Check for updates

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

Tsuyoshi Ando, (ID) * Kazuki Yamaguchi and Hiroharu Ajiro (ID) *

We first designed the thermoresponsive star-shaped polymer with heteroarm structure based on methacrylates by living radical polymerization with Ru catalyst. The lowest critical solution temperature (LCST) of the heteroarm polymer was controlled within the range 26–52 °C by changing the initial ratio of diethylene glycol methyl ether methacrylate (DEGMA) and triethylene glycol methyl ether methacrylate (TEGMA) in the copolymerization. The synthesized heteroarm star-shaped polymer consisted of P(DEGMA-*stat*-TEGMA), with a unit composition of DEGMA : TEGMA = 83 : 17 and LCST of 35 °C, and poly(methyl methacrylate) (PMMA), and possessed approximately six arms of P(DEGMA-*stat*-TEGMA) and approximately two 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 the captive bubble changed from $131 \pm 0.6°$ at 20 °C to $126 \pm 1.9°$ at 40 °C. This result indicates that such heteroarm star-shaped polymers can be promising materials for constructing thermoresponsive surfaces using simple coating methods.

Introduction

Stimuli-responsive polymer materials change their physical and chemical properties with pH, temperature, light, and so on. Among them, temperature-responsive polymers are easy to use to control the properties of materials, where the polymer solubility can be changed depending on the temperature and in a reversible manner. This leads to smart materials in which the material properties can be switched by temperature. Various such materials have been reported for applications in, for example, drug delivery,[1] cellular tissue fabrication,[2,3] stationary phase chromatography,[4] nano architecture,[5] stimuli-responsive surfaces,[6,7] and smart hydrogels.[8,9]

Thermoresponsive polymers, especially in aqueous media, have been intensively studied in the biomedical area because of their use of a safe solvent and easy application. The polymer main chain is aggregated above the cloud point temperature due to dehydration in water, although it is soluble in water because of sufficient hydration at temperatures lower than the cloud point, so there is a cold "lower critical solution temperature" (LCST). It is well known that the LCST of poly(*N*-isopropyl acrylamide) (PNIPAM) is 32 °C, which is very close to physiological temperatures.[10] However, it is important to create novel thermoresponsive polymer materials besides PNIPAM, to develop a variety of 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) (OEG) units have been reported. Furthermore, poly(vinylcaprolactam),[19] poly(*N*-vinylisobutyramide),[20,21] and some other polysaccharides and polypeptides have also been investigated, and their applications studied. Once well-designed polymer main chains are produced, it is possible to use them in various polymer structures to form materials such as micelles and gels.

Star-shaped polymers are an interesting polymer structure, in which many polymer chains are attached to a central core, and they have the characteristics of branched polymers as well as spherical morphology.[22,23] The multifunctional initiator method, in which branch polymers are elongated from initiators bearing many initiator groups, and the arm-first method, in which pre-made branch polymers are combined with coupling agents, are well-known methods for the syn-

Division of Materials Science, Graduate School of Science and Technology, Nara Institute of Science and Technology, 8916-5 Takayama-cho, Ikoma, Nara 630-0192, Japan. E-mail: tando@ms.naist.jp, ajiro@ms.naist.jp; Tel: +81(0)743-72-5508

†Electronic supplementary information (ESI) available: Schemes S1–S9 for polymer synthesis, Fig. 1, 3, 4, 6, 8, 10, 12, 14, and 16 for SEC curves and ¹H NMR spectra of the obtained polymers, Fig. 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 Fig. 18 for photo images of thermoresponsive behavior of heteroarm star-shaped polymer coating. See DOI: https://doi.org/10.1039/d2py01518h

thesis of star-shaped polymers. Star-shaped polymers with hydrophobic components in the core and hydrophilic polymers in the outer shell are called unimolecular micelles, in comparison to conventional micelles that are formed by the weak physical aggregation of amphiphilic polymers. The structural stability of star-shaped polymers is expected to be useful for applications such as gene and drug delivery and removal of organic compounds from water.
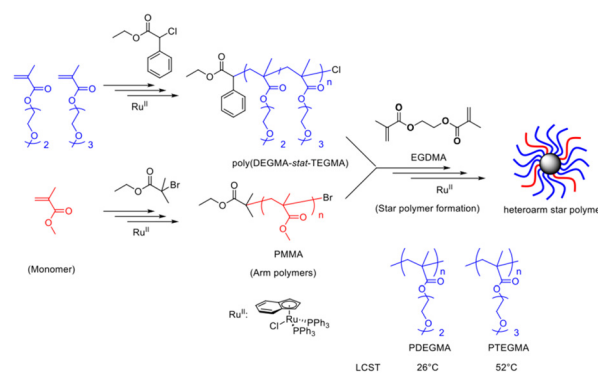
The properties of star-shaped polymers with thermoresponsive moieties have been investigated. It has been reported that the LCST values can changed depending on the number of arms,[24,25] so it is important to design and control the polymer structures for thermoresponsive star-shaped polymers. By evaluating thermoresponsive star-shaped polymers obtained by multifunctional initiator methods, the effect of the number of branches on the LCST and the construction of precise thermoresponsive networks using these polymers has been reported. Four-armed types, such as the simple star-shaped polymers, have been investigated using porphyrin[26,27] and benzene.[28] These four-arm types can be applied for gel formation as well.[29,30] Various kinds of thermoresponsive polymers have been introduced into 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 various polymer materials to be created. For example, the block copolymer of NIPAM and N-methylolacrylamide was synthesized for the arm of a star-shaped polymer,[35] and utilized as a drug delivery system. The block copolymers of acrylate and methacrylates with OEG groups were also prepared by atom transfer radical polymerization (ATRP) for use in producing star-shaped polymers,[36] as well as anionic polymerization methods.[37] Interestingly, the helical structures of the arm part were also designed as block copolymers of isocyanide.[38] Unlike simple linear polymers, the star-shaped polymer possesses unique polymer structures, so it could be utilized for some applications by tuning the properties using copolymers. For example, hydrogels with thermoresponsive moieties at cross-linking points,[39] cell adhesive control,[40] and 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 structure. 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 behavior, such as Janus particles. Lodge and co-workers reported that heteroarm star-shaped polymers consisting of three types of hydrophilic/hydrophobic/fluorinated polymer chains from hamburger-like aggregates in water can encapsulate different compounds at each aggregation site.[42,43] Chen and co-workers utilized polycaprolactone as a hydrophobic arm and polymethacrylate with OEG as a hydrophilic arm to prepare a pH-responsive heteroarm star-shaped polymer.[44]

We have previously reported heteroarm star-shaped polymers composed of hydrophilic poly(hydroxymethyl methacrylate) (PHEMA) and hydrophobic poly(methyl methacrylate) (PMMA), using Ru catalyst living radical polymerization technique as an interfacial functional material.[45] When the star-shaped polymer is coated on polyethylene terephthalate (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. The surface therefore exhibits a larger bubble contact angle in water than the linear PHEMA-coated surface, greatly reducing the adhesion of *Escherichia coli* and platelets. Therefore, by assigning roles to each branch polymer characteristic of the heteroarm, it is possible to functionalize the surface by a facile method.

Recently, several examples of thermoresponsive heteroarm star-shaped polymers have been reported. For example, Brooks, Kizhakkedathu, and co-workers reported RAFT and ATRP combination to produce thermoresponsive heteroarm star-shaped polymers with N,N-dimethylacrylamide and NIPAM.[46] Furthermore, Plamper and co-workers selected the poly(ethylene oxide), poly(propylene oxide), and poly(N,N-dimethylaminoethyl methacrylate) as heteroarms for thermoresponsive star-shaped polymers.[47] Recently, microflow systems have been utilized to tune the star-shaped polymer with heteroarms for methacrylate with OEG units and N,N-dimethylaminoethyl acrylate.[48] Aoshima and co-workers systematically synthesized thermoresponsive heteroarm star-shaped polymers,[49,50] including fluorine-containing block copolymers and heteroarm star-shaped polymers with poly(vinyl ether) backbones. However, to the best of our knowledge, there are no examples of thermoresponsive heteroarm star-shaped polymers with methacrylate with OEG chains as the hydrophilic arm and PMMA as the hydrophobic arm, using Ru catalyst.

In this study, we first designed the thermoresponsive star-shaped polymer with heteroarm structure based on the methacrylates using living radical polymerization with Ru catalyst and the arm-first method (Scheme 1). We selected diethylene glycol methyl ether methacrylate (DEGMA) and triethylene glycol methyl ether methacrylate (TEGMA) as thermo-

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

responsive moieties, and methyl methacrylate (MMA) as a hydrophobic moiety. For comparison of the star-shaped polymers, the thermoresponsive properties of the 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 from 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%) were purchased from Sigma-Aldrich Co. LLC (St Louis, USA). Tri-*n*-butylamine (*n*-Bu$_3$N, ≥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 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^{-1} at 40 °C using three columns (TSKgel GMH$_{HR}$-M, 7.8 mm internal diameter (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 dimethyl formamide (DMF) containing 10 mL LiBr. LCST was measured using the JASCO V-550 ETC-505S and JSSCO V-550 ETC-505T system. The samples for LCST measurement were prepared at 2 mg mL^{-1} concentration and the transmittance was measured using 500 nm light with a change in temperature rate of 1 °C min^{-1}. Surface contact angles were measured using a goniometer (DM-501Hi, Kyowa Interface Science Co., Ltd, Japan).

Synthesis of triethylene glycol methyl ether methacrylate (TEGMA)

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) were added to a round-bottom flask containing a stirring bar 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, R_f = 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, 3H), 1.94 (s, 3H).

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 vacuum and filling with Ar, toluene (58.3 mL), 430 mM solution of *n*-Bu$_3$N in toluene (0.8 mmol, 1.86 mL), TEGMA (80 mmol, 18.1 mL), and 490 mM solution of ECPA in toluene (0.80 mmol, 1.63 mL) were added in that 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 analyzing 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 eluent to remove the catalyst, followed by evaporation. The dried polymer was dissolved in CH$_2$Cl$_2$ to 20 wt% 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$_2$O as the solvent. During the ^{1}H NMR measurement, the water peak was eliminated. Yield: 10.4 g (69.7%). PDEGMA was also prepared using a 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), and 430 mM solution of *n*-Bu$_3$N in toluene (0.123 mM, 0.419 mL) 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 the tube was 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 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 using a 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$_3$N 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-containing Schlenk tube. Then, about 0.1 mL of the initial polymerization solution was taken as an initial polymerization solution and the remainder 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 eluent to remove the catalyst, followed by evaporation. The dried polymer was dissolved in CH$_2$Cl$_2$ to 20 wt% 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 using a 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$_3$N solution in toluene (0.10 mmol, 0.232 mL), and 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 the remainder was 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 eluent to remove the catalyst, followed by evaporation. The dried polymer was dissolved in CH$_2$Cl$_2$ to 20 wt% 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 using a similar procedure. Yield: 0.275 g (15.2%).

Surface contact angle measurement

The star-shaped polymer-coated surface was prepared by spin coating on a PET film (10 mm × 10 mm × 0.2 mm) with 50 μL solution of the heteroarm star-shaped P(DEGMA-*stat*-TEGMA)/ PMMA (1.0 wt% in THF), and dried in vacuum for 3 h. The polymer-coated surface was incubated in water for 12 h prior to 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 three times and the data are presented as the average of the measurements. Errors were determined through evaluation of the standard deviation of 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 were temperature responsive under physiological conditions.

Synthesis of linear and star PDEGMA and their thermoresponsive properties

First, polymerization of DEGMA was carried out by the Ru-catalyzed living radical polymerization using ethyl 2-chloro-2-phenylacetate (ECPA, initiator), Ru(Ind)Cl(PPh$_3$)$_2$ (catalyst), and *n*-Bu$_3$N (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. The DP$_n$ of the obtained PDEGMA was 82, indicating that the number-averaged molecular weight (M_n) was 15 800, which was in good agreement with the theoretical value expected from the monomer to initiator initial concentration ratio ([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 the PDEGMA macroinitiator in the presence of Ru(Ind) complex catalyst and *n*-Bu$_3$N 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 poly-

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

Entry	Polymer type	DEGMA : MMA[a] (mol)	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 0.2 wt% polymer solution. [d] Determined by unit concentration of the initial reaction solution. [e] Determined by SEC-RALS. [f] Insoluble in water.

mers. 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 (right angle light scattering), whereby the significant difference in M_n supports the star-shaped polymer formation. Since EGDMA incorporated in the star-shaped PDEGMA is hydrophobic and about 10 mol% of EGDMA to PDEGMA is incorporated, the effect of the 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 polymers, the LCST was evaluated by transmittance of 500 nm light using 2 mg mL^{-1} aqueous solution. In this study the LCST is defined as the point at which the transmittance is 50%. 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 incorporation of hydrophobic MMA, and the LCSTs of PDEGMA-b-PMMA and P(DEGMA-stat-MMA) 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 copoly-

mers 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 the 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 previously.[24,25]

Synthesis of linear and star PTEGMA and their thermoresponsive properties

Similar to DEGMA polymers, linear PTEGMA, block and statistical copolymers with MMA, and star-shaped PTEGMA were synthesized. The homopolymers and copolymers had M_n values 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 ~210 000 and with a $Đ$ of 1.31 was obtained by SEC-RALS measurements.

The LCSTs of the series of 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 approximately 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, at 46 °C and 43 °C, respectively. This was the same trend as for the LCST measurements of PDEGMA. On the other hand, star-shaped PTEGMA could be dissolved in water and LCST measurements were possible, with a value of 43 °C, which is close to the value for the statistical copolymer. These results indicate that the order of LCST

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

Entry	Polymer type	TEGMA : MMA[a] (mol)	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 0.2 wt% polymer solution. [d] Determined by unit concentration of the initial reaction solution. [e] Determined by SEC-RALS.

for methacrylate polymers with short ethylene glycol side chains and copolymers with MMA tends 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 an 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 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_n values of 13 000–23 000 and Đ of about 1.2 were obtained by systematically changing the initial DEGMA/TEGMA ratio (Table 3). The DEGMA/TEGMA ratio in the obtained copolymers was also close to the initial ratio.

The LCSTs were 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, the LCST could be controlled at 32–37 °C, a value that is near the physiological temperature. The relationship between molar and weight content of TEGMA in P(DEGMA-*stat*-TEGMA) and LCST is shown in Fig. 1. This relationship is roughly linear, but in regions of low TEGMA content the LCST was slightly higher than predicted by 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] where a linear relationship between molar content and LCST was observed, 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 properties

A heteroarm star-shaped polymer with a thermoresponsive P(DEGMA-*stat*-TEGMA), consisting of DEGMA : TEGMA =
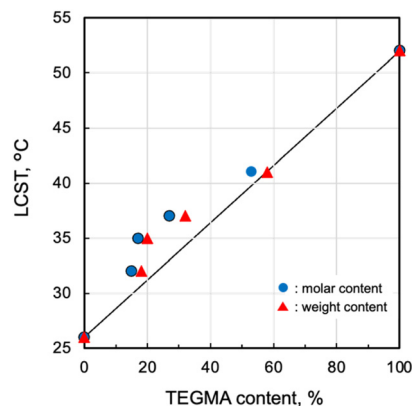

Fig. 1 Dependence of LCST on TEGMA content for P(DEGMA-*stat*-TEGMA). Circle: molar content; triangle: weight content.

83 : 17 composition, and hydrophobic PMMA as arm polymers was synthesized. The LCST of this P(DEGMA-*stat*-TEGMA) is 35 °C, which is near to the physiological temperature. The arm polymer of PMMA was synthesized by living radical polymerization using ethyl 2-bromo isobutyrate as initiator with Ru complexes to obtain a living polymer with M_n of 8200 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 (Fig. 2A). The conversion to star-shaped polymer was roughly calculated from the peak area and found 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. The 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

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

Entry	DEGMA : TEGMA[a] (mol%)	DEGMA : TEGMA[b] (wt%)	M_n[c]	Đ[c]	LCST[d], °C
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 0.2 wt% polymer solution.
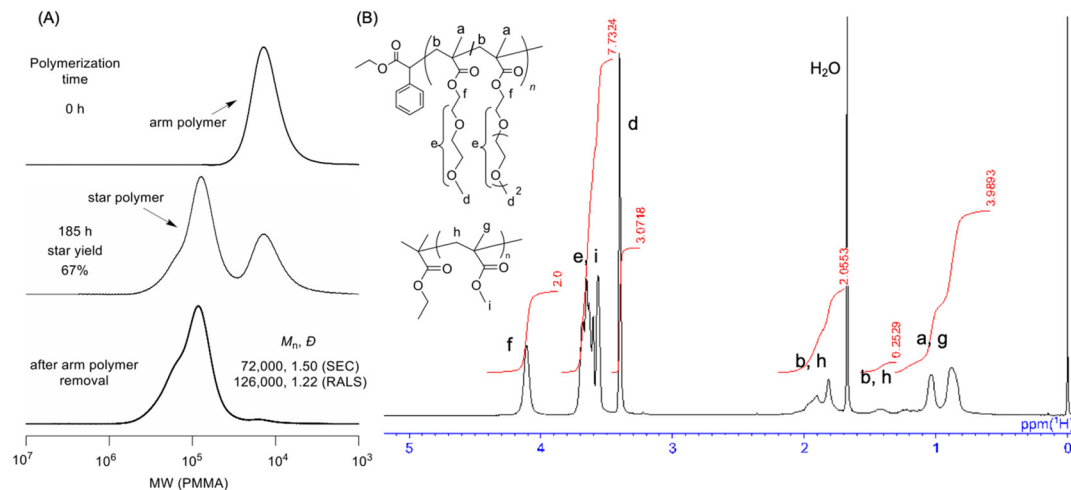
Fig. 2 (A) SEC curves of P(DEGMA-*stat*-TEGMA)/PMMA (arm polymer) and the obtained heteroarm star-shaped polymer before and after arm polymer removal. (B) ^{1}H NMR spectrum of the obtained heteroarm star-shaped polymer.

components, strongly suggesting the formation of heteroarm star-shaped polymers (Fig. 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 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 the 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 using the water contact angle. However, measurement of the water contact angle under ambient atmosphere was difficult because water droplets evaporate relatively quickly at 40 °C, which is expected to be above the LCST for this polymer. In addition, hydrophobic PMMA chains are exposed on the surface in the dry conditions 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 (Fig. 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
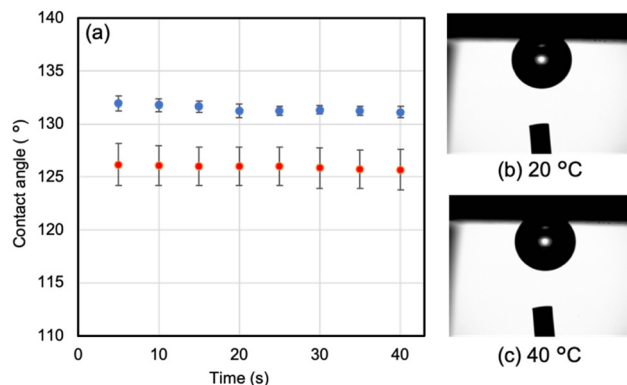

Fig. 3 (a) Contact angles of air-in-water (captive bubble) for the P(DEGMA-*stat*-TEGMA)/PMMA heteroarm star-shaped polymer-coated surface at 20 and 40 °C. Photographic images of the captive bubbles at (b) 20 °C and (c) 40 °C.

transparent at low temperatures of 20 °C and cloudy at high temperatures of >40 °C, and this response was reversible (Fig. S18†). This suggests heteroarm star-shaped polymers as a promising material for creating functional surfaces that are insoluble in water, yet thermoresponsive in water.

Conclusions

In conclusion, we designed and synthesized a 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. The 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. The LCST could be controlled to physiological temperatures by copolymerization of DEGMA and TEGMA. The heteroarm star-shaped polymer-coated surface exhibited thermoresponsivity. This polymer is a 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

References

1 A. Bordat, T. Boissenot, J. Nicolas and N. Tsapis, *Adv. Drug Delivery Rev.*, 2019, **138**, 167.

2 F. Doberenz, K. Zeng, C. Willems, K. Zhang and T. Growth, *J. Mater. Chem. B*, 2020, **8**, 607.

3 Z. Ding, G. Chen and A. S. Hoffman, *Bioconjugate Chem.*, 1996, **7**, 121.

4 I. Tan, F. Roohi and M. M. Titirici, *Anal. Methods*, 2012, **4**, 34.

5 N. Badi, *Prog. Polym. Sci.*, 2017, **66**, 54.

6 T. J. Murdoch, B. A. Humphreys, E. C. Johnson, G. B. Webber and E. J. Wanless, *J. Colloid Interface Sci.*, 2018, **526**, 429.

7 K. Nagase, T. Okano and H. Kanazawa, *Nano-Struct. Nano-Objects*, 2018, **16**, 9.

8 V. Pertici, T. Trimaille and D. Gigmes, *Macromolecules*, 2020, **53**, 682.

9 M. R. Matanovic, J. Kristl and P. A. Grabnar, *Int. J. Pharm.*, 2014, **472**, 262.

10 M. Heskins and J. E. Guillet, *J. Macromol. Sci., Chem.*, 1968, **2**, 1441.

11 S. Aoshima and S. Kanaoka, *Adv. Polym. Sci.*, 2008, **210**, 169.

12 B. Verdonck, J. F. Gohy, E. Khousakoun, R. Jerome and F. D. Prez, *Polymer*, 2006, **46**, 9899.

13 G. Vancoillie, D. Frank and R. Hoogenboom, *Prog. Polym. Sci.*, 2014, **39**, 1074.

14 T. Ishizone, A. Seki, M. Hagiwara and S. Han, *Macromolecules*, 2008, **41**, 2963.

15 S. Yamamoto, J. Pietrasik and K. Matyjaszewski, *J. Polym. Sci., Part A: Polym. Chem.*, 2008, **46**, 194.

16 J. B. Silva, P. Haddow, M. L. Bruschi and M. T. Cook, *J. Mol. Liq.*, 2022, **346**, 117906.

17 R. C. Pratt, F. Nederberg, R. M. Waymouth and J. L. Hedrick, *Chem. Commun.*, 2008, 114.

18 H. Ajiro, Y. Takahashi and M. Akashi, *Macromolecules*, 2012, **45**, 2668.

19 M. N. Mohammed, K. B. Yusoh and J. H. B. H. Shariffuddin, *Mater. Express*, 2018, **8**, 21.

20 M. Akashi, S. Nakano and A. Kishida, *J. Polym. Sci., Part A: Polym. Chem.*, 1996, **34**, 301.

21 K. Suwa, Y. Wada, Y. Kikunaga, K. Morishita, A. Kishida and M. Akashi, *J. Polym. Sci., Part A: Polym. Chem.*, 1997, **35**, 1763.

22 G. Kraus and J. G. Gruver, *J. Polym. Sci., Part A: Gen. Pap.*, 1965, **3**, 105.

23 J. M. Ren, T. G. McKenzie, Q. Fu, E. H. H. Wong, J. Xu, Z. An, S. Shanmugam, T. P. Davis, C. Boyer and G. G. Qiao, *Chem. Rev.*, 2016, **116**, 6743.

24 T. Hashimoto, H. Matsui, M. Uruchisaki and T. Sakaguchi, *J. Polym. Sci.. Part A: Polym. Chem.*, 2015, **53**, 1094.

25 K. Zhu, R. Pamies, N. Al-Manasir, J. G. H. Cifre, J. G. Torre, B. Bystrom and A. L. Kjoniksen, *ChemPhysChem*, 2020, **21**, 1258.

26 W. Yuan and X. Chen, *RSC Adv.*, 2016, **6**, 6802.

27 S. Yusa, T. Endo and M. Ito, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 6838.

28 Y. Zhou, A. Ishikawa, R. Okahashi, K. Uchida, Y. Nemoto, M. Nakayama and Y. Nakayama, *J. Controlled Release*, 2007, **123**, 239.

29 Y. Hiei, K. Ohshima, M. Hara, T. Seki, T. Hoshino and Y. Takeoka, *Soft Matter*, 2022, **18**, 5204.

30 Y. Okaya, Y. Jochi, T. Seki, K. Satoh, M. Kamigaito, T. Hoshino, T. Nakatani, S. Fujinami, M. Takata and Y. Takeoka, *Macromolecules*, 2020, **53**, 374.

31 L. A. Picos-Corrales, A. Licea-Claverie, J. M. Cornejo-Bravo, S. Schwarz and K. F. Arndt, *Macromol. Chem. Phys.*, 2012, **213**, 301.

32 N. A. C. Lemus and A. L. Claverie, *Polymer*, 2018, **10**, 20.

33 S. Park, M. Zhong, T. Lee, H. Paik and K. Matyjaszewski, *ACS Appl. Mater. Interfaces*, 2012, **4**, 5949.

34 T. Kirila, A. Smirnova, A. Razina, A. Tenkovtsev and A. Filippov, *Polymer*, 2021, **13**, 1152.

35 N. Xu, X. Huang, G. Yin, M. Bu, X. Pu, X. Chen, X. Liao and Z. Huang, *RSC Adv.*, 2018, **8**, 15604.

36 A. Kowalczuk, B. Mendrek, I. Z. Miara, M. Libera, A. Marcinkowski, B. Trzebicka, M. Smet and A. Dworak, *Polymer*, 2012, **53**, 5619.

37 A. Hirao, R. Inushima, T. Nakayama, T. Watanabe, H. S. Yoo, T. Ishizone, K. Sugiyama, T. Kakuchi, S. Carlotti and A. Deffieux, *Eur. Polym. J.*, 2011, **47**, 713.

38 Q. Wang, B. F. Chu, J. H. Chu, N. Liu and Z. Q. Wu, *ACS Macro Lett.*, 2018, **7**, 127.

39 S. Ida, S. Toda, M. Oyama, H. Takeshita and S. Kanaoka, *Macromol. Rapid Commun.*, 2021, **42**, 2000558.

40 S. Park, H. Y. Cho, J. A. Yoon, Y. Kwak, A. Srinivasan, J. O. Hollinger, H. Paik and K. Matyjaszewski, *Biomacromolecules*, 2010, **11**, 2647.

41 S. Pal, M. R. Hill and B. S. Sumerlin, *Polym. Chem.*, 2015, **6**, 7871.

42 T. P. Lodge, A. Rasdal, Z. Li and M. A. Hillmyer, *J. Am. Chem. Soc.*, 2005, **127**, 17608.

43 Z. Li, M. A. Hillmyer and T. P. Lodge, *Macromolecules*, 2006, **39**, 765.

44 W. Wu, P. Yi, J. Zhang, Y. Cheng, Z. Li, X. Hao and Q. Chen, *Phys. Chem. Chem. Phys.*, 2019, **21**, 15222.

45 M. Totani, T. Ando, K. Terada, T. Terashima, I. Y. Kim, C. Ohtsuki, C. Xi, K. Kuroda and M. Tanihara, *Biomater. Sci.*, 2014, **2**, 1137.

46 K. Ranganathan, R. Deng, R. K. Kainthan, C. Wu, D. E. Brooks and J. N. Kizhakkedathu, *Macromolecules*, 2008, **41**, 4226.

47 A. A. Steinschulte, B. Schulte, S. Rutten, T. Eckert, J. Okuda, M. Moller, S. Schneider, O. V. Borisov and F. A. Plamper, *Phys. Chem. Chem. Phys.*, 2014, **16**, 4917.

48 L. Xiang, Z. Zhong, M. Shang and Y. Su, *Polymer*, 2022, **238**, 124383.

49 Y. Oda, T. Shibata, H. Tsujimoto, S. Kanaoka and S. Aoshima, *Polym. J.*, 2012, **44**, 541.

50 H. Shimomoto, D. Fukami, T. Irita, K. Katsukawa, T. Nagai, S. Kanaoka and S. Aoshima, *J. Polym. Sci., Part A: Polym. Chem.*, 2012, **50**, 1547.