

Preparation of a Novel Copolymer of Hyperbranched Polyglycerol with Multi-arms of Poly(*N*-isopropylacrylamide)

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A novel copolymer (PG-PNIPAM) composed of polyglycerol (PG) as core and poly(*N*-isopropylacrylamide) (PNIPAM) as arms was prepared by the radical addition-fragmentation transfer polymerization (RAFT) of NIPAM in the presence of PG with multi-trithiolcarbonate groups (PG-TTC). The results showed that the RAFT polymerization was controllable and nearly all trithiolcarbonate groups on PG took part in the polymerization. The final PG-PNIPAM copolymer showed a thermally dependent hydrophobic/hydrophilic transition around 28–30 °C.

Keywords hyperbranched, polyglycerol (PG), radical addition-fragmentation transfer polymerization (RAFT), poly(*N*-isopropylacrylamide) (PNIPAM), ring-opening polymerization (ROP), micelles

Introduction

Among the thermally responsive (co)polymers, much attentions has been paid to poly(*N*-isopropylacrylamide) (PNIPAM) because it demonstrates a thermally reversible lower critical solution temperature (LCST) around 32 °C in water and the transition temperature (T_c) can be adjusted around 37 °C by the copolymerization.^{1–3} However, several limitations have been found for the conventional PNIPAM hydrogels: (1) The de-hydration of hydrogels would rapidly produce a collapsed, dense and thick hydrophobic layer that prevents its further de-hydration; (2) The re-hydration is rather slow, which depresses the sensitivity of its on-off switching response; (3) The bulk volume of conventional PNIPAM matrix limits its physiological permeating ability. Therefore, it is still a challenge to design and prepare the thermally dependent hydrophilic/hydrophobic transition (co)polymer with an ideal structure while still maintain the desired T_c . It has been noticed that the introducing of heterogeneous structure into PNIPAM matrix is an effective method to improve the temperature sensitivity of material,^{4–9} however, the synthesis of these copolymers are still rarely reported.

Recently, the hyperbranched polyglycerol (PG) becomes a very interesting research filed as a chemical scaffold and carrier. It can be conveniently prepared by anionic polymerization of glycidol, and the molecular weight and molecular weight distribution are controllable.^{10,11} Usually, the PG has hydroxyl groups distributed from core to surface, and the hydroxyl groups on sur-

face make up to 60% of total functionalities. The densely populated peripheral hydroxyl groups of PG constitute a platform for a variety of chemical modifications.

Herein, in order to improve the temperature sensitivity of poly(*N*-isopropylacrylamide) (PNIPAM), we report the synthesis of a novel copolymer PG-PNIPAM with multi-arms of PNIPAM, and the structure of these copolymers is characterized in details.

Experimental

Materials

2,2'-Azobis(2-methyl-propionitrile) (AIBN), 1,1-tris(hydroxymethyl)propane (TMP), dioxane, carbon disulfide, triethylamine, chloroform, benzyl bromide, toluene, *p*-toluenesulfonic acid, 3-mercaptopropanoic acid were used as received. *N,N*-Dimethylformide (DMF) and glycidol were dried by calcium hydride and then distilled, *N*-isopropylacrylamide (NIPAM) was recrystallized from benzene/hexane ($V : V = 3 : 2$) twice. All the other chemicals were purchased from Aldrich or Acros. Benzoylated dialysis tubing (D-7884, MWCO 1200) was purchased from Sigma.

Preparation of hyperbranched polyglycerol (PG)⁷

The improved polymerization was carried out in a reactor equipped with a mechanical stirrer and dosing pump under argon atmosphere. Firstly, 1,1,1-tris(hydroxymethyl)propane (TMP) (2.78 g) was 10% deprotonated with 0.7 mL of potassium methylate

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solution (3.7 mol/L in methanol, Fluka) by distilling off excess methanol from the melt, and a 50 g aliquot of glycidol was slowly added at 95 °C over 12 h. Then, the product was dissolved in methanol and neutralized by filtration over cation-exchange resin, and the polymer was precipitated twice into acetone from methanol solution and subsequently dried for 15 h at 80 °C *in vacuo*. PG (42.7 g) was obtained as a transparent and highly viscous liquid in yield of 80% ($M_n=2000$ g/mol, $M_w/M_n=1.4$, average 26 hydroxyls on each PG macromolecule).

Preparation of hyperbranched polyglycerol with thiol groups (PG-SH)

Firstly, into a three-neck round-bottom flask, 3-mercaptopropanic acid (5.75 g, 54 mmol) were charged. After the PG ($M_n=2000$ g/mol, 5 g, 67 mmol OH) dried with azeotrope was slowly added by dropping funnel and dissolved in the acid, toluene (5 mL) was added. Then, the reaction mixture was heated to 70 °C followed by addition of 50 mg of catalyst of *p*-toluenesulfonic acid, and the temperature was then raised to 140 °C and continued for 16 h. Finally, the polymer was precipitated into cold methanol and further purification of the polymer was carried out by twice precipitation with the PG-SH yield of 85%.

Preparation of hyperbranched polyglycerol with trithiocarbonate groups (PG-TTC)

Firstly, triethylamine (6.06 g, 60 mmol) in CHCl_3 (20 mL) was added into a stirred solution of the above PG-TTC derivative (5.94 g, 30 mmol SH) and carbon disulfide (4.56 g, 60 mmol) in CHCl_3 (20 mL) at room temperature. Then, the solution was allowed to stir for another 1 h before benzyl bromide (5.64 g, 33 mmol) was added, and the mixture was continuously stirred for 2 h and poured into a cold solution of aqueous 10% HCl, and the organic layer was separated as thick yellow oil. Finally, the product was purified by dialysis against chloroform for 8 h with the PG-TTC yield of 94%.

Synthesis of hyperbranched polyglycerol with multi-poly(*N*-isopropyl acrylamide) (PNIPAM) arms (PG-PNIPAM)

Typically, PG-TTC (0.53 g, 1.33 mmol trithiocarbonate group), NIPAM (4.56 g) and AIBN (7 mg) in 8 mL of dioxane were mixed and bubbled with nitrogen for 0.5 h, sealed and heated at 65 °C for 15 h. Then, the solution was cooled and added with a small amount of acetone, and dropped slowly into petroleum ether under stirring and the mixture was slowly heated to 42 °C and kept for 10 min. After filtration and drying, the yellow solid with the PG-PNIPAM yield of 68% was obtained.

Measurement of the LCST

Thermal transition temperature was directly observed in a water bath, generally, a sample solution at

concentration of 0.23 g/mL in water charged in a test tube was heated until cloudy; then the temperature was slowly decreased at 1 °C/3 min, and the temperature at which the solution just became transparent was recorded as the transition temperature.

Measurement

^1H NMR and ^{13}C NMR were recorded on Bruker AMX 300. Gel permeation chromatography (GPC) was performed using THF in the presence of 0.25% tetrabutylammonium bromide as eluent at a flow rate of 1.0 mL/min at 35 °C (Injection volume: 50 μL ; column set: three 5 μm (7.8 cm \times 300 cm) column in series; detectors: Waters 2487 differential refractometer and Waters 2414 UV detector operated at 350 nm). PS standards were used for the calibration of the column set.

Results and discussion

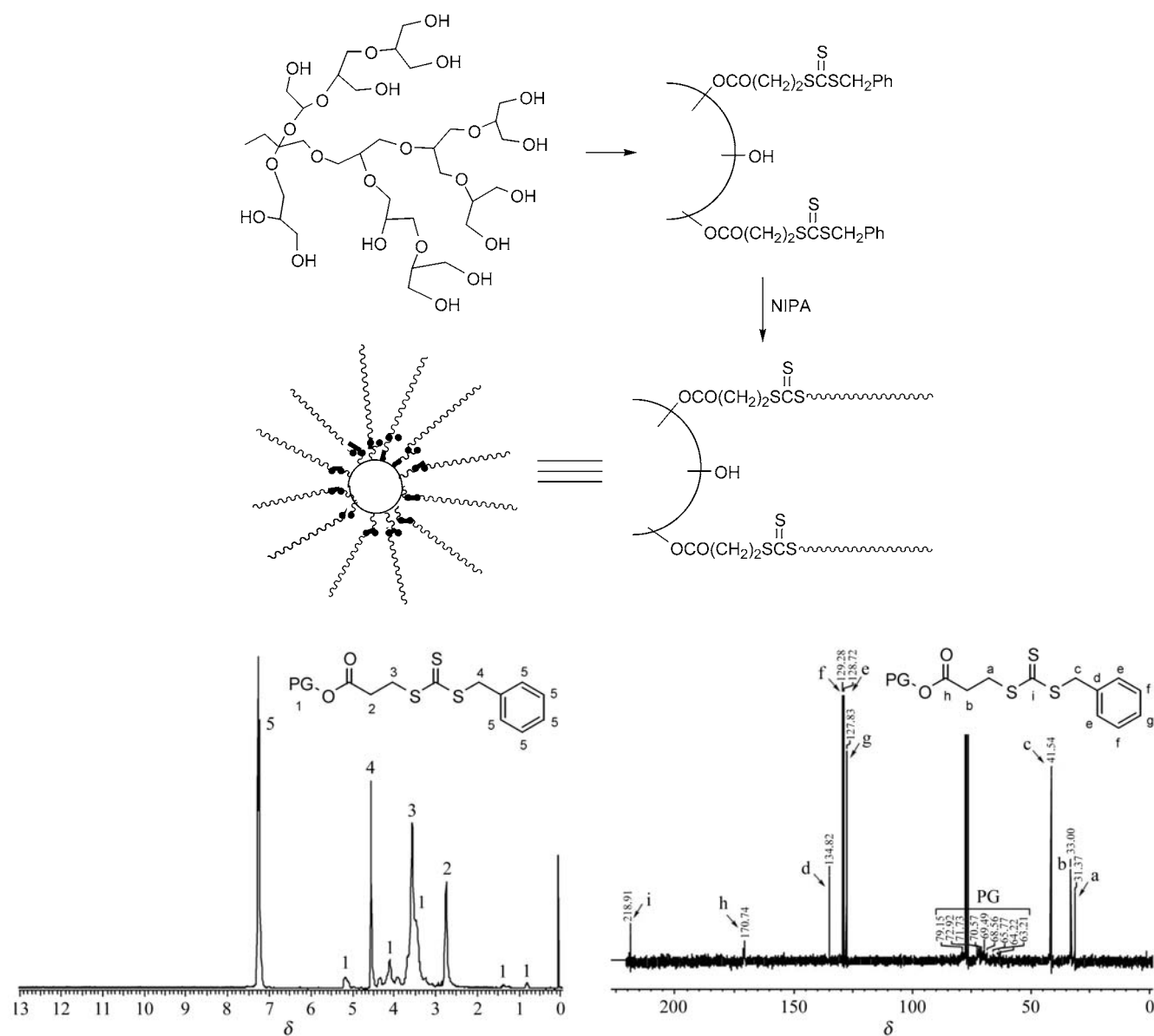
Preparation of macro-initiators PG-TTC by the transformation of hydroxyl groups on PG

The conversion of hydroxyl groups on PG to thiol and then trithiocarbonate groups could be described as the following (Scheme 1).

The PG-SH with thiol groups was characterized by ^1H NMR and the assignment of the peaks were the same as described in literature:⁷ δ 0.79 (t, CH_3CH_2 of TMP, the core of PG), 1.25 (CH_3CH_2 of TMP), 1.63 (s, SH), 2.59 (t, $\text{OCOCH}_2\text{CH}_2$), 2.68 (t, $\text{CH}_2\text{CH}_2\text{SH}$), 3.0–3.6 (m, PG), 4.07 (CH_2 of PG attached to OCO), 5.15 (CH of PG attached to OCO). According to the integral area ratio of PG core at δ 3.0–3.6 to thiol groups at δ 1.63, it could be calculated that about 65% of hydroxyl groups were transformed into thiol groups, in other words, there were average 17 thiol groups on each PG macromolecule. Figure 1 is the ^1H NMR and ^{13}C NMR spectra of PG-TTC with trithiocarbonate groups, the assignment of its peaks was as follows: δ 0.79 (t, CH_3CH_2 of TMP, the core of PG), 1.25 (CH_3CH_2 of TMP), 2.59 (t, $\text{OCOCH}_2\text{CH}_2$), 2.75 (br, CH_2S), 3.0–3.6 (m, PG), 4.07 (CH_2 of PG attached to OCO), 4.56 (s, CH_2Ph), 5.15 (CH of PG attached to OCO), 7.24 (br, Ph); ^{13}C NMR (CDCl_3): δ : 31.37 (t, CH_2S), 33.00 ($\text{CH}_2\text{C}=\text{O}$), 41.54 (CH_2Ph), 127.83, 128.72, 129.28, 134.82 (Ph), 170.74 (C=O), 218.91 (C=S) and 63.21, 64.22, 65.77, 68.56, 69.49, 70.57, 71.72, 72.92, 79.15 for PG. According to the integral area ratio of PG core at δ 3.0–3.6 to trithiocarbonate groups at δ 4.56 or thiol groups at δ 1.63 to trithiocarbonate groups at δ 4.56, we could calculate that 90% of thiol groups on PG were converted into trithiocarbonate groups, which meant that there were 16 trithiocarbonate groups on each PG macromolecule.

RAFT polymerization of NIPAM in the presence of PG-TTC

The RAFT polymerization of NIPAM was carried

Scheme 1 Outline of the synthesis procedure of multi-arms PG-PNIPAM copolymers**Figure 1** ^1H NMR (left) and ^{13}C NMR (right) of PG-TTC derivative in CDCl_3 .

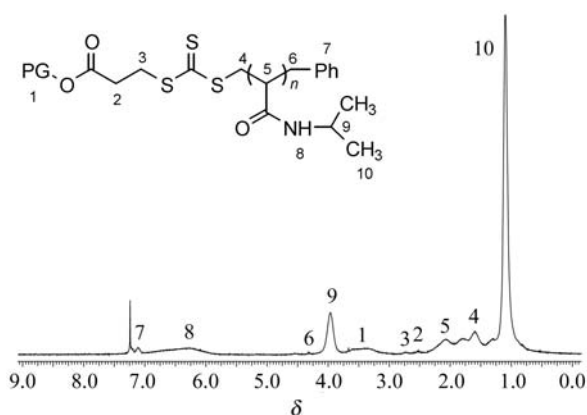
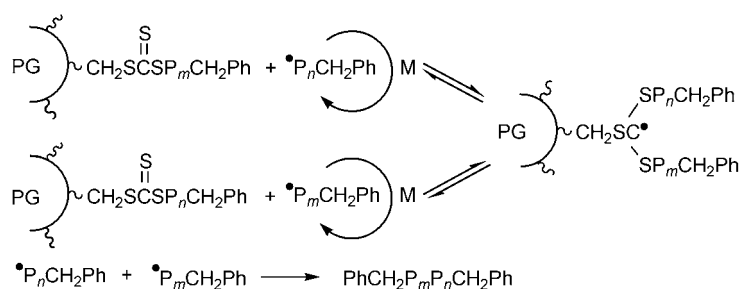
out in the presence of PG-TTC using dioxane as solvent, and the results are shown in Table 1. It was found that in the condition of constant concentration of AIBN and NIPAM, the higher concentration of PG-TTC would produce the PNIPAM with the lower molecular weight. In both cases, the molecular weight increased with the polymerization time and the molecular weight distributions were very narrow. Thus, we could conclude that the polymerization of NIPAM in the presence of PG-TTC was controllable.

Figure 2 provided the ^1H NMR of the copolymer PG-NIPAM mediated by PG-TTC, in which all the resonance signals such as δ 1.0–1.2 (CH_3 of $\text{CH}(\text{CH}_3)_2$), 4.05 (CH of $\text{CH}(\text{CH}_3)_2$), 1.6 (CH_2 of CH_2CHCOO), 2.25 (CH of CH_2CHCOO) and δ 6.0–7.0 (NH connected with carbonyl and isopropyl) for poly(NIPAM) and 2.5 (CH_2 connected with carboxyl),

Table 1 Data of molecular weight (M_n) and polydispersity index (PDI) for PG-PNIPAM mediated by PG-TTC^a

[NIPAM]/[PG-TTC]	Time/h	$M_n/(\text{g}\cdot\text{mol}^{-1})$		PDI
		GPC	NMR	
30	5	8400	9100	1.24
	10	18000	19500	1.28
	15	31000	38000	1.32
	20	49000	57000	1.36
	25	60000	71400	1.42
40	5	12500	13400	1.25
	10	29000	32500	1.28
	15	42500	47800	1.38
	20	58000	74400	1.36

^a Polymerization conditions are shown in the experimental part.

Scheme 2 Schematic formation mechanism of multi-arm star copolymers PG-PNIPAM and the linear byproducts**Figure 2** ^1H NMR of multi-arms PG-PNIPAM in CDCl_3 .

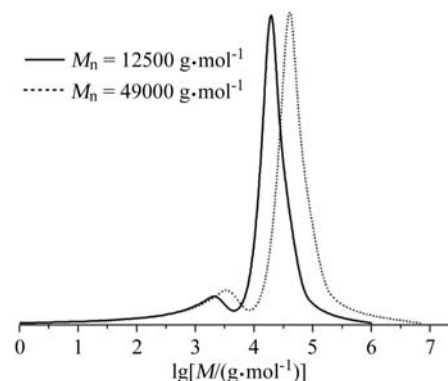
2.7 (CH_2 connected with trithiolcarbonate), 3.20–3.75 (PG), 7–7.25 (phenyl) for PG-TTC were observed.

Owing to the high contents of end benzyl groups, the average degree of polymerization (DP) of PNIPAM could be obtained, and the molecular weight based on this DP could also be derived from the ^1H NMR using the following formula:

$$M_n = \frac{5A_{\text{CH}_2\text{EA}}}{2A_{\text{PEN}}} \times M_{\text{NIPAM}}$$

where $A_{\text{CH}_2\text{EA}}$ was the integral area of methylene protons of PNIPAM at δ 4.05, A_{PEN} was the integral area of phenyl ring protons at δ 7–7.25 and M_{NIPAM} was the mass of NIPAM monomer unit. The data obtained from ^1H NMR and GPC in Table 1 were very close except the samples with high conversion (corresponding to the longer polymerization time) because the hydrodynamic volume of multi-arms PG-PNIPAM with high molecular weight was quite different from that of the linear polystyrene standard. Thus, it could be concluded that all trithiocarbonate groups in our system took part in the RAFT polymerization of NIPAM.

Figure 3 showed the typical GPC trace of PG-PNIPAM. It was observed that besides a main peak with the higher molecular weight, there was a minor peak for the lower molecular weight, and the latter was produced by the side reaction of radical-radical coupling¹² shown in Scheme 2.

**Figure 3** GPC traces of PG-PNIPAM (copolymers as shown in Table 1).

Thermal responsibility of PG-PNIPAM

The thermal responsive property of PG-PNIPAM copolymers with the PG as core and PNIPAM as arms was measured, and the lower critical transition temperature (LCST) was found around 28–30 °C, which was a little lower than 32 °C reported in the literature.¹³ And the LCST was related to the length of the PNIPAM chains. The higher of the PNIPAM/PG ratio brought the closer LCST to that of pure PNIPAM. The similar phenomenon was also described in references.^{14,15}

Conclusion

PG with multi-arms of PNIPAM was successfully synthesized by RAFT technique. In this system, the trithiolcarbonate groups were always bonded on the PG core macromolecule, whereas the growing PNIPAM macro-radical was detached. It was confirmed that the polymerization was controllable and nearly all trithiolcarbonates of PG took part in the (RAFT) polymerization of NIPAM. The copolymers PG-PNIPAM showed thermally dependent hydrophobic/hydrophilic transition around 28–30 °C.

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