

Synthesis and supramolecular self-assembly of stimuli-responsive water-soluble Janus-type heteroarm star copolymers†

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We report on the synthesis and stimuli-responsive self-assembly of novel double hydrophilic Janus-type A_7B_{14} heteroarm star copolymers with two types of water-soluble polymer arms emanating from the two opposing sides of the rigid toroidal β -CD core. Janus-type A_7B_{14} star copolymers of *N*-isopropylacrylamide (NIPAM) and 2-(diethylamino)ethyl methacrylate (DEA), (PDEA) $_7$ -CD-(PNIPAM) $_{14}$, were synthesized by coupling atom transfer radical polymerization (ATRP) and click chemistry techniques, starting from a well-defined β -CD derivative. At first, β -CD-(I) $_7$ was obtained by reacting β -CD with I $_2$ in the presence of PPh $_3$ at 70 °C, which can selectively transform seven primary hydroxyl groups of β -CD into iodine moieties. After converting to β -CD-(N $_3$) $_7$ via azidation of β -CD-(I) $_7$, the subsequent esterification reaction of β -CD-(N $_3$) $_7$ with 2-bromopropionic bromide afforded (N $_3$) $_7$ -CD-(Br) $_{14}$. The ATRP of NIPAM monomer in 2-propanol/DMF mixture at 25 °C using (N $_3$) $_7$ -CD-(Br) $_{14}$ as the multifunctional initiator led to azide-containing 14-arm star polymers, (N $_3$) $_7$ -CD-(PNIPAM) $_{14}$. Well-defined Janus-type double hydrophilic star copolymers were then prepared by the click reaction of (N $_3$) $_7$ -CD-(PNIPAM) $_{14}$ with an excess of monoalkynyl-terminated PDEA. Upon adjusting solution pH and temperatures, (PDEA $_{30}$) $_7$ -CD-(PNIPAM $_{25}$) $_{14}$ can reversibly self-assemble into two distinct types of polymeric vesicles with “inverted” nanostructures in aqueous solution.

Introduction

The past few years has evidenced ever-increasing interest in the construction of complex nanostructures with a higher level of hierarchy through directed self-assembly of Janus-type nanoparticles, micelles, dendrimers, and giant amphiphiles.^{1–10} These building units typically possess nonlinear architectures and non-centrosymmetric surface functionalities. The concept of Janus micelles was originated by Muller *et al.*,^{11–13} taking advantage of the well-defined bulk phase separation morphology of ABC triblock copolymers. They also synthesized amphiphilic Janus micelles (~13 precursor triblock chains) consisting of a cross-linked core and a corona split into hydrophobic and hydrophilic hemispheres, which can self-assemble into higher-order aggregates in aqueous solution.¹² Based on chemical intuition, chain architecture of this novel type of Janus micelles partially resembles those of heteroarm star copolymers.^{14–17} It can be envisaged that the spatial separation between two types of building blocks in A_mB_n heteroarm star copolymers, *i.e.*, Janus star copolymers, can endow them with fascinating aggregation properties, especially when such clustering can be facilitated by the application of a proper external stimuli such as pH, temperature, and introduction of additives.

However, previous reports relevant to heteroarm star copolymers exclusively consist of flexible junction points, rendering

impossible for different types of polymer arms to arrange in a persistent “Janus” manner.^{14,15,18} It is well-known that β -cyclodextrin (β -CD) possesses a rigid toroidal conformation with an overall molecular volume of ~1.5 nm³. It contains 7 primary hydroxyl groups on one side of the toroid and 14 secondary hydroxyl groups on the opposing side. β -CD has been frequently utilized as starting materials for the synthesis of star polymers. A variety of star polymers have been synthesized *via* nitroxide-mediated polymerization (NMP),¹⁹ atom transfer radical polymerization (ATRP), and reversible addition-fragmentation chain transfer (RAFT) polymerization *via* the core-first approach by using β -CD-based multifunctional initiators.^{20–28} Haddleton *et al.*²⁴ first reported the synthesis of 21-arm poly(methyl methacrylate) (PMMA) or polystyrene (PS) star polymers based on fully functionalized β -CD. Stenzel *et al.*^{26,29} and Kakuchi *et al.*^{20,23} reported the synthesis of 7-arm PS star polymer *via* RAFT and NMP techniques by using β -CD-based mediators bearing heptafunctional trithiocarbonate and nitroxide moieties, respectively. Recently, the concept of click chemistry invented by Sharpless *et al.*^{30,31} has also been incorporated into the synthesis of well-defined star polymers based on β -CD derivatives. Schubert *et al.*³² reported the synthesis of 7-arm star poly(ϵ -caprolactone) (PCL) *via* click reaction using alkynyl-functionalized linear PCL precursor, starting from heptakis(6-deoxy-6-azido)- β -cyclodextrin, β -CD-(N $_3$) $_7$.

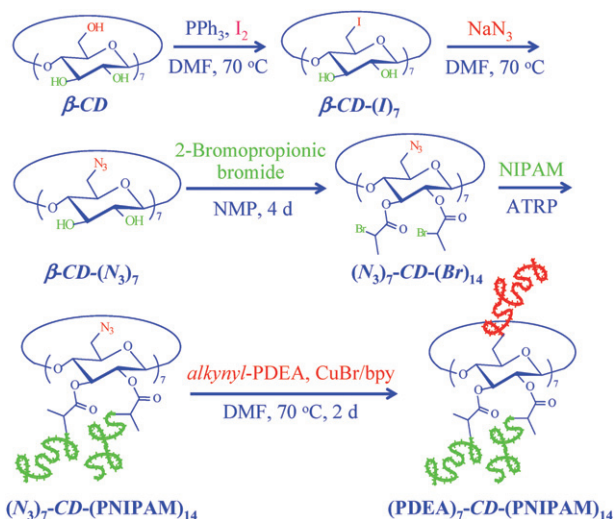
It has been well-known that stimuli-responsive double hydrophilic block copolymers (DHBCs) can supramolecularly self-assemble into more than one type of aggregate, *i.e.* the so-called “schizophrenic” aggregation, in aqueous solution upon properly tuning external conditions such as pH, temperature, and ionic strengths.^{33–37} Recent developments in this field involve

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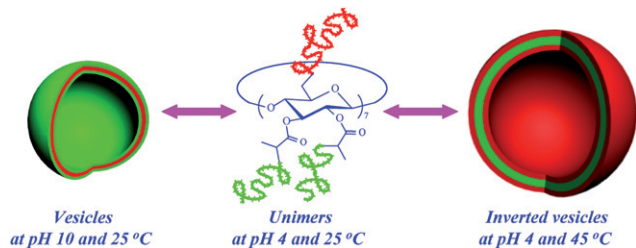
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DHBCs possessing nonlinear chain topology. Our group has a long-standing interest in the controlled synthesis of linear and non-linear stimuli-responsive DHBCs and their supramolecular self-assembly.^{38–41} Previously, we reported the synthesis of well-defined 7-arm and 21-arm thermoresponsive poly(*N*-isopropylacrylamide) (PNIPAM) star polymers possessing β -cyclodextrin (β -CD) cores *via* the combination of atom transfer radical polymerization (ATRP) and click reactions, starting from β -CD-(N_3)₇ and heptakis[2,3,6-tri-*O*-(2-azidopropionyl)]- β -cyclodextrin, β -CD-(N_3)₂₁, precursors, respectively.⁴²

Herein, we further report on the novel synthesis and self-assembly of dually responsive Janus-type star copolymers (Schemes 1 and 2). Janus-type A₇B₁₄ heteroarm star copolymers of *N*-isopropylacrylamide (NIPAM) and 2-(diethylamino)ethyl methacrylate (DEA), (PDEA)₇-CD-(PNIPAM)₁₄, were synthesized *via* a combination of ATRP and click chemistry techniques, starting from well-defined β -CD derivative (Scheme 1). β -CD-(I)₇ was obtained by reacting β -CD with I₂ in the presence of PPh₃ at 70 °C.^{42,43} After converting to β -CD-(N₃)₇ by the azidation of β -CD-(I)₇, the subsequent esterification reaction of β -CD-(N₃)₇ with 2-bromopropionic bromide afforded (N_3)₇-CD-(Br)₁₄. Subsequently, the ATRP of NIPAM monomer using (N_3)₇-CD-(Br)₁₄



Scheme 1 Synthetic schemes employed for the synthesis of well-defined stimuli-responsive double hydrophilic Janus-type A₇B₁₄ star copolymers, (PDEA)₇-CD-(PNIPAM)₁₄, based on β -CD derivative *via* the combination of ATRP and click reaction.



Scheme 2 Schematic representation of stimuli-responsive reversible self-assembly of double hydrophilic Janus-type A₇B₁₄ star copolymer, (PDEA₃₀)₇-CD-(PNIPAM₂₅)₁₄, into two types of vesicles with “inverted” nanostructures in aqueous solution.

as the multifunctional initiator led to (N_3)₇-CD-(PNIPAM)₁₄. Well-defined Janus-type double hydrophilic star copolymers, (PDEA)₇-CD-(PNIPAM)₁₄, were then prepared by the click reaction of (N_3)₇-CD-(PNIPAM)₁₄ with an excess of mono-alkynyl-terminated PDEA (*alkynyl*-PDEA). Upon adjusting solution pH and temperatures, (PDEA₃₀)₇-CD-(PNIPAM₂₅)₁₄ can reversibly self-assemble into two distinct types of polymeric vesicles with “inverted” nanostructures in aqueous solution.

Experimental

Materials

β -Cyclodextrin (β -CD, Sinopharm Chemical Reagent Co. Ltd) was recrystallized twice from water and dried in a vacuum oven at 100 °C over P₂O₅ for 2 days. *N*-Isopropylacrylamide (NIPAM, 97%, Tokyo Kasei Kagyo Co.) was recrystallized twice from benzene/hexane (65:35 v/v). 2-(Diethylamino)ethyl methacrylate (DEA, Aldrich) was vacuum-distilled over CaH₂. All monomers were stored at –20 °C prior to use. Copper(I) chloride (99%), copper(I) bromide (99%), 2,2-dipyridyl (bpy, 99%), propargyl alcohol (99%), 2-bromopropionic bromide (97%), and 2-bromo-*isobutyryl* bromide (97%) were purchased from Aldrich and used as received. Sodium azide (NaN₃, 99%) was purchased from Alfa Aesar. Merrifield Resin was purchased from GL Biochem (Shanghai) Ltd. and used as received. Tris(2-aminoethyl)amine (TREN) (96%) was purchased from Acros. 2-Propanol, *N,N*-dimethylformamide (DMF), *N*-methyl-2-pyrrolidone (NMP), and all other reagents were purchased from Sinopharm Chemical Reagent Co. Ltd. and distilled just prior to use. Tris(2-(dimethylamino)ethyl)amine (Me₆TREN),⁴⁴ azide-functionalized Merrifield resin (1% divinylbenzene, 200–400 mesh, ~0.8 mmol azide/g),⁴⁵ and propargyl 2-bromo-*isobutyrate* (PBIB)^{46,47} were synthesized according to literature procedures.

Sample synthesis

General procedures employed for the preparation of β -CD-based Janus-type A₇B₁₄ star copolymers are shown in Scheme 1.

Synthesis of Heptakis(6-Deoxy-6-Azido)- β -Cyclodextrin [β -CD-(N₃)₇].⁴² The target compound was prepared according to procedures reported by Ashton *et al.*⁴³ Ph₃P (18.36 g, 70 mmol) was dissolved in dry DMF (100 mL) under stirring. I₂ (17.77 g, 70 mmol) was then carefully added over a period of 10 min, the solution temperature increased to ~70 °C after the addition was complete. Dry β -CD (5.68 g, 5 mmol) was then added to the dark brown solution. The mixed solution was stirred under N₂ atmosphere for 24 h at 70 °C. The solution was partially concentrated under reduced pressure (removal of ~60 mL DMF). Sodium methoxide (3.0 M in methanol, 30 mL) was then added under cooling with an ice-water bath. The reaction mixture was poured into methanol (500 mL), the precipitate was washed with excess methanol and then dried in a vacuum oven for 2 h. After re-dissolving in DMF, the above precipitation–drying cycle was repeated 5 times. Heptakis(6-deoxy-6-iodo)- β -cyclodextrin was obtained as white solids after drying under vacuum at room temperature for 1 day. Heptakis(6-deoxy-6-iodo)- β -cyclodextrin (4.62 g, 2.6 mmol) was dissolved in DMF (50 mL), and NaN₃ (2.02 g, 31 mmol) was added. The resulting

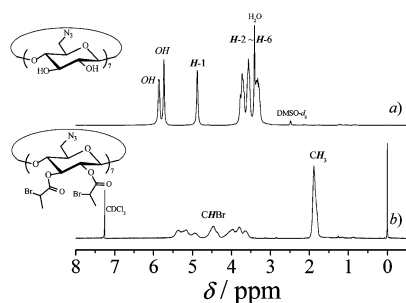


Fig. 1 ¹H NMR spectra recorded for (a) β-CD-(N₃)₇ precursor in DMSO-*d*₆ and (b) (N₃)₇-CD-(Br)₁₄ precursor in CDCl₃.

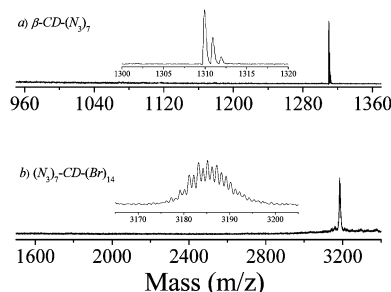


Fig. 2 MALDI-TOF mass spectra obtained for (a) β-CD-(N₃)₇ and (b) (N₃)₇-CD-(Br)₁₄ precursors.

suspension was stirred at 70 °C under an atmosphere of N₂ for 36 h. The suspension was then concentrated under reduced pressure before addition of an excess of water. A fine white powder was obtained after filtration, washing with water, and drying in a vacuum oven. (2.96 g, yield: 87%; *M*_{n, GPC} = 2.1 kDa, *M*_w/*M*_n = 1.02). ¹H NMR in DMSO-*d*₆ (δ, ppm; Fig. 1a): 3.10–3.93 (42H, *H*-2, *H*-3, *H*-4, *H*-5, *H*-6), 4.87 (7H, *H*-1), 5.73 (7H, OH), 5.89 (7H, OH). ¹³C NMR in DMSO-*d*₆ (δ, ppm; Figure S1, ESI[†]): 51.5 (*C*-6), 70.5 (*C*-5), 72.1 (*C*-2), 72.7 (*C*-3), 83.3 (*C*-4), 102.2 (*C*-1). MALDI-TOF MS *m/z*: calcd for C₄₂H₆₄O₂₈N₂₁ (M + H⁺), 1310.4; found, 1310.1 (Fig. 2a).

Synthesis of Heptakis[2,3-di-O-(2-bromopropionyl)-6-azido]-β-cyclodextrin [(N₃)₇-CD-(Br)₁₄]. Into a 250 mL three-neck round-bottom flask, β-CD-(N₃)₇ (1.97 g, 1.5 mmol) and anhydrous *N*-methyl-2-pyrrolidone (NMP, 20 mL) were added. After dissolution and cooling to 0 °C, 2-bromopropionic bromide (20.08 g, 93 mmol) in 10 mL dry NMP was added dropwise over 2 h *via* a dropping funnel. After stirring at ambient temperature for 3 days and subsequently under reduced pressure for 1 day, the reaction mixture was precipitated into an excess of cold water. The obtained brown powder was dried in a vacuum oven for 24 h. The residues were dissolved in CH₂Cl₂ (100 mL) and thoroughly washed with 1 N HCl (4 × 50 mL), saturated NaHCO₃ aq. solution (2 × 50 mL), saturated NaCl aq. solution (2 × 50 mL), and deionized water (3 × 50 mL). The organic phase was dried over Na₂SO₄ and concentrated on a rotary evaporator. The yellow residues were further purified by silica gel column chromatography using dichloromethane as the eluent, yielding a colorless powder (0.53 g, yield: 11%; *M*_{n, GPC} = 3.8 kDa, *M*_w/*M*_n = 1.02, Figure S2, ESI[†]). ¹H NMR in CDCl₃ (δ, ppm;

Fig. 1b): 1.88 (42H, CHCH₃), 3.50–5.50 (63H, *H*-1, *H*-2, *H*-3, *H*-4, *H*-5, *H*-6, CHCH₃); ¹³C NMR in CDCl₃ (δ, ppm; Figure S1, ESI[†]): 21.3 (CHCH₃), 39.9 (CHCH₃), 51.6 (*C*-6), 71.2–71.3 (*C*-2, *C*-3, *C*-4, *C*-5), 96.0 (*C*-1), 169.3 (*C* = O); MALDI-TOF MS *m/z*: calcd for C₈₄H₁₀₆O₄₂N₂₁Br₁₄ (M + H⁺), 3185.5; found, 3185.2 (Fig. 2b).

Synthesis of 14-Arm Star Poly(*N*-isopropylacrylamide) [(N₃)₇-CD-(PNIPAM)₁₄]. Typical procedures employed for the preparation of a 14-arm star polymer, (N₃)₇-CD-(PNIPAM)₁₄, are as follows.^{48,49} The mixed solution of NIPAM (3.39 g, 30 mmol), Me₆TREN (0.161 g, 0.7 mmol), 2-propanol (6 mL), and DMF (4 mL) was deoxygenated by bubbling with nitrogen for ~30 min. (N₃)₇-CD-(Br)₁₄ (0.16 g, 0.7 mmol Br moieties) was introduced and the reaction mixture was subjected to three freeze–pump–thaw cycles. CuCl (69 mg, 0.7 mmol) was then added to start the polymerization. The reaction was allowed to stir at 25 °C under N₂ protection for 4 h, reaching a monomer conversion of ~60%. After diluting with THF, the mixture was precipitated into an excess of diethyl ether. The sediments were dissolved in THF and passed through a neutral alumina column to remove copper catalysts. The apparent molecular weight and molecular weight distribution of (N₃)₇-CD-(PNIPAM)₁₄ were determined by GPC using polystyrene standards: *M*_{n, GPC} = 42.6 kDa, *M*_w/*M*_n = 1.09 (Figure S2, ESI[†]). The degree of polymerization (DP) of PNIPAM arms was determined to be 25 by ¹H NMR analysis, assuming a quantitative initiating efficiency (Fig. 3).

Synthesis of monoalkynyl-terminated PDEA (alkynyl-PDEA). Monoalkynyl-terminated PDEA, *alkynyl*-PDEA, was synthesized by ATRP of DEA monomer using PBIB as the initiator. In a typical example, PBIB (0.205 g, 1 mmol), bpy (156 mg, 1 mmol), DEA (7.41 g, 40 mmol), and 2-propanol (10 mL) were charged into a reaction flask. The flask was degassed *via* three freeze–thaw–pump cycles and back-filled with N₂. CuBr (72 mg, 0.5 mmol) was introduced into the reaction mixture under protection of N₂ flow to start the polymerization at room temperature under N₂ atmosphere. After 8 h, the polymerization

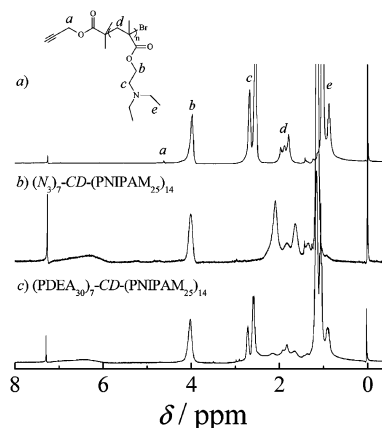


Fig. 3 ¹H NMR spectra recorded in CDCl₃ for (a) *alkynyl*-PDEA₃₀ precursor, (b) 14-arm star poly(*N*-isopropylacrylamide), (N₃)₇-CD-(PNIPAM)₂₅)₁₄, (c) double hydrophilic Janus-type A₇B₁₄ star copolymer, (PDEA₃₀)₇-CD-(PNIPAM)₂₅)₁₄.

Table 1 GPC and MALDI-TOF MS characterization of β -CD-based precursors, *alkynyl*-PDEA, and star polymers used in this work

Entry	Sample Codes	$M_{n, \text{GPC}}^a$ /kDa	M_w/M_n^a	$M_{n, \text{MALDI}}^b$
1	β -CD-(N_3) ₇	2.1	1.02	1310.1
2	(N_3) ₇ -CD-(Br) ₁₄	3.8	1.02	3185.2
3	<i>alkynyl</i> -PDEA ₃₀ ^c	7.3	1.18	—
4	(N_3) ₇ -CD-(PNIPAM ₂₅) ₁₄	42.6	1.09	—
5	(PDEA ₃₀) ₇ -CD-(PNIPAM ₂₅) ₁₄	59.7	1.15	—

^a Number-average molecular weight, M_n , and molecular weight distribution, M_w/M_n , determined by GPC using DMF as eluent and a series of polystyrene standards. ^b Measured by MALDI-TOF mass spectrometry. ^c Number-average molecular weight, M_n , and molecular weight distribution, M_w/M_n , determined by GPC using THF as eluent.

was terminated by exposing to air and diluting with THF. After passing through a column of neutral alumina to remove the copper catalysts and removing all the solvent by a rotary evaporator, the residues were dissolved in THF and precipitated into cold *n*-hexane (-50°C) to remove residual monomers. After drying in a vacuum oven overnight at room temperature, *alkynyl*-PDEA was obtained as a white viscous solid ($M_{n, \text{GPC}} = 7.3$ kDa, $M_w/M_n = 1.18$; Figure S2, a, ESI†). The actual DP of *alkynyl*-PDEA was calculated to be 30 by ¹H NMR analysis in CDCl₃. Thus, the obtained product was denoted as *alkynyl*-PDEA₃₀ (Fig. 3a; Table 1).

Synthesis of A₇B₁₄-Type Janus-type star copolymer [(PDEA)₇-CD-(PNIPAM)₁₄] by click coupling reactions. Typical procedures employed for the synthesis of Janus-type A₇B₁₄ star polymer, (PDEA)₇-CD-(PNIPAM)₁₄ are as follows. Into a Schlenk tube equipped with a magnetic stirring bar, *alkynyl*-PDEA₃₀ (0.58 g, 0.1 mmol), (N_3)₇-CD-(PNIPAM₂₅)₁₄ (0.43 g, 0.07 mmol azido moieties), bpy (62 mg, 0.4 mmol), and DMF (5 mL) were added. After one brief freeze–thaw cycle, CuBr (29 mg, 0.2 mmol) was introduced under the protection of N₂ flow. The reaction tube was carefully degassed by three freeze–pump–thaw cycles, sealed under vacuum, and placed in an oil bath thermostated at 70°C . After stirring for 48 h, azido-functionalized Merrifield resin (0.25 g, 0.2 mmol azide moieties) was added. The suspension was kept stirring for another 12 h at 70°C . After suction filtration, the filtrate was diluted with THF and passed through a basic alumina column to remove the copper catalyst. After removing all the solvents at reduced pressure, the residues were dissolved in THF and precipitated into an excess of cold *n*-hexane. The final product was dried in a vacuum oven overnight at room temperature, yielding a white solid (0.56 g, yield: 67%; $M_{n, \text{GPC}} = 59.7$ kDa, $M_w/M_n = 1.15$; Figure S2).

Characterization

Nuclear magnetic resonance (NMR) spectroscopy. All ¹H NMR spectra were performed at on a Bruker AV300 NMR spectrometer (resonance frequency of 300 MHz for ¹H and 75 MHz for ¹³C) operating in the Fourier transform mode.

Gel permeation chromatography (GPC). Molecular weight distributions were determined by GPC using a series of three linear Styragel columns HR2, HR4, HR5 and an oven temperature of 45°C . Waters 1515 pump and Waters 2414 differential refractive index detector (set at 30°C) was used. The eluent was

DMF or THF at a flow rate of 1.0 mL/min. A series of six polystyrene standards with molecular weights ranging from 800 to 400,000 g/mol were used for calibration.

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). The spectrum was recorded in the linear mode on a Bruker BIFLEXe III using a nitrogen laser (337 nm) and an accelerating potential of 20 kV. 1,8,9-Anthracenetriol (Fluka) was used as the matrix.

Laser light scattering (LLS). A commercial spectrometer (ALV/DLS/SLS-5022F) equipped with a multi-tau digital time correlator (ALV5000) and a cylindrical 22 mW UNIPHASE He-Ne laser ($\lambda_0 = 632$ nm) as the light source was employed for dynamic and static LLS measurements. In static LLS, we can obtain the weight-average molar mass (M_w) and the *z*-average root-mean square radius of gyration ($\langle R_g^2 \rangle^{1/2}$ or written as $\langle R_g \rangle$) of polymer chains in a dilute solution from the angular dependence of the excess absolute scattering intensity, known as Rayleigh ratio $R_{vv}(q)$, as

$$\frac{KC}{R_{vv}(q)} \approx \frac{1}{M_w} \left(1 + \frac{1}{3} \langle R_g^2 \rangle q^2 \right) + 2A_2C \quad (1)$$

where $K = 4\pi^2 n^2 (dn/dc)^2 / (N_A \lambda_0^4)$ and $q = (4\pi n / \lambda_0) \sin(\theta/2)$ with N_A , dn/dc , n , and λ_0 being the Avogadro number, the specific refractive index increment, the solvent refractive index, and the wavelength of the laser light in a vacuum, respectively; and A_2 is the second virial coefficient. Strictly speaking, here $R_{vv}(q)$ should be $R_{vu}(q)$ because there is no analyzer before the detector. However, the depolarized scattering of the solution studied is insignificant so that $R_{vu}(q) \sim R_{vv}(q)$. Also note that in this study, the sample solution for LLS was so dilute (1.0×10^{-4} g/mL) that the extrapolation of $C \rightarrow 0$ was not necessary, and the term $2A_2C$ in eq 1 can be neglected, the obtained M_w value is denoted as the apparent molecular weight, $M_{w, \text{app}}$.

In dynamic LLS, scattered light was collected at a fixed angle of 90° for duration of ~ 10 min. Distribution averages and particle size distributions were computed using cumulants analysis and CONTIN routines. All data were averaged over three measurements. The solution pH was adjusted as required using concentrated NaOH or HCl. Dust particles were removed by filtering the polymer solutions through $0.45 \mu\text{m}$ pore-size membrane filters (Millipore).

Fluorescence spectroscopy. Fluorescence spectra were recorded using a Shimadzu RF-5301PC spectrofluorometer. The temperature

of the water-jacketed cell holder was controlled by a programmable circulation bath. The slit widths were set at 10.0 and 2.5 nm for the excitation and the emission, respectively. Calculated volume of pyrene solution in acetone was added into a volumetric flask, followed by removing the acetone under reduced pressure. Polymer solution was then added into the volumetric flask, pyrene concentration was fixed at 5×10^{-7} mol/L. All the samples were sonicated for 2 h and then allowed to stand overnight before fluorescence measurements.

Transmission electron microscopy (TEM). Transmission electron microscopy (TEM) measurements were conducted on a Philips CM 120 electron microscope at an acceleration voltage of 100 kV. The samples for TEM observations were prepared by placing 10 μ L of solutions at a concentration of 0.5 g/L on copper grids, which were coated with thin films of Formvar and carbon successively. No staining was required.

Results and discussion

Synthesis of Janus-Type A₇B₁₄ heteroarm star copolymers, (PDEA)₇-CD-(PNIPAM)₁₄

Janus-type A₇B₁₄ heteroarm star copolymers of NIPAM and DEA, (PDEA)₇-CD-(PNIPAM)₁₄, were synthesized *via* a combination of ATRP and click chemistry techniques, starting from well-defined β -CD derivative (Scheme 1). The preparation of β -CD-(I)₇ *via* the selective transformation of seven primary hydroxyl groups of β -CD has been previously reported by Ashton *et al.*⁴³ The chemical structure of β -CD-(N₃)₇ has been confirmed by ¹H NMR, ¹³C NMR, and MALDI-TOF MS (Fig. 1 and 2, Figure S1, ESI[†]). In the next step, (N₃)₇-CD-(Br)₁₄ was synthesized by the esterification reaction of β -CD-(N₃)₇ with an excess of 2-bromopropionic bromide. Initial attempts using pyridine or pyridine/CHCl₃ mixture as the solvent failed to produce the target compound with high purity and a reasonable yield. Inspired by the work of Xiao *et al.*,²² the esterification reaction of β -CD-(N₃)₇ was conducted at room temperature in *N*-methyl-2-pyrrolidone (NMP) for 4 days. Compared to that of β -CD-(N₃)₇, ¹H NMR spectrum of (N₃)₇-CD-(Br)₁₄ revealed the appearance of a new signal at 1.88 ppm, which can be ascribed to methyl protons of BrCH(CH₃) (Fig. 1b). Peak integral ratio of resonance signals at 1.88 ppm to those in the range of 3.5–5.5 ppm verified that the esterification reaction was 100% complete. ¹³C NMR spectrum of (N₃)₇-CD-(Br)₁₄ exhibited the appearance of signals at 21.3, 39.9, and 169.3 ppm, which can be ascribed to methyl and methine carbons and carbonyl moieties, respectively (Figure S1, ESI[†]). MALDI-TOF MS analysis (Fig. 2b) further confirmed the structure of (N₃)₇-CD-(Br)₁₄ (*m/z*: calcd for C₈₄H₁₀₆O₄₂N₂₁Br₁₄ (M + H⁺), 3185.5; found, 3185.2).

The multifunctional initiator, (N₃)₇-CD-(Br)₁₄, contains 7 azido groups on one side of the stiff toroid and 14 bromine moieties on the opposing side of β -CD. Recently, a series of 7-arm and 21-arm star polymers have been controllably synthesized *via* the grafting-from approach using β -CD-based precursors as the initiator.^{20,22–25,27,29,42} In the current study, 14-arm PNIPAM star polymer was synthesized by the ATRP of NIPAM monomer in 2-propanol/DMF mixture using (N₃)₇-CD-(Br)₁₄ as the initiator and CuCl/Me₆TREN as the catalyst.^{48,49} DMF GPC

analysis based on polystyrene standards revealed a mono-modal and symmetric elution peak with an apparent *M_n* of 42.6 kDa and *M_w/M_n* of 1.09 (Figure S2, ESI[†]). Compared to that of (N₃)₇-CD-(Br)₁₄ initiator, GPC elution trace of the star polymer clearly shifted to the higher MW side. Assuming a quantitative initiating efficiency, the degree of polymerization (DP) of PNIPAM arms was calculated to be 25 from ¹H NMR analysis by comparing resonance signals in the range of 4.7–5.5 ppm characteristic of β -CD cores with that at 4.0 ppm (characteristic of PNIPAM) (Fig. 3). Thus, the obtained 14-arm star polymer was denoted as (N₃)₇-CD-(PNIPAM₂₅)₁₄. FT-IR spectrum of (N₃)₇-CD-(PNIPAM₂₅)₁₄ clearly revealed the presence of an absorbance peak at \sim 2100 cm⁻¹, which is characteristic of azide moieties (Figure S3, ESI[†]).

Janus-type A₇B₁₄ heteroarm star copolymer, (PDEA₃₀)₇-CD-(PNIPAM₂₅)₁₄ was obtained by the click reaction of (N₃)₇-CD-(PNIPAM₂₅)₁₄ with an excess of *alkynyl*-PDEA₃₀ to ensure complete consumption of azido moieties in 14-arm PNIPAM star polymers. Excess of *alkynyl*-PDEA was readily removed *in situ* “click” grafting onto azido-functionalized Merrifield resin followed by a simple filtration step.^{42,50} Compared to that of (N₃)₇-CD-(PNIPAM₂₅)₁₄, GPC elution peak of Janus heteroarm star copolymer, (PDEA₃₀)₇-CD-(PNIPAM₂₅)₁₄, clearly shifted to the higher MW region, yielding an apparent *M_n* of 59.7 kDa and *M_w/M_n* of 1.15 (Figure S2, ESI[†]). ¹H NMR analysis revealed that peak integral ratio of resonance signals characteristic of PNIPAM and PDEA sequences agrees with the relative arm lengths. Moreover, FT-IR analysis clearly confirmed the complete disappearance of characteristic azide absorbance peak at \sim 2100 cm⁻¹ after click reaction, as compared to that of (N₃)₇-CD-(PNIPAM₂₅)₁₄ (Figure S3, ESI[†]). All of these results confirmed the successful preparation of β -CD-based Janus-type heteroarm star polymers. Table 1 summarizes structural parameters of (PDEA₃₀)₇-CD-(PNIPAM₂₅)₁₄.

Multi-responsive self-assembly of Janus-type heteroarm star polymers in aqueous solution

PNIPAM and PDEA homopolymers exhibit fundamentally different stimuli-responsive water-solubility. PNIPAM homopolymer dissolves in cold and dilute aqueous solution but becomes insoluble at \sim 32 °C due to the lower critical solution temperature (LCST) phase transition behavior.⁵¹ PDEA homopolymer is a weak polybase and its conjugated acid possesses a *pK_a* of \sim 7.3. It is water-insoluble at neutral or alkaline pH; whereas below pH 6, it is soluble as a weak cationic polyelectrolyte due to protonation of tertiary amine residues.^{52,53} At pH 4 and 25 °C, it is reasonable to speculate that (PDEA)₇-CD-(PNIPAM)₁₄ will adopt a Janus conformation in solution due to the protonation of PDEA arms and that well-solvated PNIPAM and PDEA arms are respectively grafted onto two opposing sides of the stiff toroidal β -CD. In conventional heteroarm star copolymers, Janus-type conformation can be achieved *via* the selective solvent-induced collapse of one type of polymer arm.^{14,15,18} In the current case, the presence of a rigid β -CD core can endow (PDEA)₇-CD-(PNIPAM)₁₄ with a relatively persistent Janus conformation in aqueous solution, though we can not fully exclude the possibility of partial overlapping between two types of polymer arms with the star corona.

It is quite expected that (PDEA)₇-CD-(PNIPAM)₁₄ can exhibit dually responsive “schizophrenic” aggregation behavior due to presence of pH-responsive PDEA and thermoresponsive PNIPAM arms. Two characteristic solution conditions, pH 10 and 25 °C, and pH 4 and 45 °C, were then chosen to selectively render PDEA and PNIPAM arms insoluble. The formation of stable aggregates at both conditions is clearly evident by the appearance of bluish tinge characteristic of colloidal dispersions. Critical aggregation concentrations (CACs) of (PDEA₃₀)₇-CD-(PNIPAM₂₅)₁₄ at two different conditions (pH 4, 45 °C; pH 10, 25 °C) were determined by using pyrene as the fluorescent probe (Figure S4, ESI[†]). Coincidentally, CAC values of (PDEA₃₀)₇-CD-(PNIPAM₂₅)₁₄ under both conditions were *ca.* 0.015 g/L, which were considerably lower than those of typical double hydrophilic block copolymers.^{54,55} It is worth noting that below CACs, (PDEA)₇-CD-(PNIPAM)₁₄ unimers exist in a more strict Janus conformations due to the selective collapse of polymer arms on the one side of β-CD toroid.^{14,16}

The multi-responsive formation of two types of aggregates at two different solution conditions has also been further supported by ¹H NMR results (Fig. 4).^{53,56} At 25 °C and pH 4, both PNIPAM and PDEA blocks are hydrophilic, thus Janus-type star copolymers molecularly dissolves in dilute aqueous solution and ¹H NMR signals due to both PNIPAM and PDEA blocks are clearly visible. Upon increasing the temperature to 45 °C at pH 4, we can clearly observe the disappearance of characteristic PNIPAM signals at δ = 1.2 and 4.0 ppm, as well as the presence of PDEA signals at δ = 1.5 and 3.4–3.7 ppm, suggesting that PNIPAM arms are rendered insoluble. The characteristic bluish tinge of the dispersion indicates the formation of PNIPAM-core aggregates. On the other hand, upon addition of a small amount of NaOD into the molecularly dissolved solution at 25 °C, aggregation occurs above ~pH 8, as judged by the appearance of bluish tinges characteristic of colloidal dispersions. At pH 10 and 25 °C, NMR signals characteristic of PDEA sequences at δ = 1.5, 3.4, and 3.7 ppm completely disappear. This suggests the formation of another type of aggregates due to that PDEA arms become insoluble.

Fig. 5a shows the pH dependence of intensity-average hydrodynamic radius, <R_h>, obtained by dynamic LLS for (PDEA₃₀)₇-CD-(PNIPAM₂₅)₁₄ in aqueous solution. Below pH 6, it molecularly dissolves in water, exhibiting a <R_h> of *ca.* 7 nm and quite low scattering intensity. Upon addition of NaOH, aggregation occurs above pH 7–8 as judged by the characteristic

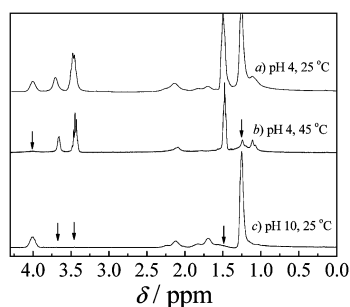


Fig. 4 ¹H NMR spectra recorded in D₂O for double hydrophilic Janus-type A₇B₁₄ star polymer, (PDEA₃₀)₇-CD-(PNIPAM₂₅)₁₄, at different conditions: (a) 25 °C, pH 4; (b) 45 °C, pH 4; and (c) 25 °C, pH 10.

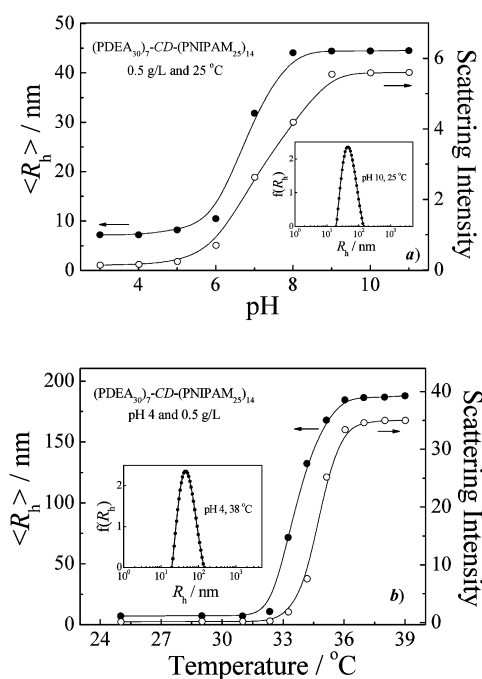


Fig. 5 Variation of intensity-averaged hydrodynamic radius, <R_h>, and scattering intensities as a function of (a) pH and (b) temperatures obtained for Janus-type A₇B₁₄ star copolymer, (PDEA₃₀)₇-CD-(PNIPAM₂₅)₁₄, in aqueous solution. The insets show typical hydrodynamic radius distribution, *f*(R_h), of aggregates formed at pH 10 and 25 °C, and pH 4 and 38 °C, respectively, as determined by dynamic LLS at a scattering angle of 90°.

bluish tinge. Above pH 8, the sizes of aggregates remain almost constant with a <R_h> of ~45 nm and a polydispersity index, μ₂/Γ², of 0.09 (inset in Fig. 5a). Fig. 5b shows temperature-dependent <R_h> changes at pH 4 and a polymer concentration of 0.5 g/L. (PDEA₃₀)₇-CD-(PNIPAM₂₅)₁₄ Janus-type star copolymer molecularly dissolves in water below ~32 °C. Above that, micellization starts to occur, which is accompanied with the dramatic increase of <R_h> and scattering intensities. Dynamic LLS only reveals one population of diffusing species at temperatures higher than 36 °C, and the aggregate sizes remain stable with <R_h> of *ca.* 185 nm and a polydispersity of 0.11 (inset in Fig. 5b). These results suggest that thermo-induced aggregates of (PDEA₃₀)₇-CD-(PNIPAM₂₅)₁₄ are much larger than pH-induced ones. It should be noted that both types of aggregates formed at pH 10 and 25 °C, as well as at pH 4 and 45 °C are stable for more than three months. Moreover, the self-assembled nanostructures are completely reversible as evidenced by LLS results, *i.e.*, the tuning of external conditions can switch between the two types of aggregates and the unimers state.

The actual morphologies of the two types of self-assembled aggregates formed at different solution conditions were further characterized by TEM studies, and representative images were shown in Fig. 6. At pH 4 and 45 °C, which is above the phase transition temperature of PNIPAM arms, TEM observation reveals the presence of robust hollow capsules with diameters in the range of 130–200 nm. In combination with ¹H NMR and dynamic LLS results presented above (Fig. 4 and 5), we can tell that in the formed vesicular aggregates, hydrophilic and

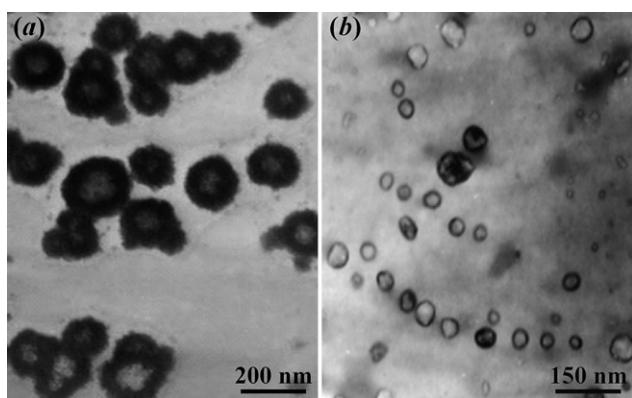


Fig. 6 Transmission electron microscopy images obtained for aggregates self-assembled from double hydrophilic Janus-type A_7B_{14} heteroarm star copolymer, $(PDEA_{30})_7-CD-(PNIPAM_{25})_{14}$, in aqueous solution at (a) pH 4 and 45 °C, and (b) pH 10 and 25 °C.

protonated PDEA arms forms the corona and PNIPAM sequences locate within the hydrophobic membrane walls (Scheme 2). Vesicle formation from PNIPAM-containing linear diblock copolymers at elevated temperatures was previously reported by McCormick *et al.*⁵⁷ Unexpectedly, at pH 10 and 25 °C, another type of vesicle aggregates with diameters in the range of 30–50 nm was formed. On the basis of chemical intuition, the second type of vesicles formed in aqueous solution should possess hydrophilic PNIPAM coronas and hydrophobic PDEA bilayers.

Static LLS measurements reveal that vesicles formed at pH 10 and 25 °C, and pH 4 and 45 °C possess apparent molar masses, $M_{w,app}$, of 3.35×10^6 and 6.72×10^7 g/mol, average aggregation numbers, N_{agg} , of 36 and 715, and average radii of gyration, $\langle R_g \rangle$, of 46 nm and 178 nm, respectively. A combination of dynamic and static LLS results (Fig. 5 and Figure S5, ESI†) reveals that $\langle R_g \rangle / \langle R_h \rangle$ ratios for the two types of vesicles formed at pH 10 and 25 °C, and pH 4 and 45 °C are 1.02 and 0.96, respectively, which are very close to the $\langle R_g \rangle / \langle R_h \rangle$ ratio of 1.0 predicated for hollow spheres. This further confirms the formation of two distinct types of vesicles under both conditions.

The stimuli-responsive formation of two types of vesicles possessing “inverted” nanostructures from purely synthetic nonlinear double hydrophilic block copolymers has been unprecedented. Previous literature reports concerning linear DHBCs mainly focus on the stimuli-responsive formation of two or more types of micellar aggregates in aqueous solution.^{57,58–62} A notable previous example, pH-induced vesicle inversion of linear poly(L- glutamic acid)-*b*-poly(L-lysine) diblock copolymer in water, was reported by Rodriguez-Hernandez and Lecommandoux in 2005.⁶⁰ The presence of secondary structures of polypeptide segment in the hydrophobic bilayer contributes to the stability of both types of vesicles. Generally speaking, the formation of vesicles from linear diblock copolymers needs a delicate design of relative block lengths and proper hydrophilic/hydrophobic balance,^{63–67} and it is almost impossible for the same block copolymer to self-assemble into two structurally inverted vesicular aggregates. In the current case, we ascribe this rare type of “schizophrenic” vesicle formation to the unique Janus-type topology of $(PDEA_{30})_7-CD-(PNIPAM_{25})_{14}$. A

schematic illustration of the stimuli-responsive reversible formation of two types of vesicular aggregates is shown in Scheme 2.

Conclusion

In summary, novel stimuli-responsive double hydrophilic Janus-type A_7B_{14} star copolymers based on the β -CD derivative have been synthesized *via* the combination of ATRP and click reaction. $(PDEA_{30})_7-CD-(PNIPAM_{25})_{14}$ Janus heteroarm star copolymer forms two types of vesicles with “inverted” nanostructures in water by properly tuning solution pH and temperatures. Moreover, the formation of and switching between both types of vesicular aggregates and the unimer state are fully reversible. This work represents a novel example of stimuli-responsive vesicle formation/inversion from purely synthetic nonlinear double hydrophilic block copolymers in aqueous solution.

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