., Ltd), 4-(dimethylamino)pyridine (> 99 %, Wako Pure

Chemical Industries, Ltd .), copper(I) chloride (CuCl, 99.999 %, Aldrich Chemical Company), and *N*,*N*-dimethylformamide (> 99.5 %, Kanto Chemical Co., Inc.) were used as received. Tris(2-(dimethylamino)ethyl)amine (Me_6TREN) was synthesized according to the published procedure.[43] *N*-Isopropylacrylamide (NIPAM) (97 %, Aldrich) was recrystallized twice from hexane/toluene (10/1, v/v) and stored in an inert atmosphere at –30 °C. All other reagents were used without further purification.

Measurements

Size exclusion chromatography (SEC) was performed at 40 ˚C using a Jasco high performance liquid chromatography (HPLC) system (PU-980 Intelligent HPLC pump, CO-965 Column oven, RI-930 Intelligent RI detector and Shodex DEGAS KT-16) equipped with a Shodex Asahipak GF-310 HQ column (linear, 7.6 mm × 300 mm; pore size, 20 nm; bead size, 5μm; exclusion limit, 4×10^4) and a Shodex Asahipak GF-7M HQ column (linear, 7.6 mm × 300 mm; pore size, 20 nm; bead size, 9 μm; exclusion limit, 4×10^7) in DMF containing lithium chloride (0.01 M) at a flow rate of 0.4 $mL \cdot min^{-1}$. The number-average molecular weight (M_n) and polydispersity (M_w/M_n) of the polymers were calculated on the basis of a polystyrene calibration.

The ^{1}H NMR spectra were recorded using a JEOL JNM-A400II instrument (400 MHz). For the determination of the monomer conversion, the ^{1}H NMR spectrum of the polymer mixture was measured in DMSO-d_6 at room temperature and analyzed on the basis of previous reports.[21]

A static laser light scattering (SLS) measurement was performed using an Otsuka Electronics CALLS-1000 light scattering spectrometer (λ = 632.8 nm). The refractive index increment (dn/dc) was measured using an Otsuka Electronics DRM-1021

double-beam differential refractometer (λ = 632.8 nm). Ultraviolet-visible (UV-vis) spectra were measured with a 10 mm path length using a Jasco V-550 spectrophotometer, which used a deuterium lamp as the light source for the UV range (190–350 nm) and a halogen lamp for the visible range (330–900 nm), equipped with an EYELA NCB-1200 temperature controller.

Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) measurements were performed using a Voyager-DE STR mass spectrometer and a 20 kV acceleration voltage was used. The positive ions were detected in the reflector mode (20 kV). A nitrogen laser (337 nm, 3 ns pulse width, 10^6-10^7 W/cm^2) operating at 3 Hz was used to produce laser desorption, and 500 shots were summed. The spectra were externally calibrated using 2,5-dihydroxybenzoic acid with linear calibration. Samples for MALDI-TOF MS were prepared by mixing the polymer, a matrix (1,8-dihydroxy-9(10*H*)-anthracenone; dithranol), and a cationizing agent (sodium trifluoroacetate) in THF.

1-Pyrenyl 2-Chloropropionate (PyCP)

2-Chloropropionyl chloride (219 mg, 1.73 mmol) was gradually added to a solution of 1-hydroxypyrene (250 mg, 1.15 mmol) and 4-(dimethylamino)pyridine (6.90 mg, 5.65×10^{-2} mmol) in dry pyridine (3.5 mL) at 0 °C. After stirring at room temperature overnight, the reaction mixture was diluted with water and then extracted with dichloromethane (50 mL × 3). The combined extracts were washed with a 1N HCl aqueous solution (100 mL × 3), $NaHCO_3$ solution (100 mL × 3), and brine (100 mL × 3), then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel with hexane/ethyl acetate

(volume ratio, 10/1, R_f = 0.25) and then distilled under pressure to give 309 mg of the initiator PyCP (yield = 87 %); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 1.98 (d, 3H); 4.89 (q, 1H); 7.90 (d, 1H); 8.12 (m, overlapping); ^{13}C NMR ($CDCl_3$, 100MHz) δ: 21.5, 52.5, 119.1, 119.7, 122.9, 124.3, 124.9, 125.4, 125.5, 125.6, 126.3, 126.9, 127.3, 128.4, 129.6, 130.8, 130.9, 143.6, 168.9. Mass Spectrum (FAB+); m/z = 308. Anal. Calcd for $C_{19}H_{13}O_2Cl$: C, 73.91; H, 4.24; Cl, 11.48. Found: C, 73.86; H, 4.37; Cl, 11.50.

General Procedure for the Polymerization

The ATRP of NIPAM was carried out at 20 °C using PyCP in DMF/water (13/2, v/v). A typical procedure is as follows: A mixture of CuCl (35.7 mg, 0.36 mmol) and Me_6TREN (82.9 mg, 0.36 mmol) in DMF (3 mL) was placed on one side of an H-shaped glass ampoule and stirred at room temperature. DMF (4.8 mL), deionized water (1.2 mL), NIPAM (2.04 g, 18 mmol), and PyCP (111.1 mg, 0.36 mmol) were added to the other side of the ampoule and stirred for 15 min. Argon was bubbled through both mixtures for 15 min to remove any oxygen. After sealing, both mixtures were combined, and heated at 20 °C for 50 min. The polymerization was stopped by exposure to air. The reaction mixture was diluted with DMF and passed through an alumina column to remove the copper complex. The polymer was purified by dialysis using a cellophane tube in DMF. After 3 days, the DMF was removed by distillation under vacuum at room temperature. The obtained polymer was dissolved in water and freeze-dried overnight under vacuum (608.2 mg; conv., 30 %). $M_{n,SEC}$ = 4,900, M_w/M_n = 1.21, $M_{n,MS}$ = 3000.

Cloud Point Measurement

A solution of 10 mg of Py-PNIPAM in 5 mL of distilled water was prepared at 0 °C. For the measurement in the presence of β-CD, a solution of 10 mg of Py-PNIPAM ($M_{n,MS}$ = 3000) and 3.8 mg of β-CD in 5 mL of distilled water was stirred at 0 °C for 30 min and the stored 2 °C for 4 days. The transmittance at 500 nm was measured at the heating rate of 0.1 °C/5 min using a 1 cm long quartz cell.

RESULTS AND DISCUSSION

Synthesis of End-Functionalized Poly(*N*-isopropylacrylamide) with Pyrenyl Group

Masci et al. reported that the ATRP of NIPAM was performed in a mixed solvent of DMF and water using ethyl 2-chloropropionate (ECP) as an initiator and CuCl/tris[2-(dimethylamino)ethyl]amine (Me_6TREN) as a catalyst system, producing poly(*N*–isopropylacrylamide) (PNIPAM) with a controlled molecular weight and low polydispersity.[31] Stöver et al. reported that the ATRP of NIPAM by CuCl/Me_6TREN proceeded in a controlled manner using methyl 2-chloropropionate (MCP) as the initiator and 2-propanol and *tert*-butyl alcohol as the solvents.[32] 1-Pyrenyl 2-chloropropionate (PyCP) is insoluble in water and hardly soluble in alcohols, while highly soluble in DMF. Thus, NIPAM was polymerized using PyCP as an initiator and CuCl/Me_6TREN as a catalyst system in the mixed solvent of DMF and water. The NIPAM conversion was directly determined from the ^{1}H–NMR spectra of the polymerization mixtures in DMSO-d_6. The respective polymerization mixtures were purified by alumina column chromatography and dialysis, followed by freeze-drying to give products as white solids. Initially, we characterized the products by size exclusion chromatography (SEC) to reveal the trends and optimize the polymerization

conditions. Table I lists the results of the polymerization under the optimized condition, which is the feed ratio of NIPAM, PyCP, CuCl, and Me_6TREN ($[NIPAM]_0/[PyCP]_0/[CuCl]_0/[Me_6TREN]_0$) of 50/1/1/1 in DMF/water of 13/2 at 20 °C. Figure 1 shows the SEC traces of the products, in which the NIPAM conversion reached 30, 43, 51, and 95 % for the polymerization times of 50, 70, 100, and 160 min, respectively. The number average molecular weights ($M_{n,SEC}$'s) ranged from 4900 to 14800, which linearly increased with the increasing conversion. The polydispersity indices (M_w/M_n's) are low values between 1.21 – 1.30, hence, the polymerization proceeded in a controlled manner. However, there are several reports in which the $M_{n,SEC}$ of PNIPAM is significantly higher than its actual molecular weight.[32,44] A plausible reason for the large difference is that molecular weights obtained from SEC using polystyrene standards are too much high.

Using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) is one convenient method to determine the accurate molecular weight for PNIPAM.[31,32,44] The MALDI–TOF MS spectrum shows one main series of peaks, which has a regular interval of ca 113.1 for the molar mass of the monomer, NIPAM. The number average molecular weight calculated from the MALDI–TOF MS ($M_{n,MS}$) is listed in Table I. The $M_{n,MS}$'s of 3000, 3400, 4200, and 5000 were in good agreement with the theoretical number average molecular weights ($M_{n,theor}$'s) of 2000, 2800, 3200, and 5700, respectively. The peaks in the MALDI–TOF MS spectra were due to PNIPAM with a pyrenyl group and chlorine in the initiating and terminating chain-ends. For example, a peak at 2781.9 mass (m/z) corresponds to the 22-mer of NIPAM with a pyrenyl group and chlorine (Figure 2), which agreed with their simulated isotope patterns. The initiator PyCP was completely consumed after

the polymerization as judged by the HPLC analysis. In addition, the polymerization system without PyCP produced no polymer after 3 days. These results indicated that the product was assigned to the end-functionalized poly(*N*-isopropylacrylamide) with the pyrenyl group, Py–PNIPAM.

Thermoresponsive Property

Py–PNIPAM gave a clear solution in cold water, which became turbid by raising the temperature. In order to determine the lower critical solution temperature (LCST) for the liquid–solid phase transition, the transmittance (%) of an aqueous Py–PNIPAM solution (2 mg/mL) was measured using UV–vis spectroscopy upon raising the temperature at the heating rate of 0.1 °C/5 min. Figure 3 shows the transmittance versus temperature plots (cloud point curves). We used 90 % transmittance points (90 % T) as the LCST. The LCST of the aqueous solutions of the Py–PNIPAMs with the $M_{n,MS}$'s of 3000, 3400, 4200, and 5000 were 21.7 °C, 24.8 °C, 26.5 °C, and 29.3 °C, respectively. As a control, PNIPAM with the $M_{n,MS}$ of 4300 was prepared using ECP as the initiator, which showed the LCST of 31.7 °C. Hence, the pyrenyl group in the chain–end plays an important role in the liquid–solid phase transition. Furthermore, the LCST of the aqueous Py–PNIPAM solution was dramatically lowered with the decreasing $M_{n,MS}$, though it was reported that the LCST of PNIPAM was lowered by increasing the molecular weight.[32]

We performed the characterization using the static laser light scattering (SLS) measurement to determine the molar mass of Py–PNIPAM in water at a temperature below its LCST, $M_{w,SLS}$. Py–PNIPAM with the $M_{n,MS}$ of 4200 showed the $M_{w,SLS}$ of 223,000 at 20 °C. PNIPAMs with the $M_{n,MS}$'s of 4300 (controlled sample) showed the

$M_{w,SLS}$ of 100,000. Py–PNIPAM with the $M_{n,MS}$ of 3400 and 5000 also exhibited the high $M_{w,SLS}$ values of 386,000 and 170,000 at 20 °C. The largest $M_{w,SLS}$ of 586,000 was obtained for Py–PNIPAM with the smallest $M_{n,MS}$ of 3000, where the SLS measurement was performed at 15 °C, because the solution was apparently turbid at 20 °C. A possible explanation for these results is that Py–PNIPAM formed PNIPAM–aggregates below its LCST, in which the driving force is the low solubility of the pyrene moiety in water. It is well-known that the liquid–solid phase transition is derived from the coil-globule transition of the PNIPAM chains in water at the LCST.[1-5] PNIPAM-aggregates were already formed in the cold aqueous solutions of Py–PMIPAM, which prompted a transition to occur into the insoluble globule-form at the lower temperature. A similar result was reported by Okano et al. in which the LCST of the aqueous solution of the alkyl–terminated PNIPAM, such as C_3–C_8 terminated PNIPAM, was shifted to lower temperatures due to the hydrophobic association.[33] We calculated the number of aggregations for Py–PNIPAM, N_{agg}, which was defined as the $M_{w,SLS}$ divided by the $M_{w,MS}$, where $M_{w,MS}$ is the weight average molecular weight estimated from the MALDI–TOF MS. The N_{agg}'s are 172, 101, 46, and 22, as listed in Table I. Consequently, the pyrenyl group in the chain–end for Py–PNIPAM acted as an efficient unit to afford PNIPAM–aggregates with high N_{agg}, thus lowering its LCST.

β–Cyclodextrin (β–CD) is known to form an inclusion complex with pyrene.[42] Thus, we added β–CD to the aqueous solutions of Py–PNIPAM with the $M_{n,MS}$ of 3000 and examined its LCST. Figure 4 shows the cloud point curves of aqueous Py–PNIPAM solutions in the presence of β–CD with the molar ratio of β–CD and Py–PNIPAM ([β–CD]/[Py–PNIPAM]) of 0.5/1, 1/1, 2/1, 3/1, and 5/1, indicating that

the LCST of Py–PNIPAM is significantly raised by adding β–CD. The curves gave the LCSTs of 24.6, 25.0, 26.0, 26.6, and 26.4. Similarly, we made the cloud point curves for Py–PNIPAM in the presence of β–CD with the [β–CD]/[Py–PNIPAM] of 6/1, 8/1, 15/1, and 20/1. The curves were quite similar to that of the [β–CD]/[Py–PNIPAM] at 2/1. The LCST estimated from the respective curves were plotted in Figure 5. The LCSTs of 21.7 °C for the aqueous Py–PNIPAM solution was effectively raised by adding β–CD and reached a constant value of ca. 26 °C above the [β–CD]/[Py–PNIPAM] of 2/1. These results suggested that β–CD formed an inclusion complex with pyrene to disturb the formation of the PNIPAM–aggregates, thus raising the LCST. We have now studied the design of the hydrophobic end-groups, which formed an inclusion complex with cyclodextrin.

CONCLUSIONS

End-functionalized PNIPAM with the pyrenyl group, Py-PNIPAM, was successfully prepared through the ATRP of NIPAM using 1-pyreneyl 2-chloropropionate, PyCP, the an initiator and CuCl/tris[2-(dimethylamino)ethyl]amine as the catalyst system. The lower critical solution temperature (LCST) of the aqueous Py–PNIPAM solution was significantly lowered to 21.7 °C, which was attributable to the formation of PNIPAM–aggregates as indicated by the SLS measurement. Hence, the pyrenyl group in the chain–end for Py–PNIPAM acted as an efficient unit to afford huge PNIPAM–aggregates, thus lowering their LCSTs. In addition, the LCST of 21.7 °C for Py–PNIPAM was raised to ca. 26 °C by adding β-cyclodextrin. Thus, the initiator of PyCP was found to be a useful tool for constructing PNIPAM with a tunable LCST.

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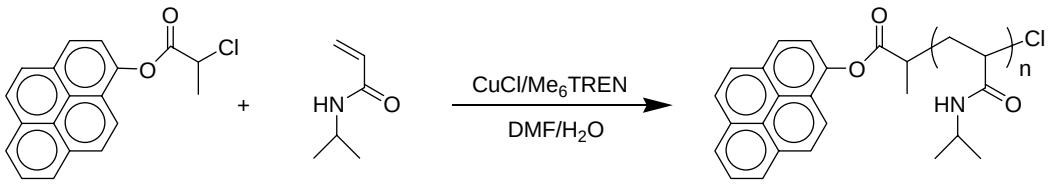
Scheme 1



PyCP NIPAM Py-PNIPAM

Me_6TREN; $N(CH_2CH_2N(CH_3)_2)_3$

Table I. Synthesis [a], Characterization, and LCST of Py–PNIPAM

Time min	Conv. [b] %	$M_{n,theor}$ [c]	$M_{n,MS}$ [d]	$M_{w,MS}$ [d]	$M_{w,SLS}$ [e]	N_{agg} [g]	LCST °C
50	30	2,000	3,000	3,400	586,000[f]	172	21.7
70	43	2,800	3,400	3,800	386,000	101	24.8
100	51	3,200	4,200	4,900	223,000	46	26.3
160	95	5,700	5,000	7,900	170,000	22	29.3

[a] Solvent, DMF/water (v/v, 13/2); temp., 20 °C; $[NIPAM]_0/[PyCP]_0/[CuCl]_0/[Me_6TREN]_0 = 50/1/1/1$; $[NIPAM]_0 = 2.0$ M.

[b] Determined from ^{1}H NMR spectrum of the reaction mixture in DMSO–d_6.

[c] $M_{n,theor} = M_{NIPAM}[NIPAM]_0 conv/100[PyCP]_0 + M_{PyCP}$.

[d] Determined by MALDI–TOF–MS.

[e] Determined by SLS measurement in water at 20 °C.

[f] At 15 °C.

[g] $N_{agg} = M_{w,SLS}/M_{w,MS}$.

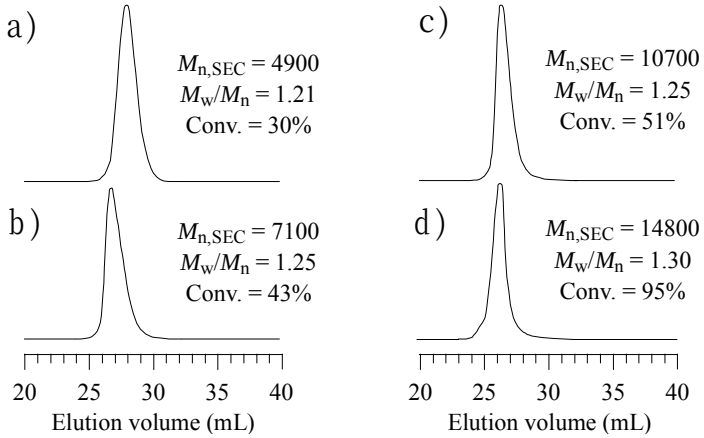


Figure 1. SEC traces of the Py-PNIPAMs obtained through the ATRP at 20 °C with $[NIPAM]_0/[PyCP]_0/[CuCl]_0/[Me_6TREN]_0$ of 50/1/1/1 in DMF/water for a) 50 min, b) 70 min, c) 100 min, and d) 160 min.

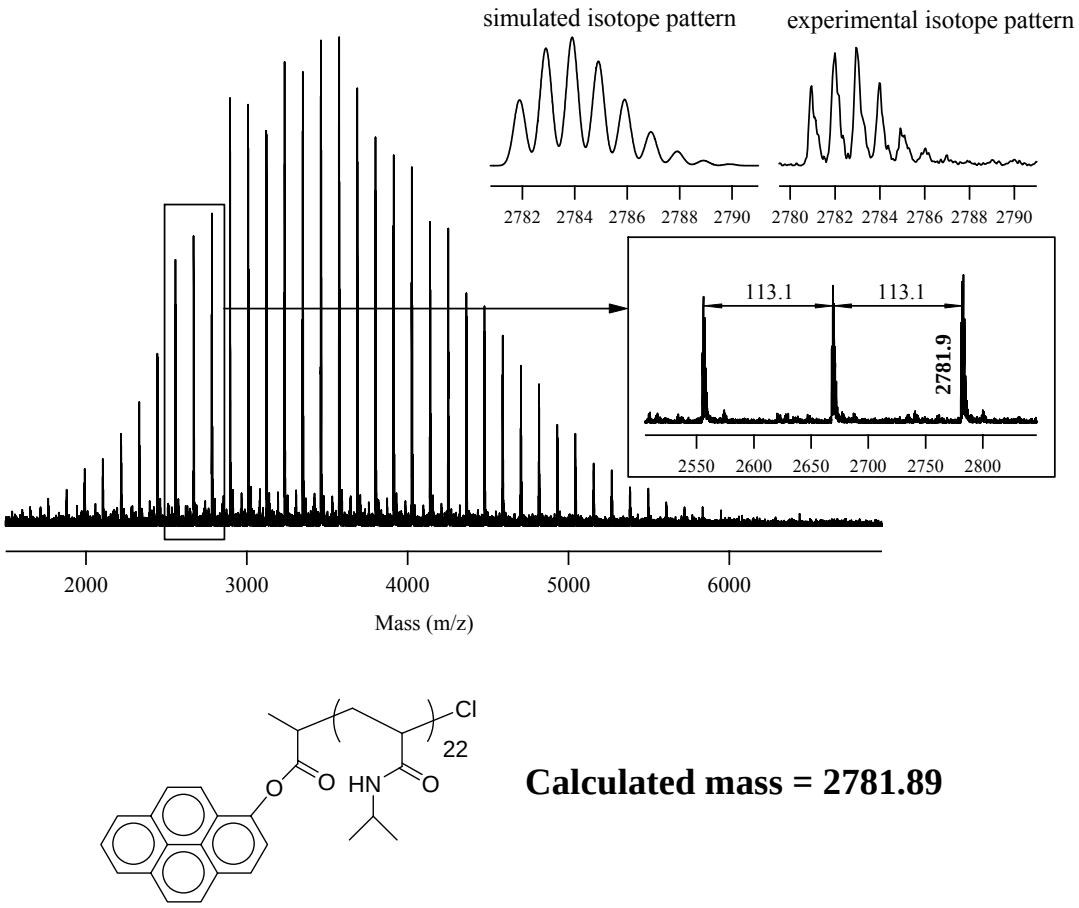


Figure 2. MALDI-TOF mass spectrum of the Py-PNIPAM ($M_{n,MS}$ = 3400, M_w/M_n = 1.25, Conv. = 43%). Bottom: calculated chain-end structure.

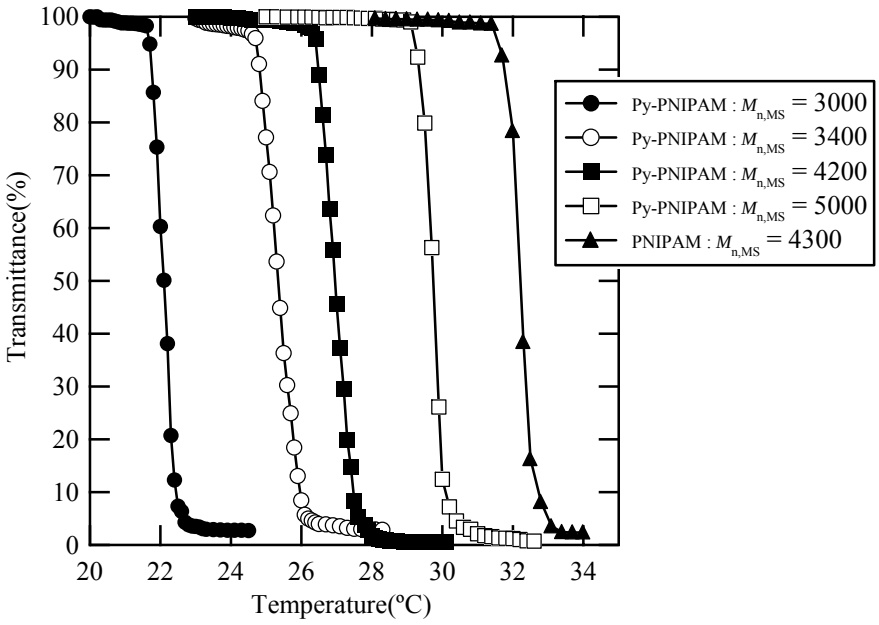


Figure 3. Cloud point curves for the aqueous Py-PNIPAM solutions (2 mg/mL).

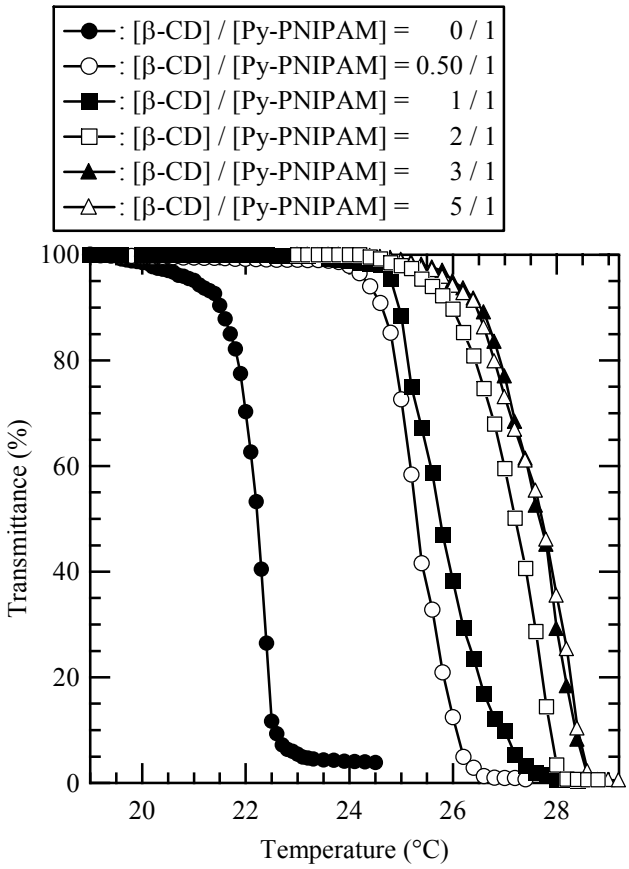


Figure 4. Cloud point curves of the aqueous Py–PNIPAM solution (2 mg/mL) in the presence of β–CD with the different molar ratios of β–CD and Py–PNIPAM ([β–CD]/[Py–PNIPAM]).

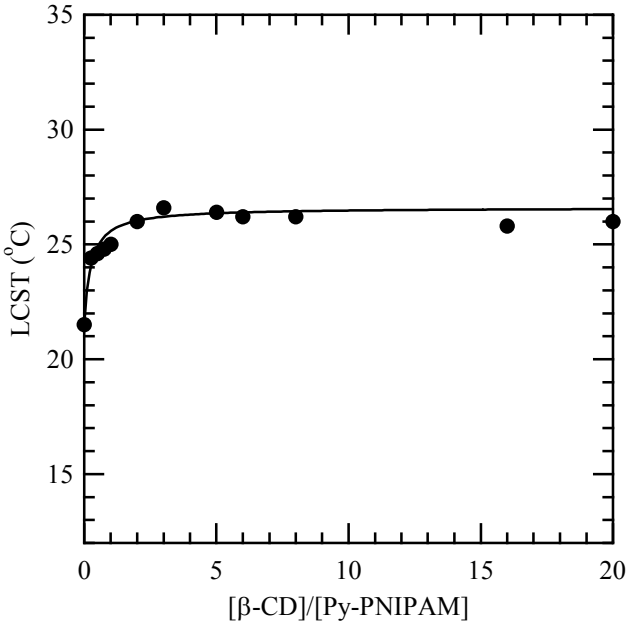
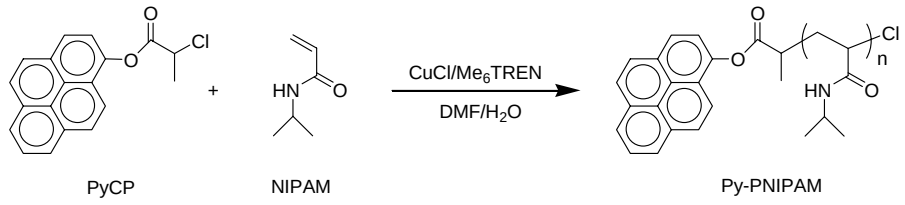


Figure 5. Relationship between the LCST of Py-PNIPAM in the presence of β-CD and the molar ratio of β-CD and Py-PNIPAM ([β-CD]/[Py-PNIPAM]).

Short Synopsis

End-functionalized poly(*N*-isopropylacrylamide) with the pyrenyl group, Py-PNIPAM, was prepared through the ATRP of *N*-isopropylacrylamide using 1-pyreneyl 2-chloropropionate, PyCP, as the initiator and CuCl/tris[2-(dimethylamino)ethyl]amine as the catalyst system. The LCST of the aqueous Py–PNIPAM solution showed the low value of 21.7 °C, which was raised to ca. 26°C after the addition of β-cyclodextrin (β-CD).



PyCP NIPAM Py-PNIPAM

Me_6TREN; $N(CH_2CH_2N(CH_3)_2)_3$