Thermoresponsive star-shaped polymer with heteroarm type with methacrylates: Preparation by living radical polymerization method and its topological effect

Journal:	*Polymer Chemistry*
Manuscript ID	PY-ART-12-2022-001518.R1
Article Type:	Paper
Date Submitted by the Author:	14-Jan-2023
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ARTICLE

Thermoresponsive star-shaped polymer with heteroarm type with methacrylates: Preparation by living radical polymerization method and its topological effect

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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We firstly designed the thermoresponsive star-shaped polymer with heteroarm structure based on methacrylates by living radical polymerization with Ru catalyst. Lowest critical solution temperature (LCST) of the arm polymer was controlled with the range of 26-52 °C by changing the initial ratio of diethylene glycol methyl ether methacrylate (DEGMA) and triethylene glycol methyl ether methacrylate (TEGMA) in copolymerization. The synthesized heteroarm star-shaped polymer consisted of P(DEGMA-stat-TEGMA), whose unit composition was DEGMA:TEGMA = 83:17 and LCST was 35 °C, and poly(methyl methacrylate) (PMMA) and possessed ca. 6 arms of P(DEGMA-stat-TEGMA) and ca. 2 arms of PMMA. This heteroarm star-shaped polymer was insoluble in water, however, the star-shaped polymer coated surface showed thermoresponsivity, in which the contact angle of captive bubble changed from 131 ± 0.6° at 20 °C to 126±1.9° at 40 °C. This result indicates such heteroarm star-shaped polymers can be promising materials for constructing thermoresponsive surfaces by simple coating methods.

Introduction

Stimuli-responsive polymer materials are changed their physical and chemical properties by pH, temperature, light, and so on. Among them, temperature responsive polymers are rather easy to use to control the material properties, which the polymer solubility could be changed depending on the temperature at reversible manner. This leads to the smart materials, that the material properties can be switched by the temperature. So, various materials have been reported, such as drug deliveries,[1] cellular tissue fabrications,[2,3] stationary phase of chromatography,[4] nano architectures,[5] stimuli-responsive surfaces,[6,7], and smart hydrogels.[8,9]

Thermoresponsive polymer, especially in the aqueous media, has been intensively studied in the biomedical area because of the safe solvent and facile application. The polymer main chain is aggregated at over could point temperature due to the dehydration in the water, although it is soluble in water because of the enough amount of hydration at lower temperature than the cloud point, so cold "Lower critical solution temperature" (LCST). It is well known that LCST of poly(*N*-isopropyl acrylamide) (PNIPAM) is shown at 32 °C, which is very close to the physiological temperature.[10] However, it is important to create novel thermoresponsive polymer materials except for PNIPAM, to develop the various polymer materials. For example, poly(vinyl ether) [11,12], polyacrylate[13] and polymethacrylate[14-16] and poly(trimethylene carbonate) derivatives[17,18] bearing oligo(ethylene glycol) units have been reported. Furthermore, poly(vinylcaprolactam), [19] poly(*N*-vinylisobutyramide), [20-21] and some other polysacharrides and polypeptides have been also investigated and their application were studied. Once the polymer main chains were well designed, it is also possible to used them to the various polymer structures for materials, such as micelle and gel formation.

On the other hand, star-shaped polymer is one of the interesting polymer structures, which many polymer chains attached to a central core, and have the characteristics of branched polymers and a spherical morphology.[22,23] The multifunctional initiator method, in which branch polymers are elongated from initiators bearing many initiators, and the arm-first method, in which pre-made branch polymers are combined with coupling agents, are well known for the synthesis of star-shaped polymers. Star-shaped polymer with hydrophobic components in the core and hydrophilic polymers in the outer shell are called unimolecular micelles and it was compared to conventional micelles formed by the weak physical aggregation of amphiphilic polymers. The structural stability of star-shaped polymers is expected to be utilized for applications such as gene delivery and drug delivery and removal of organic compounds from water.

The properties of star-shaped polymers with thermoresponsive moieties have been investigated. It has been

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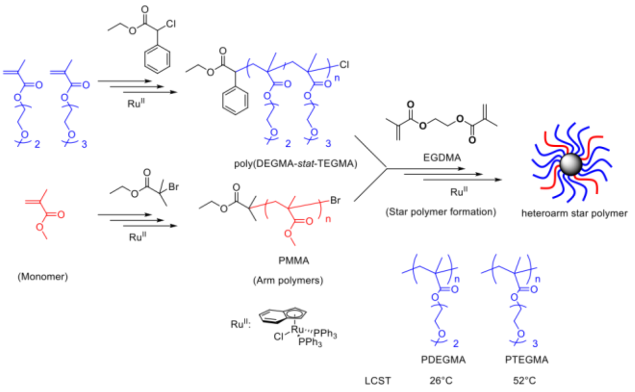
Electronic Supplementary Information (ESI) available: Scheme S1-S9 for polymer synthesis, Figure 1, 3, 4, 6, 8, 10, 12, 14, and 16 for SEC curves and ^{1}H NMR spectra of the obtained polymers, Figure 2, 5, 7, 9, 11, 13, 15, and 17 for UV diagrams, traced by the transmittance with a 500 nm light beam in LCST measurements, and Figure 18 for photo images of thermoresponsive behavior of heteroarm star-shaped polymer coating. See DOI: 10.1039/x0xx00000x reported that the LCST values could be changed depending on the numbers of arm,[24,25] so it is important to design and control the polymer structures for the thermoresponsive star-shaped polymers. By evaluating the thermoresponsive star-shaped polymers obtained by the multifunctional initiator methods, the effect of the number of branches on LCST and the construction of precise thermoresponsive networks using these polymers have been reported. Four armed type, as the simple star-shaped polymers, has been investigated, using porphyrin[26,27] and benzene[28] . These 4-arm types could be applied for the gel formation, too.[29,30]. Various kinds of thermoresponsive polymers have been introduced into the star-shaped polymers, such as NIPAM,[31] *N*-vinylcaprolactam,[32] methacrylate, [33] and oxazoline.[34] Since the arm part is a partially linear structure, the copolymers were sometimes used as arm structures. These approaches enable to create various polymer materials. For examples, the block copolymer of NIPAM and *N*-methylolacrylamide was synthesized for the arm of star-shaped polymer,[35] and it was utilized as drug delivery system. The block copolymers of acrylate and methacrylates with OEG groups were also prepared by atom transfer radical polymerization (ATRP) to utilize for star-shaped polymers,[36] as well as the anionic polymerization methods.[37] Interestingly, the helical structures of arm part were also designed as block copolymer of isocyanide.[38] Unlike the simple linear polymers, star-shaped polymer possesses the unique polymer structures, so it could be utilized for some applications with tuning the properties by copolymers. For example, hydrogels with thermoresponsive moieties at crosslinking points,[39] cell adhesive control,[40] reduction-controlled drug delivery,[41]

Moreover, heteroarm star-shaped polymers or miktoarm star-shaped polymers are defined as polymers in which different types of branch polymers are introduced into the same star-shaped polymer structures. Unlike the case of using random or block copolymers as the branch polymers of star-shaped polymers, the different properties of the branch polymers cause phase separation within the star-shaped polymer, resulting in unique aggregation behaviour, such as Janus particles. Lodge and coworkers reported that heteroarm star-shaped polymers consisting of three types of hydrophilic/hydrophobic/fluorinated polymer chains from hamburger-like aggregates in water and can encapsulate different compounds at each aggregation site.[42,43] Chen and coworkers utilized polycaprolactone as hydrophobic arm and polymethacrylate with OEG as hydrophilic arm to prepare the pH responsive heteroarm star-shaped polymer.[44]

On the other hand, we have also previously reported heteroarm star-shaped polymer composed of hydrophilic poly(hydroxymethyl methacrylate) (PHEMA) and hydrophobic poly(methyl methacrylate) (PMMA), using Ru catalyst as living radical polymerization technique as an interfacial functional material.[45] When the star-shaped polymer was coated on PET film, the star-shaped polymer is physically anchored to the surface due to hydrophobic interactions between PMMA and PET, and the PHEMA chains are considered to adopt a polymer brush-like structure swollen in water. Theis surface exhibits therefore a larger bubble contact angle in water than linear PHEMA coated surfaces, greatly reducing the adhesion of E. coli and platelets. Therefore, by assigning roles to each branch polymer a characteristic of heteroarm, it is possible to functionalize the surface in a facile method.



Scheme 1 Synthetic route of thermoresponsive heteroarm star polymer via Ru-catalyzed living radical polymerization using the arm first method.

Recently, several examples of thermoresopnsive heteroarm star-shaped polymers have been reported, for example. Brooks, Kizhakkedathu, and cowokers has reported RAFT and ATRP combination to produce thermoresponsive hetero arm star-shaped polymers with *N*,*N*-dimetylacrylamide and NIPAM.[46] Furthermore, Plamper and coworkers selected the poly(ethylene oxide), poly(propylene oxide), and poly(*N*,*N*-dimethylaminoethyl methacrylate) as heteroarms for thermoresponsive star-shaped polymer.[47] Recently, microflow systems were utilized to tune the star-shaped polymer with heteroarm with methacrylate with OEG units and *N*,*N*-dimethylaminoethyl acrylate.[48] Aoshima and coworkers systemativally synthesized thermoresponsive heteroarm star-shaped polymer,[49,50] including fluorine-containing block copolymers, heteroarm star-shaped polymers with poly(vinyl ether)s backbone. However, to best of our knowledge, there is no example of thermoresponsive heteroarm star-shaped polymers with methacrylate with OEG chain as hydrophilic arm and PMMA as hydrophobic arm, using Ru catalyst.

In this study, we firstly designed the thermoresponsive star-shaped polymer with heteroarm structure based on the methacrylates, by living radical polymerization with Ru catalyst using the arm-first method (Scheme 1). We selected di(ethylene glycol) methyl ether methyacrylate (DEGMA) and tri(ethylene glycol) methyl ether methacrylate (TEGMA) as thermoresponsive moieties, and methyl methacrylate (MMA) as a hydrophobic moiety. As a comparison of star-shaped polymers, the thermoresponsive properties of their linear homopolymers, random copolymers, and block copolymers were also evaluated.

Experimental

Materials

2,2'-Azobisisobutyronitrile (AIBN) (≥98.0%), hydroquinone (≥99.0%), methacrylic acid (≥99.0%), *p*-toluenesulfonic acid monohydrate (*p*TsOH) (≥99.0%), triethylene glycol monomethyl ether (≥98.0%), and cyclohexane (≥99.5%) were purchased from FUJIFILM WAKO Pure Chemical Corporation (Osaka, Japan) and used as received. Toluene (≥99.5%) was purchased FUJIFILM WAKO Pure Chemical Corporation and dried over molecular sieves 4A before use. Chloro(indenyl)bis(triphenylphosphine)-ruthenium(II) [Ru(Ind)Cl(PPh_3)$_2$] was purchased from Santa Cruz Biotechnology, Inc (Texas, USA) and used as received. Diethylene glycol methyl ether methacrylate (95%), ethyl 2-chloro-2-phenylacetate (ECPA, 97%), and ethylene glycol dimethacrylate (EGDMA, 98%) was purchased from Sigma-Aldrich Co. LLC (St. Louis, USA). Tri-*n*-butylamine (*n*-Bu_3N, ≥98.0%) and methyl methacrylate (≥99.8%) were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan) and distilled over CaH_2.

Methods

Nucleic magnetic resonance (NMR) spectroscopy was conducted for the samples dissolved in $CDCl_3$ using a 400-MHz spectrometer (JNM-ECP400, JEOL Ltd., Japan). Size-exclusion chromatography (SEC) was performed with chloroform as the solvent at a flow rate of 1.0 mL/min at 40°C using three columns (TSKgel GMH$_{HR}$-M, 7.8 mm I.D. × 300 mm, Tosoh Corporation, Japan) connected in series with a pump (PU-2080, JASCO International Co. Ltd., Japan), a degasser (DG-2080, JASCO International Co. Ltd., Japan), a column oven (CO-2065plus, JASCO International Co. Ltd., Japan), a refractive index detector (RI-2031, JASCO International Co. Ltd., Japan), and a light scattering detector (Viscotek 270 dual detector, Malvern Panalytical, UK). The relative molecular weight was calculated based on the calibration curve of PMMA standards (MW = 870–1,916,000 g mol^{-1}) in DMF containing 10 mL LiBr. LCST was measured by the JASCO V-550 ETC-505S and JSSCO V-550 ETC-505T system. The samples for LCST measurement was prepared with 2 mg mL^{-1} concentration and transmittance was measured using 500 nm light with changing temperature rate of 1 °C min^{-1}. Surface contact angle was measured using a gomiometer (DM-501Hi, Kyowa Interface Science Co., Ltd., Japan).

Synthesis of triethylene glycol methyl ether methacrylate (TEGMA)

To a round bottom flask containing a stir bar was added methacrylic acid (45 mL, 390 mmol), triethylene glycol monomethyl ether (50 mL, 260 mmol), cyclohexane (222 ml), *p*TsOH (5.13 g, 27 mmol), and hydroquinone (1.3 g, 12 mmol) and stirred. Then a Dean-stark apparatus was attached and the dehydration reaction was conducted for 11 h while refluxing. The cyclohexane was removed from the reaction solution using an evaporator. Dichloromethane (600 mL) and water (120 mL) were added, and washed three times with saturated sodium bicarbonate solution and once with saturated brine. The organic layer was then dried with magnesium sulfate, and the solvent was evaporated to obtain the crude product. The crude product was purified by silica gel column chromatography to afford the desired product (hexane:ethyl acetate, 6:4, Rf=0.4). As a result, the target product was obtained. Yield: 43.4 g (72.5%). *1*H NMR (400 MHz, $CDCl_3$, δ): 6.02 (s, 1H), 5.56 (s, 1H), 4.29 (t, *J* = 4.9 Hz, 2H), 3.74 (t, *J* = 4.9 Hz, 2H), 3.66 (m, 6H), 3.54 (m, 2H), 3.37 (s, 3 H), 1.94 (s, 3 H).

Synthesis of PTEGMA

A Schlenk tube containing a stir bar was equipped with a three-way stopcock. The polymerization catalyst [Ru(Ind)Cl(PPh_3)$_2$] (0.08 mmol, 68.8 mg) was added. After degassing with vacuuming and filling with Ar, toluene (58.3 mL), 430 mM solution of *n*-Bu_3N in toluene (0.8 mmol, 1.86 mL), TEGMA (80 mmol, 18.1 mL), 490 mM solution of ECPA in toluene (0.80 mmol, 1.63 mL) were added in this order and the mixture was stirred. The Schlenk tube was immersed in an oil bath set at 80 °C to start polymerization and the reaction was monitored by taking a small amount of the polymerization solution and analysing with ^{1}H NMR. The Schlenk tube was removed from the oil bath and immersed in cold water to stop the polymerization. The reaction solution was then passed through a silica gel column using toluene as an eluent to remove the catalyst, followed by evaporation. The dried polymer was dissolved in CH_2Cl_2 to 20wt% solution and precipitated with hexane twice. The purified polymer was then dissolved in $CHCl_3$ for SEC measurements. ^{1}H NMR measurements were also performed using D_2O as the solvent. During the ^{1}H NMR measurement, the water peak was eliminated. Yield: 10.4 g (69.7 %). PDEGMA was also prepared with the similar procedure. Yield: 5.78 g (47.8 %).

Synthesis of star-shaped PTEGMA

A Schlenk tube containing a stir bar was equipped with a three-way stopcock. The polymerization catalyst [Ru(Ind)Cl(PPh_3)$_2$] (18 µmol, 15.1 mg) and the internal standard trimethoxybenzene (0.36 mmol, 60.5 mg) were added. To another tube was added PTEGMA (90 µmol, 2.02 g), toluene (13.7 mL), 460 mM solution of EGDMA in toluene (0.90 mmol, 1.84 mL), 430 mM solution of n-Bu3N in toluene (0.123 mM, 0.419 mL) was added to make a polymer solution. The polymer solution was added to the catalyst containing Schlenk tube. Then, about 0.1 mL of the initial polymerized solution was sampled as an initial polymerization solution and immersed in an oil bath set at 80 ºC to start polymerization. The reaction was monitored by analyzing a small amount of the polymerization solution with ^{1}H NMR. The Schlenk tube was removed from the oil bath and immersed in cold water to stop the polymerization. The reaction solution was then passed through a silica gel column using toluene as an eluent to remove the catalyst, followed by evaporation. The dried polymer was then dissolved in toluene (10 wt%), and the arm polymers were removed by adding hexane dropwise. Yield: 0.473 g (19.8 %). Star-shaped PDEGMA was also synthesized with the similar procedure. Yield: 0.732 g (37.1 %).

Synthesis of PTEGMA-b-PMMA

A Schlenk tube containing a stir bar was equipped with a three-way stopcock. The polymerization catalyst [Ru(Ind)Cl(PPh_3)$_2$] (7.5 µmol, 4.31 mg) and the internal standard 1,4-dimethoxybenzene (80 µmol, 11.5 mg) were added. To another tube was added PTEGMA (0.045 mmol, 1.01 g), toluene (7.78 mL), 430 mM of *n*-Bu_3N solution in toluene (0.09 mM, 0.210 mL), and MMA (1.02 mmol, 0.109 mL) to make a polymer solution. The polymer solution was added to the catalyst

Table 1. Number-averaged molecular weights, polydispersites of PDEGMA (co)polymers and their thermoresponsive properties.

Entry	Polymer type	DEGMA:MMA (mol)[a]	M_n[b]	Đ[b]	LCST, °C[c]
1	Homo	100:0	15,800	1.19	26
2	Block	83:17	17,400	1.26	19
3	Statistical	83:17	18,500	1.26	14
4	Star	89:11[d]	265,000[e]	1.50[e]	NA[f]

a: Determined by ^{1}H NMR using the signal integrations of ester methylene and ether methylene of DEGMA and ester methyl of MMA.

b: Determined by SEC using PMMA standard calibration.

c: Determined by 50% transmittance at 500 nm light of 0.2wt% polymer solution.

d: Determined by unit concentration of the initial reaction solution.

e: Determined by SEC-RALS.

f: Insoluble in water.

containing Schlenk tube. Then, about 0.1 mL of the initial polymerization solution was taken as an initial polymerization solution and immersed in an oil bath set at 80 °C to start polymerization. The reaction was monitored by analyzing a small amount of the polymerization solution with ^{1}H NMR. The Schlenk tube was removed from the oil bath and immersed in cold water to stop the polymerization. The reaction solution was then passed through a silica gel column using toluene as an eluent to remove the catalyst, followed by evaporation. The dried polymer was dissolved in CH_2Cl_2 to 20wt% solution and precipitated with hexane twice. The purified polymer was then dissolved in $CHCl_3$ for SEC measurements. ^{1}H NMR measurements were also performed using $CDCl_3$ as the solvent. Yield: 0.473 g (40.9 %) PDEGMA-*b*-PMMA was also prepared with the similar procedure. Yield: 0.732 g (42.5 %).

Synthesis of Poly(TEGMA-*stat*-MMA)

A Schlenk tube containing a stir bar was equipped with a three-way stopcock. The polymerization catalyst [Ru(Ind)Cl(PPh_3)$_2$] (10 μmol, 8.61 mg) and the internal standard 1,4-dimethoxybenzene (0.70 mmol, 96 mg) were added. To another tube was added TEGMA (10 mmol, 2.26 mL), MMA (2.0 mmol, 0.213 mL), toluene (7.78 mL), 430 mM of *n*-Bu_3N solution in toluene (0.10 mmol, 0.232 mL), 490 mM of ECPA solution in toluene (0.10 mmol, 0.204 mL) to make a monomer solution. The monomer solution was added to the catalyst containing Schlenk tube. Then, about 0.1 mL of the initial polymerization solution was taken as an initial polymerization solution and immersed in an oil bath set at 80 °C to start polymerization. The reaction was monitored by analyzing a small amount of the polymerization solution with ^{1}H NMR. The Schlenk tube was removed from the oil bath and immersed in cold water to stop the polymerization. The reaction solution was then passed through a silica gel column using toluene as an eluent to remove the catalyst, followed by evaporation. The dried polymer was dissolved in CH_2Cl_2 to 20wt% solution and precipitated with hexane twice. The purified polymer was then dissolved in $CHCl_3$ for SEC measurements. ^{1}H NMR measurements were also performed using $CDCl_3$ as the solvent. Yield: 0.591 g (23.4 %). P(DEGMA-*stat*-MMA) was also prepared with the similar procedure. Yield: 0.275 g (15.2 %).

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Surface contact angle measurement

The star-shaped polymer-coated surface was prepared by spin coating on a PET film (10 mm x 10 mm x 0.2 mm) with 50 µL solution of the heteroarm star-shaped P(DEGMA-stat-TEGMA)/PMMA (1.0 wt% in THF), dried in vacuum for 3 h. The polymer-coated surface was incubated in water for 12 h prior to the measurement. The air bubble was attached from underneath by using a microsyringe at 20 °C or 40 °C and the contact angle was monitored for 40 s. The measurement was conducted for three times and the data are presented by the average of the measurement. Errors were determined through evaluation of the standard deviation of the measurements.

Results and Discussion

In this study, we synthesized a thermoresponsive heteroarm star-shaped polymer based on oligo(ethylene glycol) methacrylate (Scheme 1). Since the LCST of PDEGMA and PTEGMA are 26 °C and 52 °C, respectively, we adjusted the LCST of the branch polymers by copolymerization so that they are temperature responsive under physiological conditions. Therefore, the LCST of the arm polymers was adjusted by copolymerization of DEGMA and TEGMA to show thermoresponsivity under physiological conditions.

Synthesis of linear and star PDEGMA and their thermoresponsive propety

First, polymerization of DEGMA was carried out by Ru-catalyzed living radical polymerization using ethyl 2-chloro-2-phenylacetate (ECPA, initiator), Ru(Ind)Cl(PPh_3)$_2$ (catalyst), and *n*-Bu_3N (additive) initiating system in toluene at 80°C. The polymerization proceeded and reached 80% monomer consumption after 72 hours. The SEC curve of the obtained polymer was unimodal with a narrow polydispersity (*Đ*) of 1.19 (Table 1). ^{1}H NMR of the obtained PDEGMA was measured in DMSO-d_6 to determine the number-averaged degree of polymerization (DP_n) from the intensity ratio of the phenyl group at the initiating end of the polymer to the methylene group of the ester in the polymer side chain. DP_n of the obtained PDEGMA was 82, indicating that the number-averaged molecular weight (M_n) was 15,800, which was in very good agreement with the theoretical value expected from the monomer to initiator initial concentration ratio

Table 2. Number-averaged molecular weights, polydispersites of PTEGMA (co)polymers and their thermoresponsive properties.

Entry	Polymer type	TEGMA:MMA (mol)[a]	M_n[b]	$Đ$[b]	LCST, °C[c]
1	Homo	100:0	22,400	1.12	52
2	Block	81:19	24,300	1.17	46
3	Statistical	83:17	24,100	1.17	43
4	Star	90:10[d]	207,000[e]	1.31[e]	43

a: Determined by ^{1}H NMR using the signal integrations of ester methylene and ether methylene of TEGMA and ester methyl of MMA.

b: Determined by SEC using PMMA standard calibration.

c: Determined by 50% transmittance at 500 nm light of 0.2wt% polymer solution.

d: Determined by unit concentration of the initial reaction solution.

e: Determined by SEC-RALS.

($[DEGMA]_0/[ECPA]_0$) and the monomer conversion. Separately, PDEGMA with M_n of 17,100 and $Đ$ of 2.83 was synthesized by conventional free radical polymerization with AIBN as a comparison.

Star-shaped PDEGMA was synthesized by polymerization of EGDMA, a linking agent with 10 equivalents to PDEGMA macroinitiator in the presence of Ru(Ind) complex catalyst and *n*-Bu_3N additive. The star-shaped polymer synthesis was carried out in toluene at 80°C. After 188 hours of reaction, 82% of the macroinitiator was converted to star-shaped polymers. The star-shaped PDEGMA was purified by precipitation with toluene/hexane to remove the unreacted arm polymers. The obtained star-shaped PDEGMA had M_n of 55,500 by SEC and M_n of 265,000 by SEC-RALS, in which the significant difference of M_n supports the star-shaped polymer formation. Since EGDMA incorporated in the star-shaped PDEGMA is hydrophobic and about 10mol% of EGDMA to PDEGMA is incorporated, the effect of hydrophobic EGDMA units on the thermoresponsivity cannot be ignored. Therefore, in addition to PDEGMA, block and statistical copolymers with MMA, corresponding to the structure of the linking moiety cut in half, were synthesized as well. The polymerizations were controlled and resulted in PDEGMA-*b*-PMMA with a DEGMA:MMA unit ratio of 83:17, M_n of 17,400, $Đ$ of 1.26 and P(DEGMA-*stat*-MMA) with a DEGMA:MMA unit ratio of 83:17, M_n of 18,500, $Đ$ of 1.26.

For evaluation of the thermoresponsivity of the series of PDEGMA, LCST was evaluated by the transmittance of 500 nm light using 2 mg mL^{-1} aqueous solution. The LCST is defined as the point where the transmittance is 50% in this study. Linear PDEGMA, obtained by both living radical and conventional free radical polymerization, dissolved homogeneously at low temperatures, and the transmittance decreased rapidly at 26 °C as the temperature increased. The obtained LCSTs were consistent with the reported values and did not depend on the molecular weight dispersion. As expected, the LCSTs of the P(DEGMA-*co*-MMA) decreased with the incorporation of hydrophobic MMA, and the LCSTs of PDEGMA-*b*-PMMA and P(DEGMA-*stat*-MMA), respectively, were 19 °C and 14 °C, respectively. This may be because the hydrophobic MMA units of the block copolymers aggregate in aqueous solution, but PDEGMA can still form micelles and elongate, whereas the aggregation of MMA units in statistical copolymers makes it difficult for the PDEGMA chains to hydrate and elongate. In contrast to linear PDEGMA and copolymers with MMA, star-shaped PDEGMA hardly dissolved in water even at low temperatures. Since the content of hydrophobic units was close to that of the block and statistical copolymers, this difference could be due to a molecular weight effect or a topological effect. Some examples of a decrease in LCST with increasing number of branches in star-shaped polymers compared to linear polymers have been reported.[24,25]

Synthesis of linear and star PTEGMA and their thermoresponsive property

Similar to DEGMA polymers, linear PTEGMA, block and statistical copolymers with MMA, and star-shaped PTEGMA were synthesized. The homopolymers and copolymers had M_ns of 22, 000~25,000 and a narrow polydistribution with $Đ$ <1.2 (Table 2). The synthesis of star-shaped PTEGMA using the obtained PTEGMA as a macroinitiator also proceeded successfully. After removal of unreacted PTEGMA, star-shaped PTEGMA with M_n of ca 210,000 and $Đ$ of 1.31 was obtained by SEC-RALS measurements.

The LCSTs of the series of the obtained PTEGMA and copolymers were measured. The LCST of the linear PTEGMA was 52 °C, consistent with literature values (Table 2). Block and statistical copolymers containing ca. 20% MMA units had almost the same molecular weight and molecular weight dispersion, but their LCSTs were different and lower than those of the homopolymers, 46 °C and 43 °C, respectively. This was the same trend as the LCST measurements of PDEGMA. On the other hand, star-shaped PTEGMA could be dissolved in water and LSCT measurements were possible, with a value of 43 °C, the close value to that of the statistical copolymer. These results indicate that the LCST of methacrylate polymers with short ethylene glycol side chains and copolymers with MMA tend to be homopolymer > block copolymer > statistical copolymer ≥ star-shaped polymer.

LCST control by copolymerization of DEGMA and TEGMA

Thermoresponsive polymers are being considered for a wide range of applications, especially in the biomedical field, and therefore polymers with LCST near physiological temperatures are desirable. The LCSTs of PDEGMA and PTEGMA are 26 °C and 52 °C, which are outside the physiological temperature range. Therefore, we attempted to control the

Table 3. Number-averaged molecular weights, polydispersites of P(DEGMA-stat-TEGMA) and their thermoresponsive properties.

Entry	DEGMA:TEGMA (mol%)[a]	DEGMA:TEGMA (wt%)[b]	M_n[c]	$Đ$[c]	LCST, °C[d]
1	100:0	100:0	15,700	1.19	26
2	85:15	82:18	14,300	1.25	32
3	83:17	80:20	15,700	1.16	35
4	73:27	68:32	13,600	1.15	37
5	47:53	42:48	14,000	1.22	41
6	0:100	0:100	22,400	1.12	52

a: Determined by ^{1}H NMR using the signal integrations of ester methylene, ether methylene and ether methyl of DEGMA and TEGMA.

b: Calculated from the results of DEGMA and TEGMA molar composition considering their molecular weight.

c: Determined by SEC using PMMA standard calibration.

d: Determined by 50% transmittance at 500 nm light of 0.2wt% polymer solution.

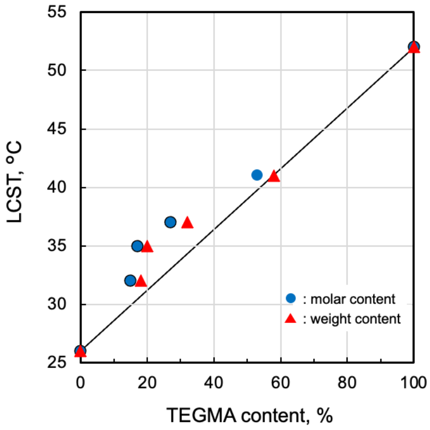

Figure 1. Dependence of LCST on TEGMA content for P(DEGMA-stat-TEGMA). Circle: molar content, Triangle: weight content.

LCST around the physiological temperature by copolymerization of DEGMA and TEGMA. DEGMA/TEGMA copolymerization was performed by living radical polymerization using Ru complexes, and copolymers of uniform length with M_ns of 13,000~23,000 and $Đ$ of about 1.2 were obtained by systematically changing initial DEGMA/TEGMA ratio (Table 3). The DEGMA/TEGMA ratio in the obtained copolymers was also close to the initial ratio.

The LCST was evaluated for the series of P(DEGMA-*stat*-TEGMA) obtained. As expected, LCST increased with increasing TEGMA content from 26 °C for PDEGMA homopolymer to 52 °C for PTEGMA homopolymer. In particular, in the range of 15~27% molar content of TEGMA, LCST could be controlled to 32~37 °C, a value near the physiological temperature. the relationship between molar and weight content of TEGMA in P(DEGMA-*stat*-TEGMA) and LCST is shown in Figure 1. This relationship is roughly close to a linear relationship, but in regions of low TEGMA content, LCST was slightly higher than predicted from the linear relationship, and the nature of TEGMA tended to be strongly expressed. In addition, when comparing molar content and weight content, weight content tended to be closer to the linear relationship. This result is slightly different from that reported by Yamamoto et al.,[15] a linear relationship between molar content and LCST, but may be due to differences in the molecular weight of the polymer measured and the LCST measured concentration.

Synthesis of heteroarm star-shaped P(DEGMA-*stat*-TEGMA)/PMMA and its surface property

A heteroarm star-shaped polymer with a thermoresponsive P(DEGMA-*stat*-TEGMA), consisting of DEGMA:TEGMA = 83:17 composition, and a hydrophobic PMMA as arm polymers was synthesized. LCST of this P(DEGMA-*stat*-TEGMA) is 35 °C, which is near the physiological temperature. The arm polymer of PMMA was synthesized by living radical polymerization using ethyl 2-bromoisobutyrate as initiator with Ru complexes to obtain a living polymer with M_n of 8,200 and $Đ$ of 1.25. The heteroarm star-shaped polymer was synthesized by Ru-catalyzed polymerization of EGDMA from a mixed macroinitiator of P(DEGMA-*stat*-TEGMA) (M_n of 15,700, $Đ$ of 1.16) and PMMA in a ratio of P(DEGMA-*stat*-TEGMA):PMMA = 75:25. The ratio of hydrophilic to hydrophobic chains was determined with reference to our previous study of PHEMA/PMMA heteroarm star-shaped polymers.[45] In the SEC curve of the reaction solution at 185 hours after the start of the reaction, a new peak appeared on the higher molecular weight side than the macroinitiator, confirming the formation of star-shaped polymers (Figure 2A). The conversion to star-shaped polymer was roughly calculated from the peak area to be 67%. The star-shaped polymer was precipitated by gradually adding hexane to 10 wt% polymer solution in toluene to remove unreacted branch polymers. M_n of the resulting star-shaped polymers was 72,000 by SEC and 126,000 by SEC-RALS, suggesting the formation of star-shaped polymers even from the large molecular weight difference based on the difference in exclusion volume. The ^{1}H NMR spectrum of the obtained polymers contained both P(DEGMA-*stat*-TEGMA) and PMMA components, strongly suggesting the formation of heteroarm star-shaped polymers(Figure 2B). Calculating the ratio of arm polymers from the composition of DEGMA, TEGMA, and MMA in the star-shaped polymer and the degree of polymerization of each arm polymer gave P(DEGMA-*stat*-TEGMA):PMMA = 73:27, which was consistent with the initial ratio (see ESI). The average number of arms was estimated to be 8.7 from the molecular

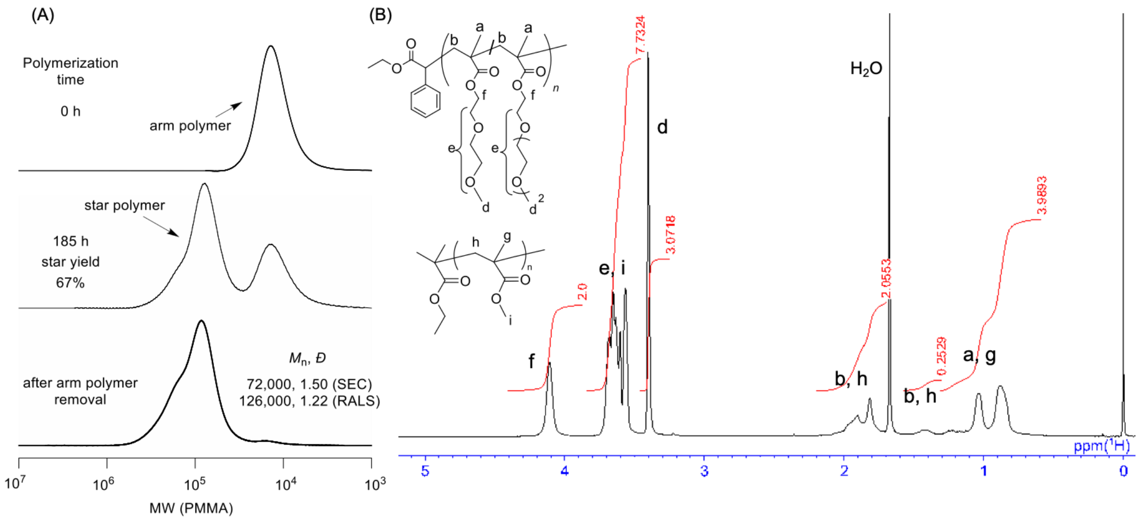

Figure 2. (A) SEC curves of P(DEGMA-*stat*-TEGMA)/PMMA (arm polymer) and the obtained heteroarm star-shaped polymer before and after arm polymer removal and (B) ^{1}H NMR spectrum of the obtained heteroarm star-shaped polymer.

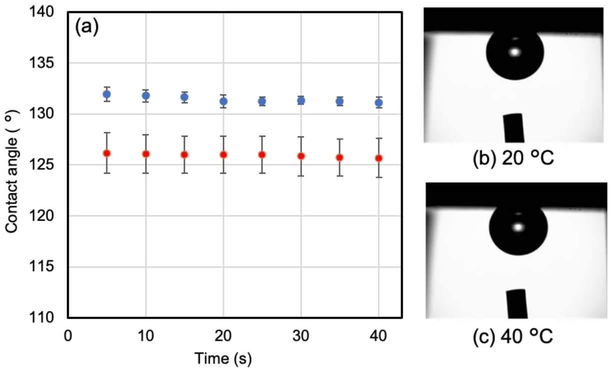

Figure 3. (a) Contact angles of air-in-water (captive bubble) for the P(DEGMA-*stat*-TEGMA)/PMMA heteroarm star-shaped polymer-coated surface at 20 and 40 °C, and photo images of the captive bubbles at (b) 20 °C and (c) 40 °C.

weight, indicating that this heteroarm star-shaped polymer has about 6.4 arms of P(DEGMA-*stat*-TEGMA) and 2.3 arms of PMMA.

The obtained P(DEGMA-*stat*-TEGMA)/PMMA heteroarm star-shaped polymer was insoluble in water and LCST could not be measured. Therefore, we spin-coated this heteroarm star-shaped polymer onto PET film and attempted to evaluate its thermoresponsivity through surface hydrophilicity by water contact angle. However, measurement of water contact angle in ambient atmosphere was difficult because water droplets evaporate relatively quickly at 40°C, which is expected to be above the LCST of this polymer. In addition, hydrophobic PMMA chains are exposed on the surface in the dry condition under air since air is hydrophobic, and rearrangement of the arm polymers is expected upon contact with water, which makes correct evaluation difficult. Therefore, the hydrophilicity was evaluated by the contact angle of the captive bubble in water at different temperatures. The contact angle of the captive bubble on the heteroarm star-shaped polymer-coated surface at 20 °C was stable immediately after bubble attachment and was 131 ± 0.6° at 40 s after bubble attachment (Figure 3). The contact angle of the captive bubble at 40 °C was also stable and almost independent of time, reaching 126±1.9° after bubble attachment, indicating an increase in hydrophobicity. This confirms that the heteroarm star-shaped polymer coating also shows thermoresponsivity, and that a thermoresponsive functional surface can be created simply by coating. When a thick coated film of this polymer was made using the drop-cast method, it was transparent at low temperatures of 20°C and cloudy at high temperatures of >40 °C, and this response was reversible (Figure S18). This suggests heteroarm star-shaped polymers a promising material for creating functional surfaces that are insoluble in water, yet thermoresponsive in water.

Conclusions

In conclusion, we designed and synthesized the thermoresponsive star-shaped polymer with heteroarm structure based on the methacrylates by living radical polymerization with Ru catalyst, in which the heteroarm star-shaped polymer possessed P(DEGMA-stat-TEGMA) as the thermoresponsive arm and PMMA as the hydrophobic substrate-binding arm. We also prepared PDEGMA, PTEGMA, and related copolymers with MMA to clarify the effect on the thermoresponsivity. LCST of the thermoresponsive polymers depended on the monomer sequence and their topology and decreased in the order: linear homopolymer > block copolymer > statistical copolymer > star-shaped polymer. LCST was able to be controlled by copolymerization of DEGMA and TEGMA to physiological temperature. The heteroarm star-shaped polymer-coated surface exhibited thermoresponsivity. This polymer would be promising material for constructing smart surfaces by simple coating.

Author Contributions

Conceptualization, T.A. and H.A.; methodology, T.A. and H.A.; data curation, K.Y.; formal analysis, K.Y., T.A. and T.A.; writing – original draft, T.A.; writing – reviewing and editing, T.A. and H.A., supervision, H.A. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by Adaptable and Seamless Technology transfer Program through Target-driven R&D (A-STEP) from Japan Science and Technology Agency (JST) Grant Number VP30118067682.

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