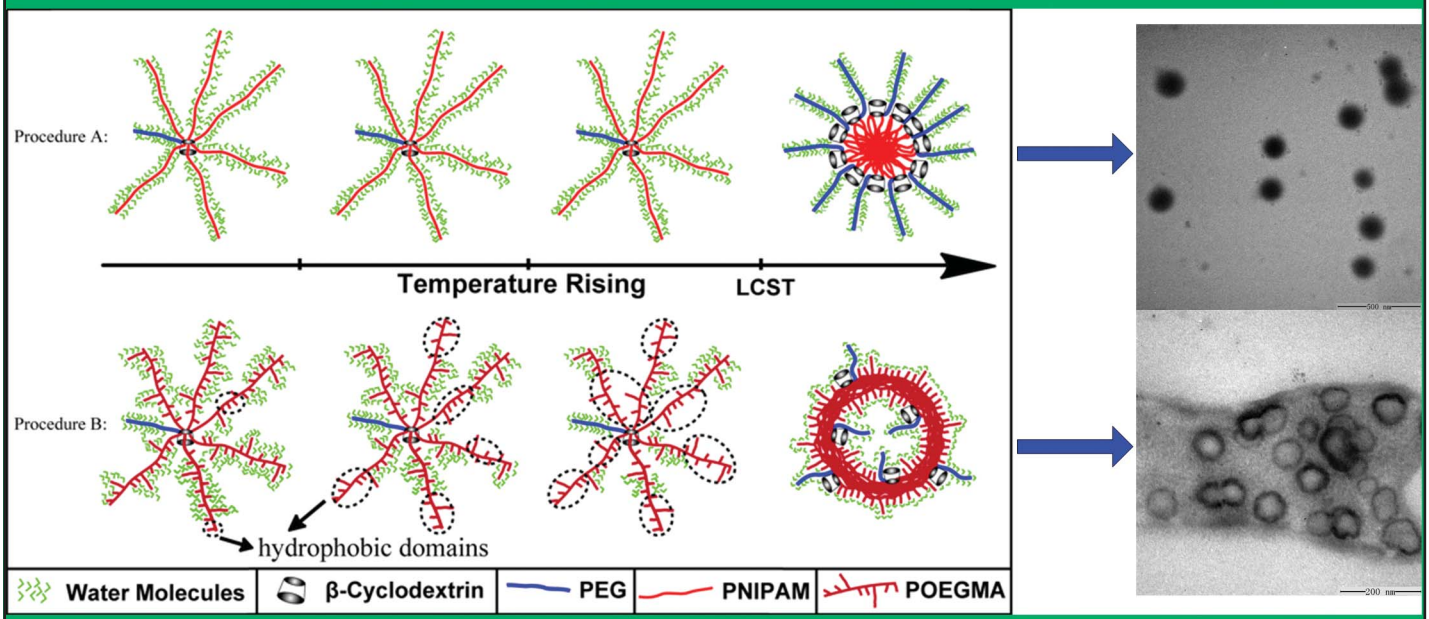

Showcasing research from the Xiaodong Fan and Wei Tian lab, University of Northwestern Polytechnical University.

Title: Miktoarm star polymers with poly(*N*-isopropylacrylamide) or poly(oligo(ethylene glycol) methacrylate) as building blocks: synthesis and comparison of thermally-responsive behaviors

Thermally-responsive miktoarm star polymers with poly(*N*-isopropylacrylamide) or poly(oligo(ethylene glycol) methacrylate) as building blocks exhibit different dehydration procedures. They can self-assemble into architecturally different nano-aggregates driven from the thermally-induced dehydration.

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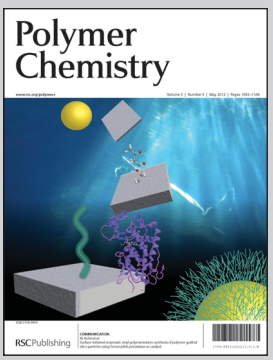

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PAPER

Miktoarm star polymers with poly(*N*-isopropylacrylamide) or poly(oligo(ethylene glycol) methacrylate) as building blocks: synthesis and comparison of thermally-responsive behaviors

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We synthesized two thermally-responsive miktoarm star polymers in which poly(*N*-isopropylacrylamide) (PNIPAM) or poly(oligo(ethylene glycol) methacrylate) (POEGMA) served as the thermosensitive building blocks. Firstly, linear methoxypolyethylene glycol (PEG) with β-cyclodextrin (β-CD) bearing about six chlorines as a terminal (PEG-CD-Cl_x, $x \approx 6$) was synthesized. Then, the thermally-responsive miktoarm star polymer, PEG-CD-$PNIPAM_x$ or PEG-CD-$POEGMA_x$, was achieved by atom transfer radical polymerization using *N*-isopropylacrylamide or oligo(ethylene glycol) methacrylate as the monomer and PEG-CD-Cl_x as the macroinitiator. The obtained miktoarm star polymers were comprised of a β-CD core, a PEG arm and about six PNIPAM or POEGMA arms. Furthermore, the thermally-responsive behaviors of the miktoarm star polymers were investigated by a combination of UV-vis spectroscopy, DLS, TEM, ^{1}H NMR, fluorescence spectroscopy and DCS. Above the LCST of the polymers in aqueous solution, PEG-CD-$PNIPAM_x$ can self-assemble into nano-structures with PNIPAM as the core and PEG as the corona, whereas PEG-CD-$POEGMA_x$ self-assembled into nano-architectures possessing hydrophilic surfaces which were constructed by the hydrated oligo(ethylene glycol) side chains of the POEGMA arms. The hydrophobic moiety of the nano-architectures was formed by the methacrylate backbone and the dehydrated oligo(ethylene glycol) side chains of POEGMA. Furthermore, it was found that the thermally-induced dehydration of PEG-CD-$PNIPAM_x$ is completely different from that of PEG-CD-$POEGMA_x$. For the former, the dehydration occurs abruptly and intensively near the LCST of PEG-CD-$PNIPAM_x$, whereas the dehydration for the latter is gradual and continuous throughout the whole temperature rise. The architecture of the nano-assemblies formed by PEG-CD-$PNIPAM_x$ or PEG-CD-$POEGMA_x$ was affected by the thermally-induced dehydration of the polymers.

Introduction

Miktoarm star polymers possess a three-dimensional branched architecture in which chemically different building blocks are linked to a single junction point.[1–10] Due to their unique structures, miktoarm star polymers usually exhibit interesting chemical and physical properties in solution or bulk, and special performances as compared with the corresponding linear block analogues.[8–36] Therefore, for the past decades, considerable attention has been paid to miktoarm star polymers.[1–39]

One of the most fascinating properties of miktoarm star polymers is the self-assembly of these polymers in selective solvents or under an outer stimulus.[8–36] Polymeric nano-assemblies with unique architectures and properties, such as micelles with a mixed core or corona, as well as nano-assemblies with multi-stimulus-responsive ability, have been easily constructed from miktoarm star polymers.[23–35] Normally, to endow a miktoarm star polymer with thermally-responsive ability, thermosensitive polymers are usually introduced as a building block into the stars. Poly(*N*-isopropylacrylamide) (PNIPAM), as an extensively studied thermosensitive polymer, has been successfully incorporated into various miktoarm star polymers[29–36] to provide thermosensitivity for the stars or the constructed nano-assemblies. Recently, a new class of thermosensitive polymer, poly(oligo(ethylene glycol) methacrylate) (POEGMA), which consists of a poly(methacrylate) backbone with very short ethylene glycol side chains, was reported to possess similar or even superior thermosensitivity than PNIPAM.[40,41] POEGMA has good phase transition reversibility and a defined lower critical solution temperature (LCST) in aqueous medium.[40,41] The biocompatibility of POEGMA is also excellent.[42,43] Moreover, by the copolymerization of two OEGMA monomers with different

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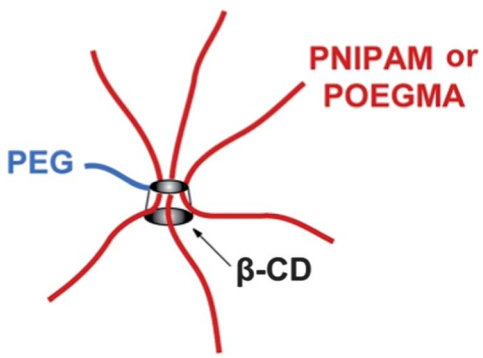
side-chain lengths and by varying the feed molar ratio of the comonomers, the LCST of POEGMA can be conveniently adjusted.[40] To date, POEGMA has been widely incorporated into dendrimers,[44] microgels,[45–48] block or star copolymers,[49–53] polymeric brushes[54–58] and gold surfaces,[59,60] which endow these materials with more interesting properties. However, very little work has been done on introducing POEGMA into miktoarm star polymers to serve as a thermosensitive component. Furthermore, although Lutz *et al.*[41] have compared the thermo-responsive properties of the linear POEGMA to those of the linear PNIPAM, the role of POEGMA in a thermally-induced self-assembly process, especially when POEGMA serves as a thermosensitive component of a heteropolymer, has still not been sufficiently studied and has not been compared with PNIPAM.

Based on the considerations above, we intend to synthesize two miktoarm star polymers in which PNIPAM or POEGMA serves as the thermosensitive component. A highly water-soluble linear polymer, such as methoxypolyethylene glycol (PEG) is expected to be introduced as another type of arm to provide hydrophilicity. To incorporate these polymeric chains into one macromolecule, β-cyclodextrin (β-CD) is selected as the core of the miktoarm star polymers. β-CD is a native cyclic oligomer composed of 7 glucopyranose units linked by α-1,4-glycosidic bonds.[61] The cyclic structure and its richness in activated hydroxyl groups make β-CD an ideal core material for the synthesis of star polymers.[62–66] Furthermore, according to the literature[37–39] and our previous work,[67–72] β-CD can also be modified into an excellent core component, even for miktoarm star polymers, *via* selective reactions at its hydroxyl groups.

Herein, by combining a click reaction with an atom transfer radical polymerization (ATRP), we grafted one PEG chain and about six PNIPAM or POEGMA chains onto a β-CD core, leading to the successful synthesis of two β-CD cored miktoarm star polymers, PEG-CD-PNIPAM$_x$ and PEG-CD-POEGMA$_x$ (Scheme 1). When subjected to an outer thermal stimulus, both of them can self-assemble into nano-sized aggregates. However, the architecture of the aggregates formed by PEG-CD-PNIPAM$_x$ was found to be different to that of PEG-CD-POEGMA$_x$. Therefore, the thermally-induced dehydration process of the two polymers was investigated. The relationship between the dehydration process and the architecture of the aggregates was attempted to be revealed and was discussed in this paper.



Scheme 1 An illustration of the miktoarm star polymers.

Experimental

Materials

PEG (M_n = 2000 Da) was purchased from Aldrich and was used as received. Mono-6-deoxy-6-azido-β-cyclodextrin (CD-N_3) was prepared according to the literature.[73] 2-Chloropropionic acid (97%, Alfa Aesar), propiolic acid (98%, Alfa Aesar), tris[2-(dimethylamino)ethyl]amine (Me_6TREN, 99%, Alfa Aesar), pyrene (Alfa Aesar, 99%), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA, 99%, Aldrich), 2-(2-methoxy-ethoxy)ethyl methacrylate (MEO_2MA, 98%, Aldrich), oligo(ethylene glycol) methacrylate ($OEGMA_{475}$, M_n = 475 g mol^{-1}, 98%, Aldrich), and *N*-isopropylacrylamide (NIPAM, 99%, Acros) were used as received. *N*,*N*′-Dicyclohexylcarbodiimide (DCC, 95%) and 4-dimethylaminopyridine (DMAP, 95%) were from Sinopharm Chemical Reagent Co., Ltd., Shanghai, China. CuCl was stirred with acetic acid overnight, then washed with ethanol and dried under vacuum at 25 °C. *N*,*N*-Dimethyl formamide (DMF), *N*,*N*-dimethylacetamide (DMAc), methyl ethyl ketone (MEK), isopropyl alcohol (IPA) and CH_2Cl_2 were dried with a 3 Å grade molecular sieve before use.

Synthesis of alkynyl-terminated PEG (PEG-alkynyl)

PEG (10 g, 5 mmol), DCC (2060 mg, 10 mmol) and DMAP (244 mg, 2 mmol) were dissolved in dried CH_2Cl_2 (30 mL). After cooling to 0 °C, propiolic acid (700 mg, 10 mmol dissolved in 10 mL dried CH_2Cl_2) was added dropwise to the solution. The mixture was then stirred at room temperature for 24 h. After filtration, the filtrate was precipitated into an excess of cold diethyl ether. The collected precipitate was dissolved in acetone and precipitated again with cold diethyl ether. The obtained PEG-alkynyl was dried under vacuum at 30 °C for 2 days. Yield: 82.8%. FT-IR (KBr): 3211 cm^{-1} (ν, ≡C–H); 2868 cm^{-1} (ν, C–H); 2112 cm^{-1} (ν, C≡C); 1714 cm^{-1} (ν, C=O); 1109 cm^{-1} (ν, C–O–C). ^{1}H NMR (DMSO-d_6, TMS): δ = 4.4–4.2 (2H, HC≡C–COOCH_2–); 3.8–3.3 (178H, –OCH_2CH_2O–); 3.3–3.2 (3H, CH_3O–).

Synthesis of β-CD-terminated PEG (PEG-CD)

The synthesis of PEG-CD was accomplished by the click coupling between CD-N_3 and PEG-alkynyl. A typical procedure was as follows. CD-N_3 (1160 mg, 1 mmol), PEG-alkynyl (3078 mg, 1.5 mmol), and PMDETA (173 mg, 1 mmol) were first dissolved in 18 mL of DMF. The solution was bubbled with nitrogen for 15 min. CuBr (143.5 mg, 1 mmol) was added to the mixture. The mixture was bubbled with nitrogen again for 30 min and sealed under N_2 atmosphere. The reaction was conducted at 60 °C for 24 h. The mixture was dialyzed (molecular weight cut off: 3000) against distilled water for 5 days. PEG-CD was obtained by lyophilization. Yield: 36.6%. FT-IR (KBr): 3385 cm^{-1} (ν, O–H); 2870 cm^{-1} (ν, C–H); 1720 cm^{-1} (ν, C=O); 1106 cm^{-1} (ν, C–O–C in PEG); 1035 cm^{-1} (ν, C–O–C in β-CD). ^{1}H NMR (DMSO-d_6, TMS): δ = 7.95 (1H, methine proton in 1,2,3-triazole); 5.7–6.0 (14H, 2,3-OH); 4.7–4.9 (7H, 1-H); 4.4–4.6 (6H, 6-OH, overlaps with HC≡C–COOCH_2–); 3.9–3.3 (178H, –OCH_2CH_2O–, overlaps with 2,3,4,5,6-H in β-CD); 3.3–3.2 (3H, CH_3O–, overlaps with 3,5,6-H in β-CD).

Synthesis of PEG and β-CD based macroinitiator (PEG-CD-Cl_x)

To a 25 mL round-bottomed flask in an ice-acetone bath, PEG-CD (643 mg, 0.2 mmol), DCC (247.2 mg, 1.2 mmol) and DMAP (29.3 mg, 0.24 mmol) were added and dissolved with 5 mL of dried DMAc. 2-Chloropropionic acid (130 mg, 1.2 mmol dissolved in 2 mL dried DMAc) was added dropwise to the flask. The mixture was then stirred at room temperature for 24 h. After filtration, the filtrate was precipitated into an excess of cold diethyl ether. The dissolution–precipitation cycle was repeated three times. After drying in a vacuum oven overnight at 30 °C, PEG-CD-Cl_x was obtained. Yield: 91.7%. FT-IR (KBr): 3356 cm^{-1} (ν, O–H); 2870 cm^{-1} (ν, C–H); 1745 cm^{-1} (ν, C=O); 1103 cm^{-1} (ν, C–O–C in PEG); 1039 cm^{-1} (ν, C–O–C in β-CD). ^{1}H NMR (DMSO-d_6, TMS): δ = 7.9 (1H, methine proton in 1,2,3-triazole); 6.1–5.7 (14H, 2,3-OH); 5.0–4.8 (7H, 1-H); 4.8–4.6 (6H, –CH_2OOC–CH(CH_3)Cl); 4.6–4.4 (6H, –CH_2OOC–CH(CH_3)Cl, overlaps with HC≡C–COOCH_2–); 4.4–4.1 (6H, –CH(CH_3)Cl); 3.9–3.3 (178H, –OCH_2CH_2O–, overlaps with 2,3,4,5-H in β-CD); 3.3–3.2 (3H, CH_3O–, overlaps with 3,5-H in β-CD); 1.7–1.4 (36H, –CH(CH_3)Cl).

Synthesis of β-CD cored miktoarm star polymers: PEG-CD-PNIPAM$_x$ and PEG-CD-POEGMA$_x$

Two β-CD cored miktoarm star polymers: PEG-CD-PNIPAM$_x$ and PEG-CD-POEGMA$_x$, were synthesized by ATRP using PEG-CD-Cl_x as the macroinitiator. The typical procedure for synthesizing PEG-CD-PNIPAM$_x$ was as follows. A mixture of PEG-CD-Cl_x (55 mg, 0.015 mmol), NIPAM (1220 mg, 10.8 mmol) and Me_6TREN (20.7 mg, 0.09 mmol) in 5 mL of IPA–MEK (4 : 1, v/v) was bubbled with nitrogen gas for 15 min; CuCl (9 mg, 0.09 mmol) was then added. The solution was bubbled with nitrogen gas again for 30 min and sealed under N_2 atmosphere. The polymerization was conducted at room temperature for 4 h and terminated by exposing to air and diluting with THF. After passing though a column of neutral alumina for the removal of the copper catalyst and evaporating most of the solvent, the residue was precipitated into an excess of diethyl ether. The product (PEG-CD-PNIPAM$_x$) was purified by repeating the precipitation and dried in a vacuum oven overnight at 30 °C. Yield: 41%. ($M_{n,SEC}$ = 87 800g mol^{-1}, M_w/M_n = 1.09).

The synthesis of PEG-CD-POEGMA$_x$ was similar to that of PEG-CD-PNIAPM$_x$. A mixture of PEG-CD-Cl_x (55 mg, 0.015 mmol), MEO_2MA (2030 mg,10.8 mmol), $OEGMA_{475}$ (513 mg, 1.08 mmol), PMDETA (15 mg, 0.09 mmol) and MEK (4 mL) was bubbled with N_2 for 15 min. CuCl (9 mg, 0.09 mmol) was then introduced. After bubbling with N_2 for another 30 min, the polymerization was conducted at room temperature for 4 h. The mixture was diluted with THF and passed though a neutral alumina column. After concentration and precipitation by petroleum ether, the sticky solid was dissolved in distilled water and dialyzed (molecular weight cut off: 3500) for 5 days. PEG-CD-POEGMA$_x$-**1** (641 mg) was obtained by lyophilization. By varying the molar ratio of MEO_2MA and $OEGMA_{475}$ to 20 : 1 or 30 : 1, two counterparts of PEG-CD-POEGMA$_x$-**1** (named as PEG-CD-POEGMA$_x$-**2**, PEG-CD-POEGMA$_x$-**3**) were also obtained.

Investigation of the thermally-responsive self-assembly of the miktoarm star polymers

The LCST of the miktoarm star polymers was determined by UV-vis spectroscopy (Shimadzu UV-2550 model) first. The transmittance of the polymeric aqueous solutions (1 mg mL^{-1}) was recorded at temperatures ranging from 25 °C to 50 °C. The temperature corresponding to the onset of the decrease in transmittance was defined as the LCST.

The self-assembly process of the miktoarm star polymers was revealed by dynamic light scattering (DLS) and transmission electron microscopy (TEM). DLS measurements were carried out by a Malvern Zetasizer Nano ZS instrument. The DLS data of the polymeric solutions (0.2 mg mL^{-1} for PEG-CD-PNIPAM$_x$ and 0.5 mg mL^{-1} for PEG-CD-POEGMA$_x$) at 25 °C, 37 °C, 42 °C and 50 °C were recorded. Each sample was kept at a predetermined temperature for 3 min before data collection. TEM observations were conducted on a Hitachi H-600 electron microscope at an acceleration voltage of 75 kV. The samples were prepared by placing 10 μL of polymer aqueous solution on copper grids in a biochemical incubator thermostatted at 25 °C (or 50 °C). The samples prepared at 25 °C were stained with phosphotungstic acid.

The architecture of the assemblies formed by the miktoarm star polymers was revealed by ^{1}H NMR. The polymer concentration in D_2O was set as 0.2 mg mL^{-1} for PEG-CD-PNIPAM$_x$ and 0.5 mg mL^{-1} for PEG-CD-POEGMA$_x$, which was equal to the concentration used in DLS measurements and TEM observations.

The thermally-responsive behaviors of the polymers were also explored by fluorescence spectroscopy (Hitachi F-4600) and differential scanning calorimetry (DSC, Model MDSC2910, TA Instruments). The emission spectra of pyrene aqueous solution (6×10^{-6} mol L^{-1}) in the presence of miktoarm star polymers at various temperatures were recorded from 370 to 650 nm with an excitation wavelength of 350 nm. In the DSC measurements, 50 mg mL^{-1} aqueous samples were scanned from 0 to 50 °C at a heating rate of 1 K min^{-1}.

Characterization

Fourier transform infrared (FT-IR) spectra were recorded on a NICOLET iS10 IR spectrometer. The ^{1}H NMR spectra were conducted on a Bruker Avance 300 spectrometer (Bruker Bio-Spin, Switzerland) operating at 300 MHz (^{1}H) in DMSO-d_6 or D_2O. The molecular structure parameters of the miktoarm star polymers were determined on a DAWN EOS size exclusion chromatography/multiangle laser light scattering (SEC/MALLS). HPLC grade DMF containing LiCl (0.01 mol L^{-1}) (at 40 °C) was used as eluent at a flow rate of 0.5 mL min^{-1}. A Waters 515 pump and a differential refractometer (Optilab rEX) were used.

Results and discussion

Synthesis of the macroinitiator (PEG-CD-Cl_x)

As shown in Scheme 2, the synthesis of the miktoarm star polymers started from the esterification reaction of PEG with

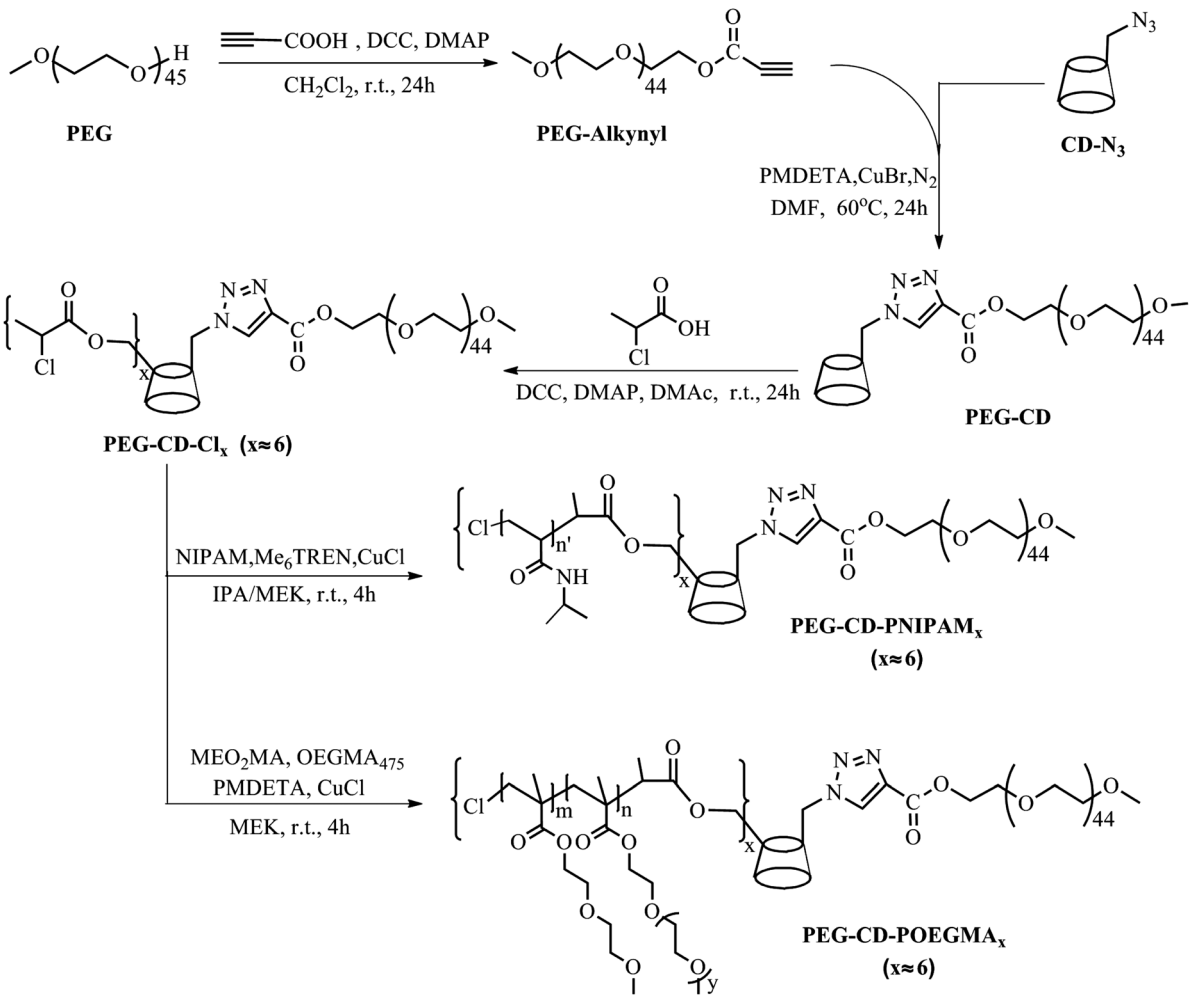
propiolic acid. DCC/DMAP was used to activate or catalyze the reaction.

Fig. 1(I) shows the ^{1}H NMR spectrum of the resultant PEG-alkynyl. The peak of proton g shifts to 4.2, as its adjacent group changes from hydroxyl to ester. The calculated peak integral ratio of proton a to g was 86, demonstrating that the degree of esterification is up to 98%.

Moreover, in the FT-IR spectrum of PEG-alkynyl (Fig. 2(b)), the disappearance of the stretching vibration peak of the hydroxyl group at 3443 cm^{-1}, together with the appearance of the characteristic absorption peaks of alkynyl and ester groups (2111 cm^{-1}, $\nu_{C\equiv C}$; 3218 cm^{-1}, $\nu_{C\equiv C-H}$ and 1715 cm^{-1}, $\nu_{C=O}$) suggest that the terminal hydroxyl groups of PEG completely reacted with propiolic acid.

Next, the click reaction between CD-N_3 and an excess of PEG-alkynyl afforded β-CD terminated PEG (PEG-CD). Unreacted CD-N_3 and PEG-alkynyl were attempted to be removed by dialysis. Fig. 1(II) shows the ^{1}H NMR spectrum of PEG-CD. Characteristic signals for β-CD at $\delta = 4.5$, 4.8, 5.7 and the proton peak of the 1,2,3-triazole ring at $\delta = 7.9$ appear, indicating the occurrence of the 1,3-dipolar cycloaddition reaction. The signals of 3,5,6-H (protons on C-3, C-5 and C-6 position of β-CD) and 2,4-H overlap with the ones of the methylene protons and the methoxyl protons in PEG in the region of $\delta = 3.40$–4.10 and $\delta = 3.20$–3.28, respectively. Therefore, the chemical structure of PEG-CD could not be assessed by ^{1}H NMR integration. However, the signal of proton g shifts from $\delta = 4.3$ to $\delta = 4.5$, as described in the literature,[83] and overlaps with the signal resonated by 6-OH (the hydroxyl proton on the C-6 position of β-CD). This low field shift can be ascribed to their adjacent group changing from the alkynyl-ester conjugated system to the ester-(triazole ring) system. Therefore, the complete disappearance of the proton g peak from $\delta = 4.3$ means that the excess PEG-alkynyl was completely removed. Moreover, in the FT-IR spectrum of PEG-CD (Fig. 2(c)) the stretching vibration peak of the hydroxyl re-emerges, suggesting that β-CD was bonded to the PEG end. Meanwhile, the characteristic absorption of the azido group at 2104 cm^{-1} and those of the alkynyls at 2111 cm^{-1} and 3218 cm^{-1} disappear, which further confirms the complete removal of the unreacted CD-N_3 and the excess of PEG-alkynyl.

To graft another type of polymeric chain to the β-CD moiety, selective esterification was first conducted on the β-CD moiety to introduce chlorine into PEG-CD. DCC and DMAP were used again to catalyze the esterification of 2-chloropropionic acid with the hydroxyl groups of β-CD. As a result, a PEG-CD based macroinitiator bearing several chlorines at the β-CD moiety,



Scheme 2 Synthetic routes for preparing PEG-CD-PNIPAM$_x$ and PEG-CD-POEGMA$_x$.

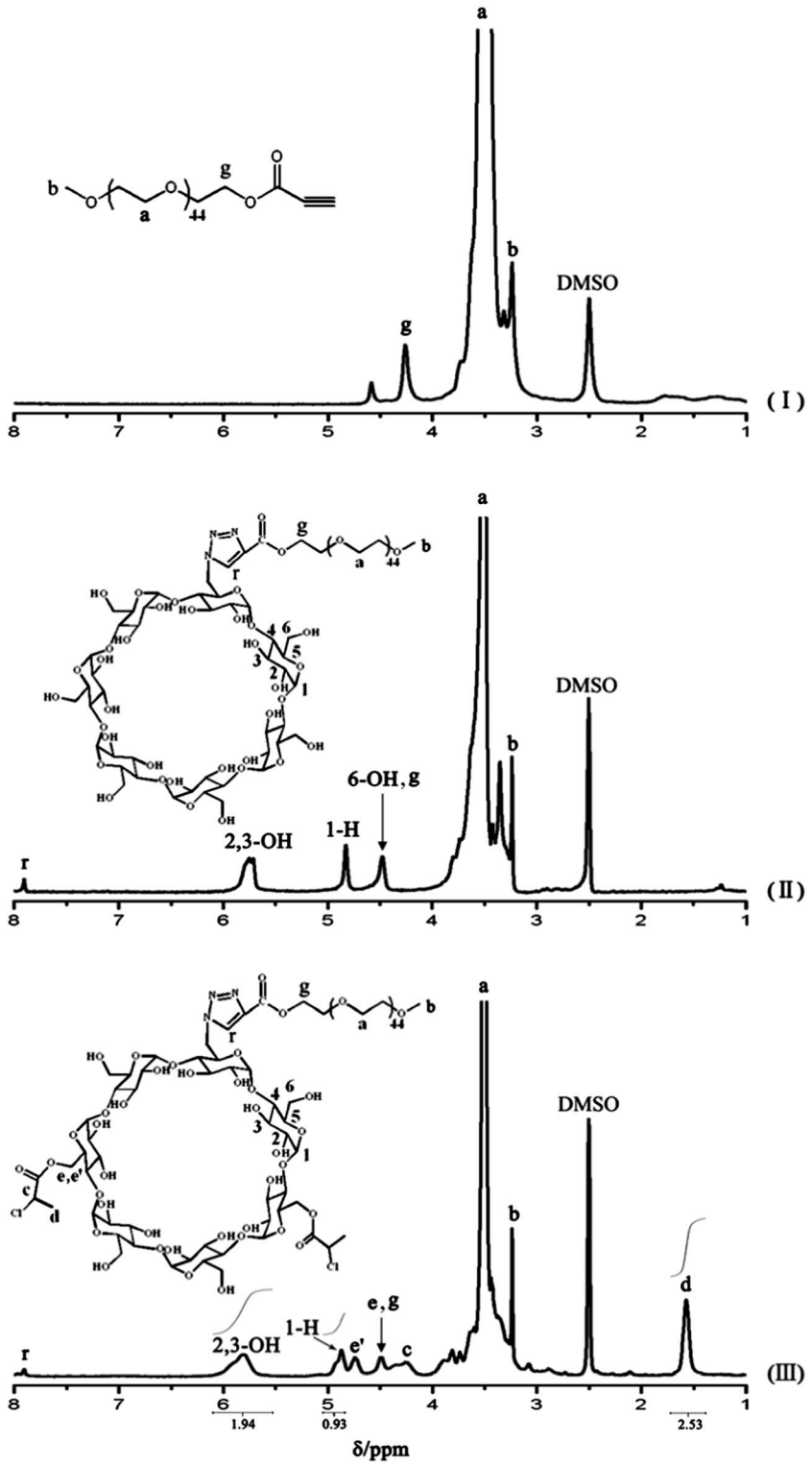


Fig. 1 ^{1}H NMR spectra of MPEG-alkynyl (I), MPEG-CD (II), MPEG-CD-Cl$_x$ (III).

PEG-CD-Cl$_x$, was obtained. Fig. 1(III) shows the ^{1}H NMR spectrum of PEG-CD-Cl$_x$. Signals associated with the 2-chloropropionate residue in PEG-CD-Cl$_x$ are clearly discernible at $\delta = 1.6$ (peak d) and 4.3 ppm (peak c), indicating that chlorine has been successfully introduced into PEG-CD *via* the esterification. Normally, the hydroxyls adjacent to C-2, -3 and -6 of β-CD (2,3,6-OH) are all able to react with 2-chloropropionic acid during a typical esterification procedure. However, due to the difference in activity among the 2,3,6-OHs, selective modification can be fulfilled by carefully controlling the reaction

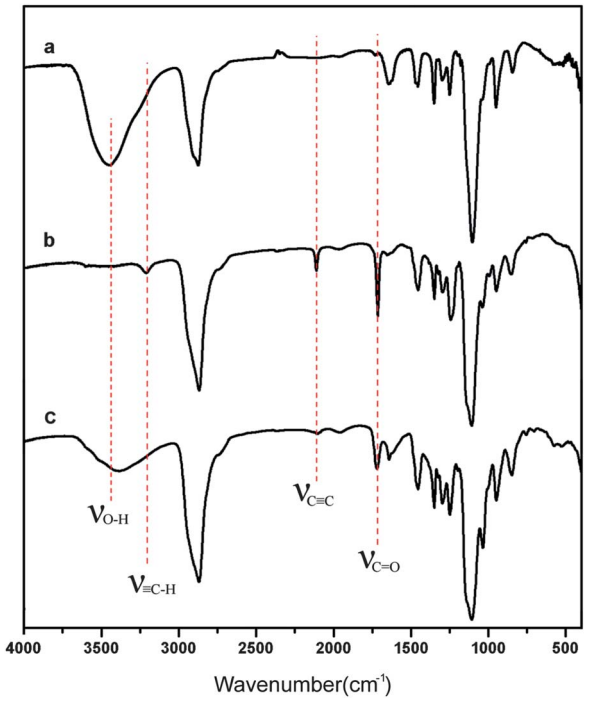


Fig. 2 FT-IR spectra of MPEG (a), MPEG-alkynyl (b) and MPEG-CD (c).

conditions.[74] Here, 6 equiv. 2-chloropropionic acid was used to react with PEG-CD in order that the esterification occurs at the 6-OHs of β-CD as much as possible. By integrating the proton peaks in Fig. 1(III), the molar ratio of 2,3-OH to 1-H (protons present at 1-C) was calculated as 2.08, indicating that the 2,3-OHs were not involved in the esterification and the 2-chloropropionic acid only reacted with the 6-OH of β-CD. Furthermore, the molar ratio of the 2-chloropropionate residue to the β-CD molecule was calculated as 5.97, suggesting that each β-CD molecule bears 6 chlorines on average and the degree of substitution (the value of x in PEG-CD-Cl$_x$) is about 6. In general, after the selective esterification, all of the 2,3-OH remained, whereas almost all 6-OHs were substituted by 2-chloropropionate groups. In addition, the peak integral ratio of proton e to e′ was calculated to be 1 and that of 1-H to e (or e′) was close to 7 : 6, which were consistent with the chemical structure of PEG-CD-Cl$_x$.

Synthesis of β-CD cored miktoarm star polymers: PEG-CD-PNIPAM$_x$ and PEG-CD-POEGMA$_x$

Using PEG-CD-Cl$_x$ ($x \approx 6$) as the macroinitiator and NIPAM as the monomer, a β-CD cored AB$_x$ type miktoarm star polymer, PEG-CD-PNIPAM$_x$, was synthesized by ATRP, where A and B represent PEG and PNIPAM, respectively.

Fig. 3 shows the ^{1}H NMR spectrum of PEG-CD-PNIPAM$_x$. The characteristic peaks of the PNIPAM arms at $\delta = 7.2$, 3.8, 1.1 and that of the PEG arm at $\delta = 3.5$ are clearly observed. The degree of polymerization (DP) of PNIPAM was determined as 741 by calculating the integral ratio of peak v (methine protons of PNIPAM side chain) to peak a (methylene protons of the PEG main chain). Thus, the molecular weight of PEG-CD-PNIPAM$_x$

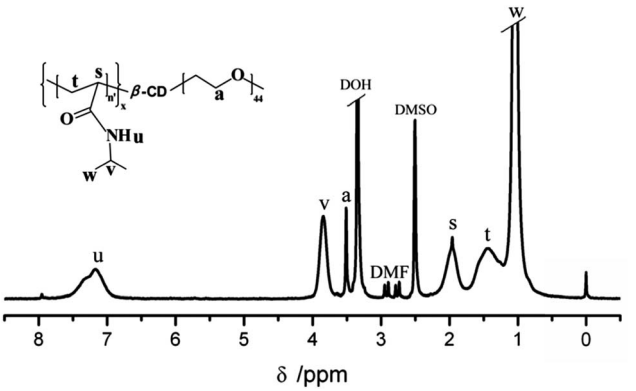


Fig. 3 ^{1}H NMR spectrum of PEG-CD-PNIPAM$_x$.

was calculated to be 87 300 from NMR analysis, which is in accordance with the result measured by SEC/MALLS (M_n = 87 800 g mol^{-1}, $M_w/M_n = 1.09$).

Initiated by PEG-CD-Cl$_x$, another series of β-CD cored miktoarm star polymers, PEG-CD-POEGMA$_x$, were synthesized using MEO$_2$MA and OEGMA$_{475}$ as comonomers.

Fig. 4 displays the ^{1}H NMR spectrum of PEG-CD-POEGMA$_x$-**1**. Besides the resonance peaks of the PEG and POEGMA segments in the range of $\delta = 0.5$–4.5, the characteristic signals of β-CD, together with that of the 1,2,3-triazole ring, can also be observed at $\delta = 4.8$, 5.5–6.0 and 7.7, indicating that PEG-CD-POEGMA$_x$ was successfully synthesized. Furthermore, by varying the feed molar ratio of MEO$_2$MA and OEGMA$_{475}$ as 10 : 1, 20 : 1 and 30 : 1, three counterparts of PEG-CD-POEGMA$_x$ were obtained in this paper.

The polymerization conditions and results were summarized in Table 1. As reported by Lutz *et al.*,[40] increasing the feed molar ratio of MEO$_2$MA to OEGMA$_{475}$ leads to a decrease in the LCST of PEG-CD-POEGMA$_x$. A detailed discussion of the LCST and other related thermally-responsive behaviors of the miktoarm star polymers are in our following text.

Thermally-induced self-assembly of the miktoarm star polymers

PEG is well known for its highly hydrophilic or water-soluble nature. Both PNIPAM and POEGMA can exhibit a LCST in

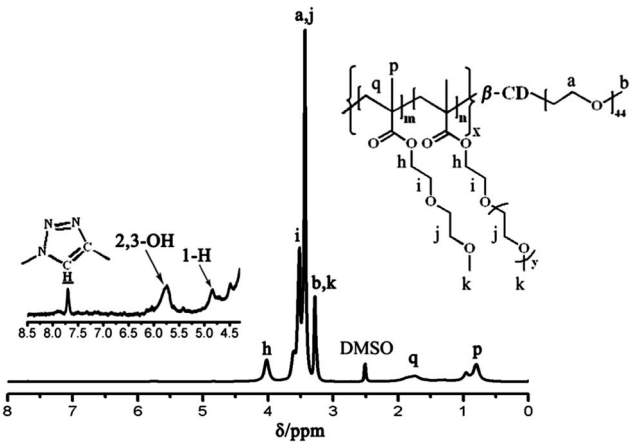


Fig. 4 ^{1}H NMR spectrum of PEG-CD-POEGMA$_x$-**1**.

Table 1 Polymerization conditions and results of PEG-CD-POEGMA$_x$

Samples	MEO_2MA/mg	$OEGMA_{475}$/mg	Feed molar ratio[a]	dn/dc[b]/mL g^{-1}	$M_{n,SEC}$[b]/g mol^{-1}	M_w/M_n[b]	LCST[c]/°C
PEG-CD-POEGMA$_x$-**1**	2030	513	10 : 1	0.0748	111700	1.01	41.0
PEG-CD-POEGMA$_x$-**2**	2030	257	20 : 1	0.0766	240600	1.09	34.6
PEG-CD-POEGMA$_x$-**3**	2030	171	30 : 1	0.0744	194000	1.10	32.6

[a] Molar ratio of MEO_2MA: $OEGMA_{475}$. [b] Measured by SEC/MALLS. [c] Measured by UV-vis.

aqueous solution. They are water-soluble and water-insoluble below and above their LCST.[41] Thus, the miktoarm star polymers, PEG-CD-PNIPAM$_x$ and PEG-CD-POEGMA$_x$, were expected to self-assemble into nano-sized aggregates or micelles in their aqueous solutions by altering the temperature. In our study, the thermally-induced self-assembly of the β-CD cored miktoarm star polymers was investigated in detail by a combination of UV-vis, DLS, TEM and ^{1}H NMR in D_2O.

(1) Determination of the LCST of the miktoarm star polymers. UV-Vis was first used to determine the LCST of the miktoarm star polymers. The results are shown in Fig. 5. A sharp decline in the solution transmittance can be observed with elevated temperature, indicating that the four miktoarm star polymers are all thermally-responsive. The LCST of PEG-CD-PNIPAM$_x$ was determined to be 33.5 °C, and those for PEG-CD-POEGMA$_x$-**1**, PEG-CD-POEGMA$_x$-**2** and PEG-CD-POEGMA$_x$-**3** were 41.0 °C, 34.6 °C and 32.6 °C, respectively.

(2) Size and morphology of the assemblies formed by the miktoarm star polymers. By DSL measurements and TEM observations, it was found that both PEG-CD-PNIPAM$_x$ and PEG-CD-POEGMA$_x$ can self-assemble into nano-sized aggregates in their aqueous solutions above their LCST.

As detected by DLS, the size distributions of the miktoarm star polymers in aqueous solutions all present a wide polydispersity below the LCSTs (see curve (a) in Fig. 6(A–D) and curve (b,c) in Fig. 6B), indicating that the star macromolecules exist as a random coil conformation in aqueous solution.

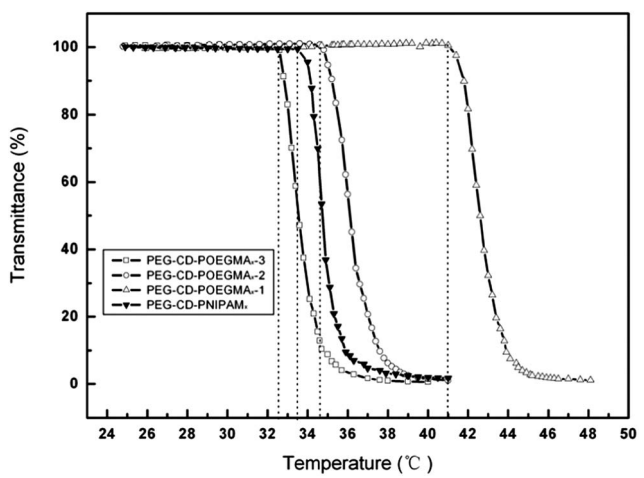


Fig. 5 Determination of the LCSTs of β-CD cored miktoarm star polymers (1 mg mL^{-1}).

However, when the temperature rose above the LCSTs, uniform aggregates formed with a Z-average diameter (D_Z) ranging from 100 nm to 250 nm, revealing the occurrence of thermally-induced self-assembly of the miktoarm star polymers.

This self-assembly was further confirmed by comparing the TEM images of the polymeric solutions, which were prepared at 25 °C (Fig. 7) and 50 °C (Fig. 8). At 25 °C, as shown in Fig. 7, the four miktoarm star polymers dissolved in water as uneven and loose single- or multi-molecular coils with a diameter ranging from 10 nm to 40 nm. In contrast, spherical nano-assemblies of around 200 nm or 100 nm in diameter were observed at 50 °C, which agreed quite well with the results measured by DLS at the same temperature, demonstrating that uniform nano-sized aggregates indeed formed *via* the thermally-induced self-assembly of the polymers. Furthermore, obvious differences in morphology can be observed by comparing the TEM images of the nano-assemblies. The nano-assemblies constructed from PEG-CD-PNIPAM$_x$ (Fig. 8A) show a dark dense core surrounded by a relatively light corona, presenting a typical micellar characteristic. For the ones formed from PEG-CD-POEGMA$_x$, a strong contrast between the light center and the dark thin periphery is seen (Fig. 8(B–D)), which is characteristic of a vesicular nano-structure. Hence, from the results of DLS and TEM it was found that nano-assemblies with different morphology could be constructed from the miktoarm star polymers by simply elevating the temperature, with PEG-CD-PNIPAM$_x$ forming micelle-like nano-structures and the three (PEG-CD-POEGMA$_x$)s organized into vesicle-like nano-aggregates.

(3) Architecture of the nano-assemblies formed by the miktoarm star polymers. The architecture of the nano-assemblies was explored by ^{1}H NMR. Fig. 9 shows the ^{1}H NMR spectra recorded for the miktoarm star polymers in D_2O at 25 °C and 50 °C, respectively. At 25 °C, as the four miktoarm star polymers were fully solvated in D_2O, all signals expected for each star polymer are visible. After adjusting the temperature to 50 °C, the ^{1}H NMR spectrum of PEG-CD-PNIPAM$_x$ changed significantly. As seen in Fig. 9(A), almost all signals of PNIPAM disappeared at 50 °C, except for the signal of PEG which remained with a slight downfield shift.[75–77] This indicates that the nano-assemblies formed by PEG-CD-PNIPAM$_x$ consist of a hydrophobic PNIPAM core and a hydrophilic PEG corona. However, in the case of the (PEG-CD-POEGMA$_x$)s, only the signals from the methacrylate backbone vanished or weakened at 50 °C (such as protons p and h). The peaks from the side chain of POEGMA are still visible or slightly weakened (protons j and k). Although the proton peaks of PEG should also appear in the same region, it is still not possible that the strong signal of the methoxyl protons at δ = 3.5–3.7 was produced by PEG alone. This point

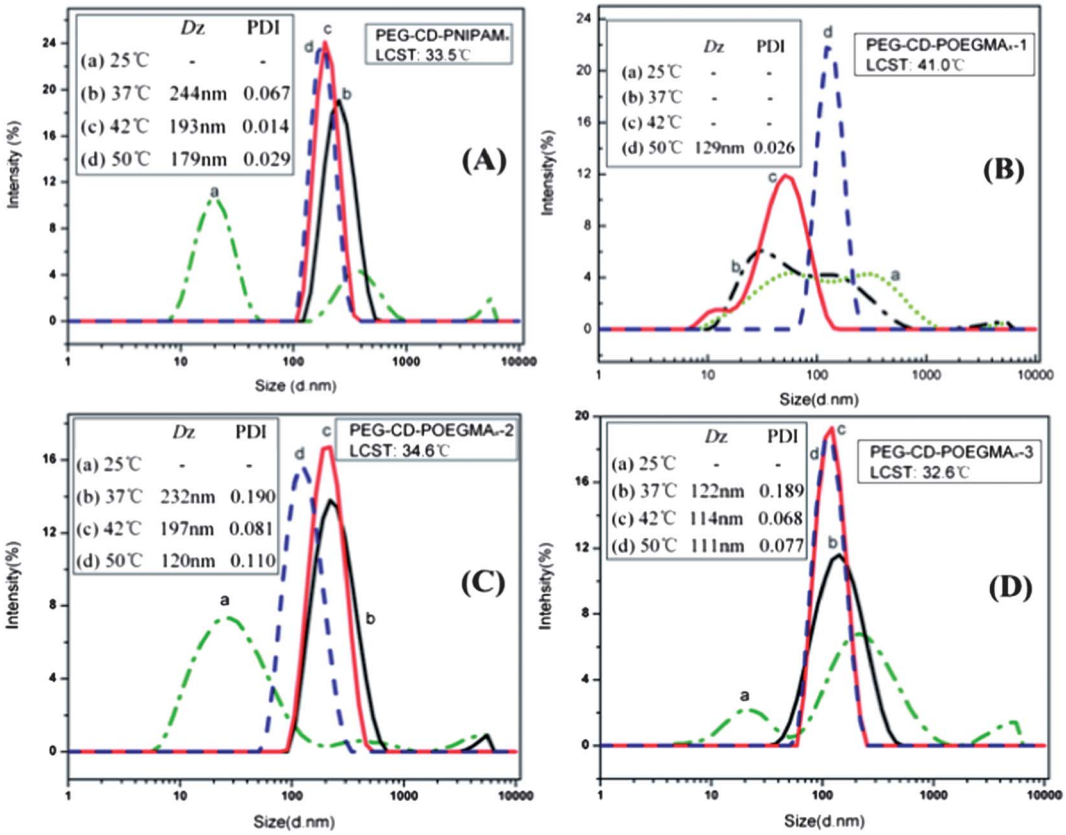


Fig. 6 Size distributions of the aggregates formed by PEG-CD-PNIPAM$_x$ (A) (0.2 mg mL^{-1}) and PEG-CD-POEGMA$_x$ (B)–(D) (0.5 mg mL^{-1}) in aqueous solution.

can be verified by calculating the integral ratio of the methylene proton peak at δ = 3.7–4.0 to the methoxyl end group proton peak at δ = 3.5–3.7. Taking PEG-CD-POEGMA$_x$-**1** as an example, in Fig. 9 (B, 50 °C) the integral ratio of the two peaks was 2.1, which is much lower than the theoretical ratio of the methylene proton in the PEG main chain to the methoxyl proton at the PEG end. However, it would be reasonable if the two peaks in the region of δ = 3.5–4.0 were mainly from the protons of the POEGMA side chain (j and k). Therefore, it can be asserted that the two proton peaks appearing at δ = 3.5–3.7 and δ = 3.7–4.0 (recorded at 50 °C) were mainly produced by the oligo(ethylene glycol) side chains of the POEGMA arms. The same conclusion can be drawn in the case of PEG-CD-POEGMA$_x$-**2** and PEG-CD-POEGMA$_x$-**3**. Based on the analysis above, it can be concluded that the nano-assemblies formed by the (PEG-CD-POEGMA$_x$)s are stabilized by the side oligo(ethylene glycol) chains of POEGMA. These side chains are distributed on the surfaces of the nano-assemblies. The hydrophobic moiety of the nano-assemblies is comprised of the methacrylate backbone of POEGMA and the partially dehydrated oligo(ethylene glycol) side chains. It is noteworthy that the location of the PEG arm of PEG-CD-POEGMA$_x$ in the nano-assemblies cannot be verified *via* the ^{1}H NMR spectra due to the corresponding signals overlapping with those of the PEG-CD-POEGMA$_x$ side chain. However, we still believe that at least part of the PEG may exist at the surfaces of the nano-assemblies because of their high hydrophilicity.

Thermally-induced dehydration of the miktoarm star polymers

From the results of UV-vis and DLS, we have realized the similarities in the thermally-responsive behavior between PEG-CD-PNIPAM$_x$ and PEG-CD-POEGMA$_x$: (i) both of them are responsive to an outer thermal stimulus and possess a defined LCST, and (ii) both can self-assemble into nano-sized structures above their LCST. However, as revealed by ^{1}H NMR, the architectures of the nano-assemblies formed by PEG-CD-PNIPAM$_x$ and PEG-CD-POEGMA$_x$ are completely different from each other. These facts suggest that the mechanism of thermal-sensitivity of the miktoarm star polymers might be different. It is known that the thermally-responsive behaviors of linear PNIPAM and POEGMA originated from the thermally-induced hydration and dehydration between the polymer segments and water molecules.[77–80] Here, for investigation of the thermally-induced dehydration process of the miktoarm star polymers, fluorescence spectroscopy was performed using pyrene as a probe. It is well known that pyrene fluorescence reports the polarity or hydrophobicity of the region where it is solubilized.[81,82] The emission intensity ratio of the first to the third vibronic band of the pyrene fluorescence, usually defined as the I_1/I_3 ratio, has been used widely for studying the formation and properties of aggregated systems.[81,82] We recorded the I_1/I_3 values of the pyrene aqueous solution in the presence of the four miktoarm star polymers during a temperature rising process, as shown in Fig. 10.

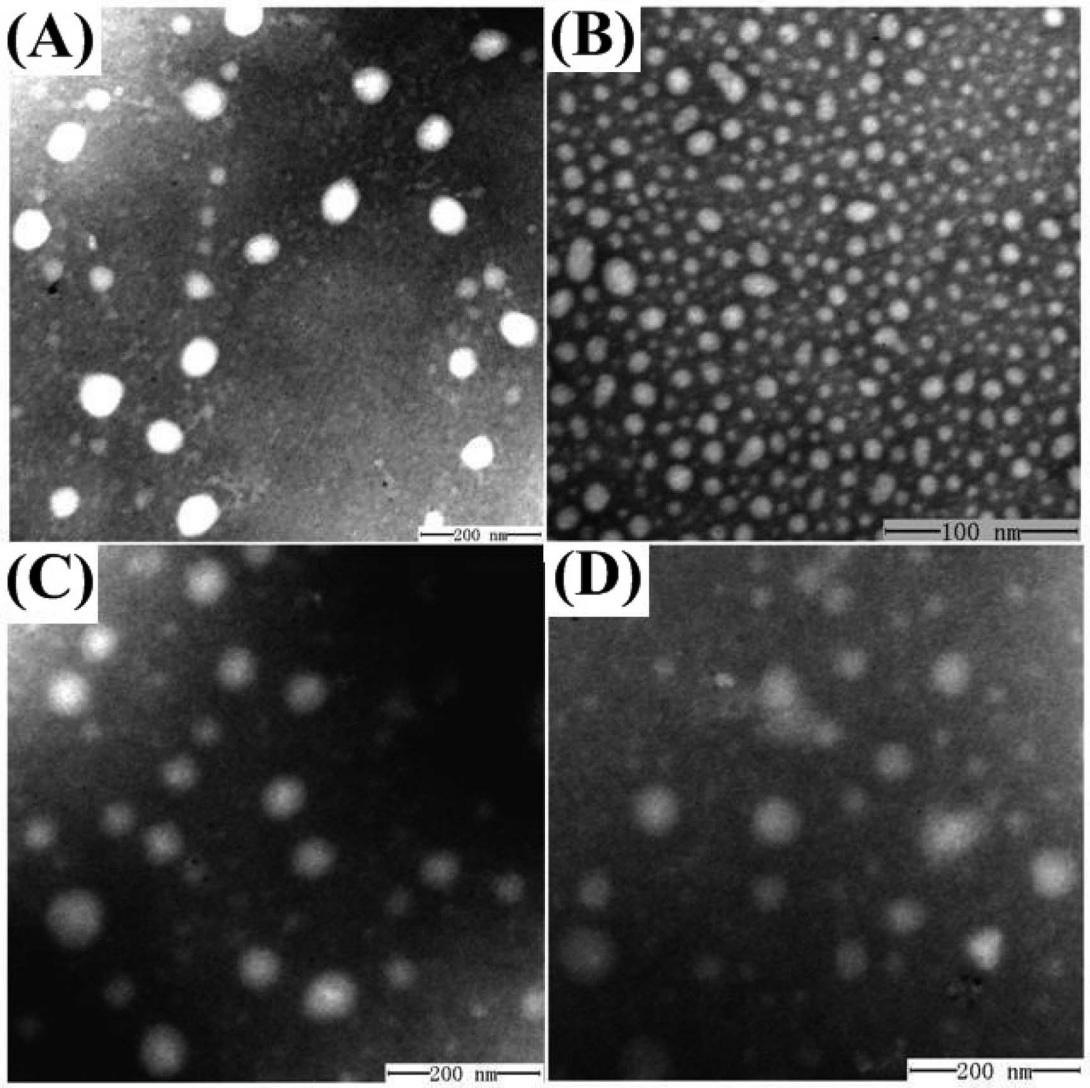


Fig. 7 Typical TEM images obtained by drying aqueous solutions of PEG-CD-PNIPAM$_x$ (A, 0.2 mg mL^{-1}) and PEG-CD-POEGMA$_x$-**1**, -**2**, -**3** (B, C, D, 0.5 mg mL^{-1}) at 25 °C.

At 25 °C, the I_1/I_3 value of the pyrene aqueous solution without the presence of the polymers was 1.453. After the addition of the miktoarm star polymers, the I_1/I_3 values of all four polymer solutions decreased to some extent. This is attributed to the formation of some hydrophobic domains by mild aggregation of the backbone or unhydrated side chains of the star polymers. Solubilization of pyrene in these domains lowered the I_1/I_3 value of the systems. However, the initial I_1/I_3 value of the PEG-CD-PNIPAM$_x$ system was only slightly lower than that of the blank pyrene solution (1.453). In comparison, the values of the three pyrene/PEG-CD-POEGMA$_x$ systems decreased significantly. This suggests that PEG-CD-PNIPAM$_x$ was sufficiently hydrated while the (PEG-CD-POEGMA$_x$)s were insufficiently hydrated at 25 °C.

With rising temperature, the I_1/I_3 value of the pyrene/PEG-CD-PNIPAM$_x$ system is maintained with slight fluctuations until the temperature reaches the vicinity of the LCST of PEG-CD-PNIPAM$_x$ and then exhibits an abrupt decrease at the LCST (33.5 °C), which indicates a significant decline in polarity and a sudden formation of hydrophobic domains. As for the (pyrene/PEG-CD-POEGMA$_x$)s, the decrease of the I_1/I_3 value presents a mild and persistent manner, no abrupt decrease is observed, demonstrating that the hydrophobicity of the systems is gradually increasing. Thus it can be inferred that the thermally-induced dehydration of PEG-CD-POEGMA$_x$ is a subtle but continuous process throughout the whole temperature rise, whereas that for PEG-CD-PNIPAM$_x$ is abrupt and intensive, occurring near the LCST of PEG-CD-PNIPAM$_x$. This inference was further proven by DSC measurements, in which the ΔH of the concentrated aqueous samples of the miktoarm star polymers during a temperature rise was recorded.

Fig. 11 shows the resultant DSC curves. An evident endothermic peak appears in the curve of PEG-CD-PNIPAM$_x$. The corresponding temperature at the maxima of the endotherm is 33.6 °C, very close to the LCST of PEG-CD-PNIPAM$_x$ measured by UV-vis (33.5 °C), which further confirmed the abrupt and intensive dehydration between the amide group of PNIPAM and the water molecules around the LCST. By

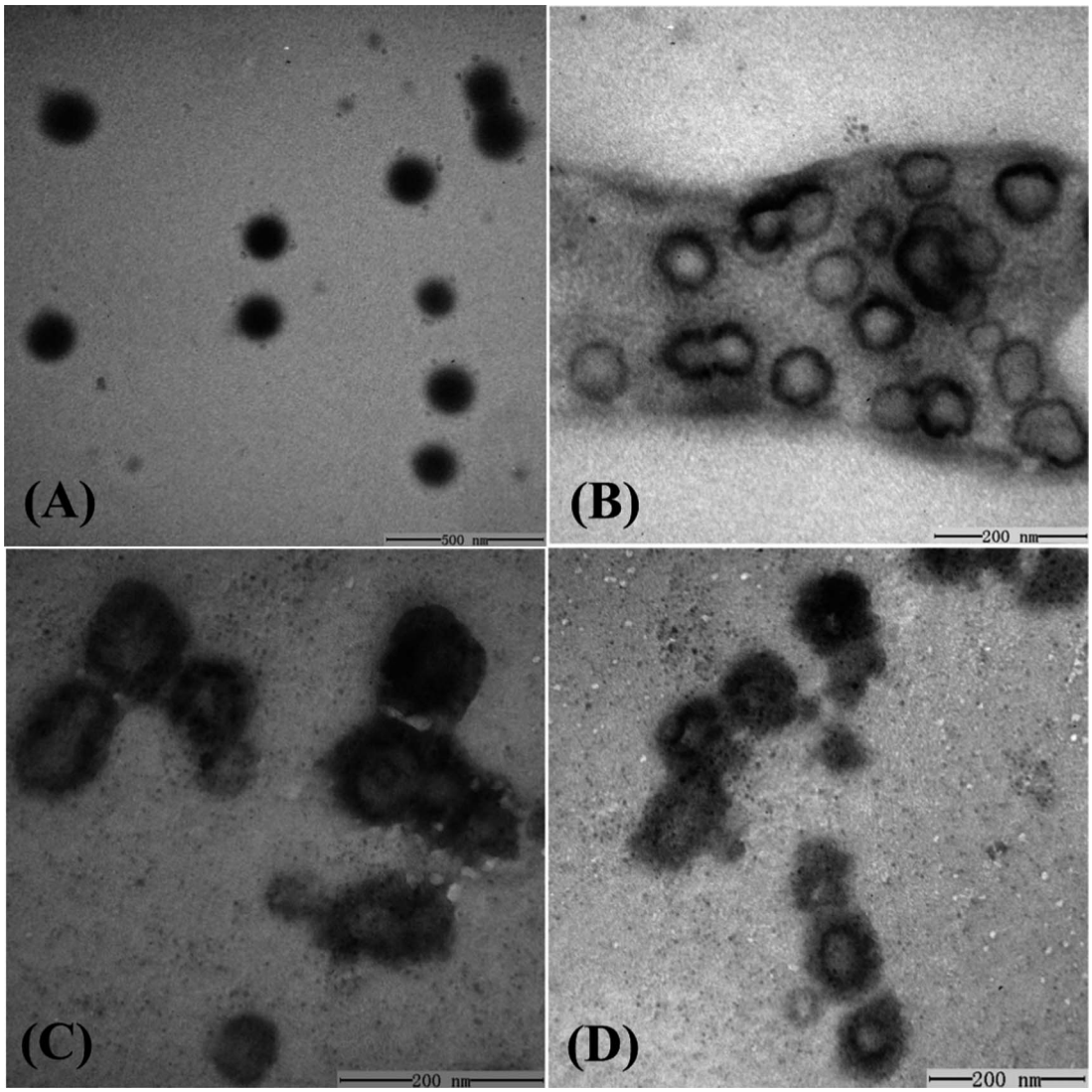


Fig. 8 Typical TEM images obtained by drying aqueous solutions of PEG-CD-PNIPAM$_x$ (A, 0.2 mg mL^{-1}) and PEG-CD-POEGMA$_x$-**1**, -**2**, -**3** (B, C, D, 0.5 mg mL^{-1}) at 50 °C.

contrast, there is no endothermic peak in all of the three DSC curves of PEG-CD-POEGMA$_x$, indicating that no intensive dehydration took place during the temperature rise. Thus, the subtle but continuous dehydration of PEG-CD-POEGMA$_x$ was evidenced again.

Relationship between the thermally-induced dehydration process and the architecture of the nano-assemblies

The abrupt and intensive dehydration of the PNIPAM segments near the LCST of PEG-CD-PNIPAM$_x$ causes all of the PNIPAM segments to become hydrophobic instantly and all were involved in the formation of the hydrophobic core of the nano-assemblies. This is why on the ^{1}H NMR spectrum of PEG-CD-PNIPAM$_x$ (in D_2O at 50 °C), only the signal of PEG (still hydrophilic at 50 °C) was observed. With respect to PEG-CD-POEGMA$_x$, the dehydration was gradual and continuous with temperature. At 25 °C, due to insufficient hydration, there was a portion of unhydrated oligo(ethylene glycol) side chains, which provide hydrophobic forces and lead to the formation of some hydrophobic domains, as revealed by pyrene fluorescence. Meanwhile, the hydrated oligo(ethylene glycol) side chains provided hydrophilic forces and caused the dissolution of PEG-CD-POEGMA$_x$ in water. With rising temperature, more dehydrated side chains formed and the hydrophobic force became stronger than the hydrophilic one at the LCST. As a result, PEG-CD-POEGMA$_x$ self-assembled in aqueous solution, which was mainly reflected by the sharp decline of the solution transmittance as detected by UV-vis (Fig. 5) and the formation of uniform nanoparticles as revealed by DLS and TEM (Fig. 6–8). During this self-assembly process, the dehydrated oligo(ethylene glycol) side chains, together with the methacrylate backbone of PEG-CD-POEGMA$_x$, formed the hydrophobic moiety of the nano-architectures. The side chains which were still hydrated construct the hydrophilic surfaces. In other words, the gradual and continuous dehydration of the POEGMA segments results in the existence of hydrated oligo(ethylene glycol) side chains when self-assembly occurred.

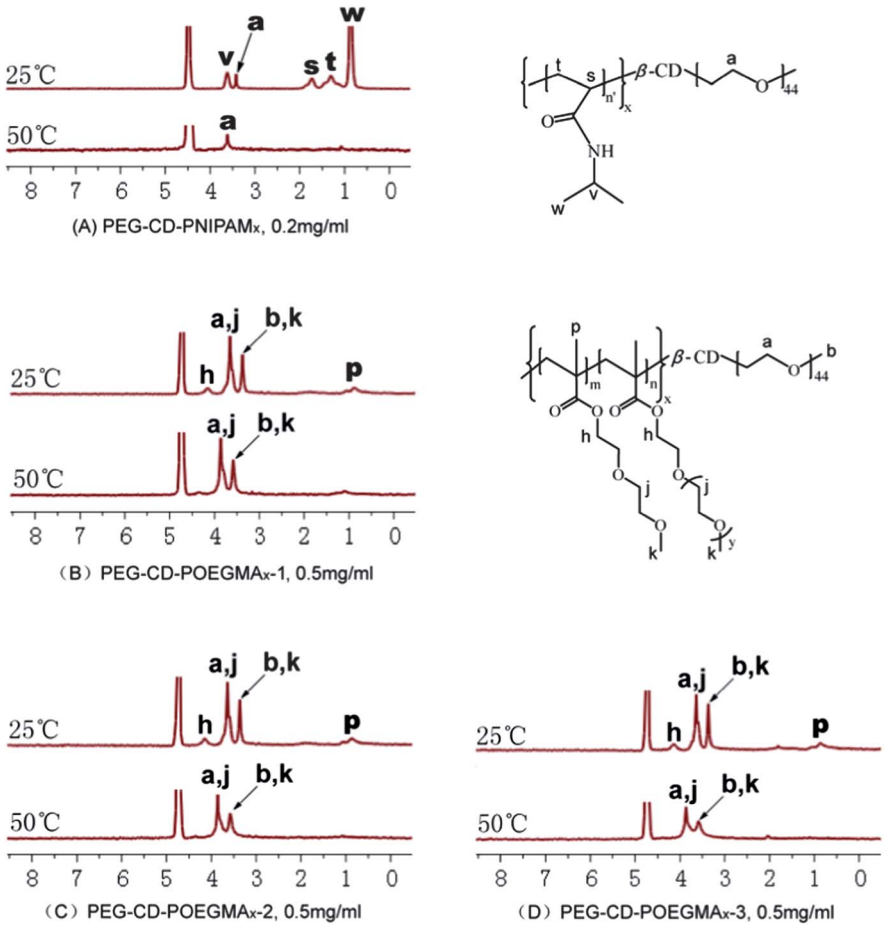


Fig. 9 ^{1}H NMR spectra of the miktoarm star polymers in D_2O at 25 °C and 50 °C.

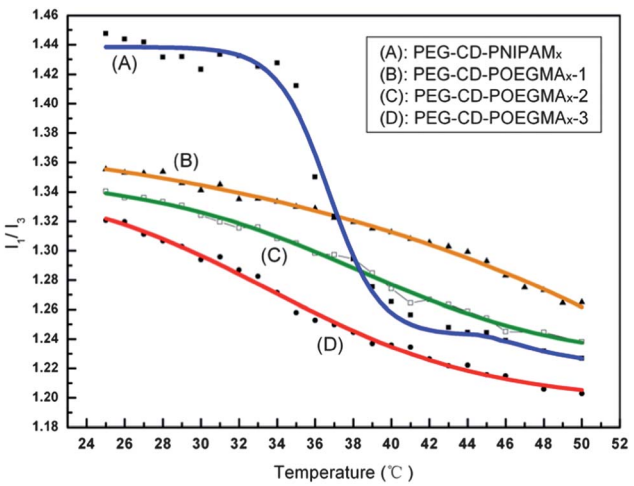


Fig. 10 I_1/I_3 values of pyrene aqueous solution in the presence of the miktoarm star polymers ([PEG-CD-PNIPAM$_x$]: 0.2 mg mL^{-1}, [PEG-CD-POEGMA$_x$]: 0.5 mg mL^{-1}, [pyrene]: 6×10^{-6} mol L^{-1}) as a function of temperature.

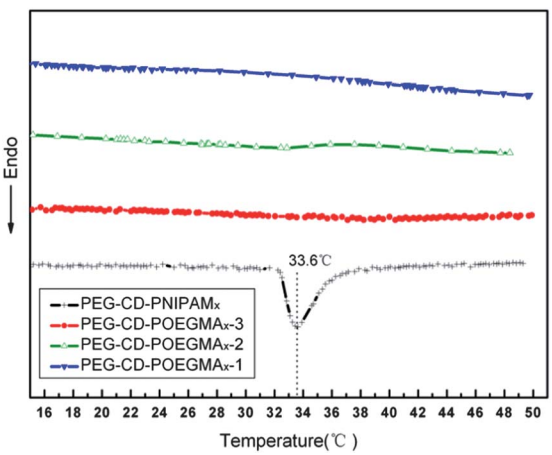
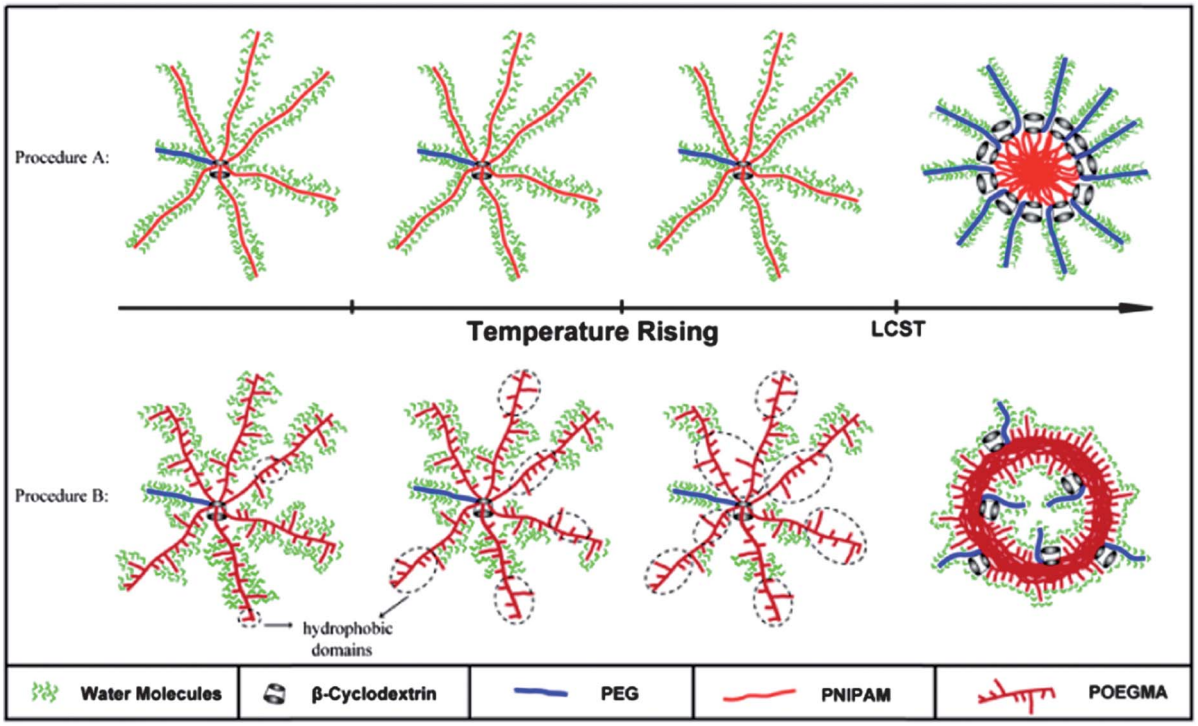


Fig. 11 DSC thermograms of the miktoarm star polymers in water (polymer concentration: 50 mg mL^{-1}).

These hydrated side chains participated in the construction of the hydrophilic surfaces of the nano-architectures. Thus, the proton signals of the oligo(ethylene glycol) side chains could still be observed in the ^{1}H NMR spectra of the (PEG-CD-POEGMA$_x$)s, even when the temperature was beyond the LCSTs. Hence, it is clear that the architecture of the nano-assemblies formed by PEG-CD-PNIPAM$_x$ or PEG-CD-POEGMA$_x$ is related to the dehydration process of the polymers. The procedures for the thermally-induced dehydration



Scheme 3 Dehydration procedure and subsequent self-assembly of PEG-CD-PNIPAM$_x$ (A) and PEG-CD-POEGMA$_x$ (B) with rising temperature.

and subsequent self-assembly of the miktoarm star polymers have been illustrated in Scheme 3.

Conclusions

The thermally-responsive miktoarm star polymers, PEG-CD-PNIPAM$_x$ and PEG-CD-POEGMA$_x$, were synthesized by using a combination of click reactions and selective modification of β-CD and ATRP. The miktoarm star polymers consist of a β-CD core, a PEG arm and about six PNIPAM or POEGMA arms. Above the LCSTs of the miktoarm star polymers in aqueous solution, PEG-CD-PNIPAM$_x$ can self-assemble into nano-structures with PNIPAM as the core and PEG as the corona, while the (PEG-CD-POEGMA$_x$)s self-assemble into nano-architectures possessing hydrophilic surfaces constructed from the hydrated oligo(ethylene glycol) side chains of POEGMA. The hydrophobic moiety of the nano-architectures is formed by the methacrylate backbone and the dehydrated oligo(ethylene glycol) side chains of POEGMA. In aqueous solution, the thermally-induced dehydration of PEG-CD-PNIPAM$_x$ occurred abruptly and intensively near the LCST of PEG-CD-PNIPAM$_x$, leading to all of the PNIPAM segments becoming hydrophobic instantly and almost all of them were involved in the formation of the hydrophobic core of the PEG-CD-PNIPAM$_x$ assemblies. The dehydration of PEG-CD-POEGMA$_x$ was gradual and continuous throughout the whole temperature rise. As a result, the hydrophilic surfaces of the PEG-CD-POEGMA$_x$ assemblies were constructed by the oligo(ethylene glycol) side chains which were still hydrated when self-assembly occurred. The architecture of the nano-assemblies formed by PEG-CD-PNIPAM$_x$ or PEG-CD-POEGMA$_x$ is related to the dehydration process of the polymers.

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