Synthesis and properties of couplable ABCDE star copolymers by orthogonal CuAAC and Diels-Alder click reactions

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The exploration on robust methods to construct star copolymers has attracted much attention. Owing to the great challenge in synthesis, the examples of miktoarm stars with chemical compositions up to five or more are very scarce. This study aims at developing modular and orthogonal approach to synthesize multicomponent stars via one-pot strategy using distinct building blocks. Tandem CuAAC and Diels-Alder reactions were utilized to generate ABCDE star comprising poly(ε-caprolactone) (PCL, A), poly(*tert*-butyl acrylate) (P*t*BA, B), poly(L-lactide) (PLLA, C), poly(*N*-isopropylacrylamide) (PNIPAM, D) and poly(5-methyl-5-allyloxycarbonyl-1,3-dioxane-2-one) (PMAC, E) arms, and a subsequent hydrolysis afforded poly(acrylic acid) (B') bearing AB'CDE star with clickable and dual-sensitive segments. The star copolymers were liable to self-assemble into intriguing morphologies involving vesicles, spherical micelles and large compound micelles which could be tuned by adopting thermo and pH stimuli. The modular synthesis using orthogonal chemistry allows us to prepare ABCDE-type stars with well-controlled molecular weight, tunable composition, and versatile functions. The success of this study further paves way for facile synthesis of multifunctional star quintopolymers and their derivatives with multipurpose applications.

Introduction

Precise synthesis and versatile applications of complex macromolecular architectures are eternal topics in current polymer science. As an important member of nonlinear macromolecules, star polymers with outer arm segments and inner central core can be roughly classified into homoarm star with same composition and miktoarm star bearing chemically different arm species. Synthesis and properties of miktoarm stars have attracted increasing attention in recent years due to the great challenge in controlled synthesis, unique morphologies and supramolecular assemblies different from their linear analogues, and multipurpose applications.[1–30] With enhanced compositions, variable functional segments can be readily introduced into miktoarm stars, further endowing the polymeric materials with a wide range of tunable functions and applications. Thus far, a wide range of miktoarm star copolymers,[5–10] terpolymers[11–22] and quaterpolymers[23–30] have been controllably synthesized. However, synthesis of star copolymers with compositions beyond 4 remains scarce since multistep polymerizations are required to introduce different arms and several selective linking and postmodification reactions are necessary to attach different arms to the central core.[31–40]

In previous researches, Hirao and coworkers have systematically developed iterative methodologies via individually introducing various arms to achieve miktoarm stars with 5-9 chemical compositions.[31–38] Considering some monomers are difficult to be directly polymerized via living anionic polymerization, we have developed a novel "1+2+2" synthetic strategy to generate 5-arm ABCDE stars via selective and successive copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reactions,[41] in which "1" and "2" stand for the segment number of building blocks.[39,40] This approach has been proven to be efficient as selective reaction between A and BC performs smoothly, however, there are two remaining limitations when it acts as a robust synthetic method. First, excess diazide-functionalized A should be efficiently removed from the mixture of A and ABC star via some approaches such as fractional precipitation and HPLC separation. Second, two azide moieties of A may simultaneously participate in the initial click reaction to give low-component AB_2C_2 star as steric hindrance can't be ignored,[42] leading to the eventual production of AB_2C_2 and ABCDE mixed stars. In this context, it is extremely urgent to further explore more versatile routes to create well-defined star quintopolymers.

On the other hand, orthogonal and modular ligation techniques have revolutionized advanced polymer synthesis.[43–58] Orthogonal strategy with high chemoselectivity allows for versatile synthesis and postmodification via stepwise and one-pot linking reactions, and modular synthesis enables straightforward construction of functional copolymers using different building blocks based on polymer segments. For instance, the orthogonal synthesis has been widely used to generate a wide range of topological polymers involving dendrimers,[59–63] multiarm and miktoarm stars,[20,21,64] dendroinized,[65,66] tadpole,[67] comblike,[68–70] and supramolecular copolymers[71–75] in addition to the application in postmodification to

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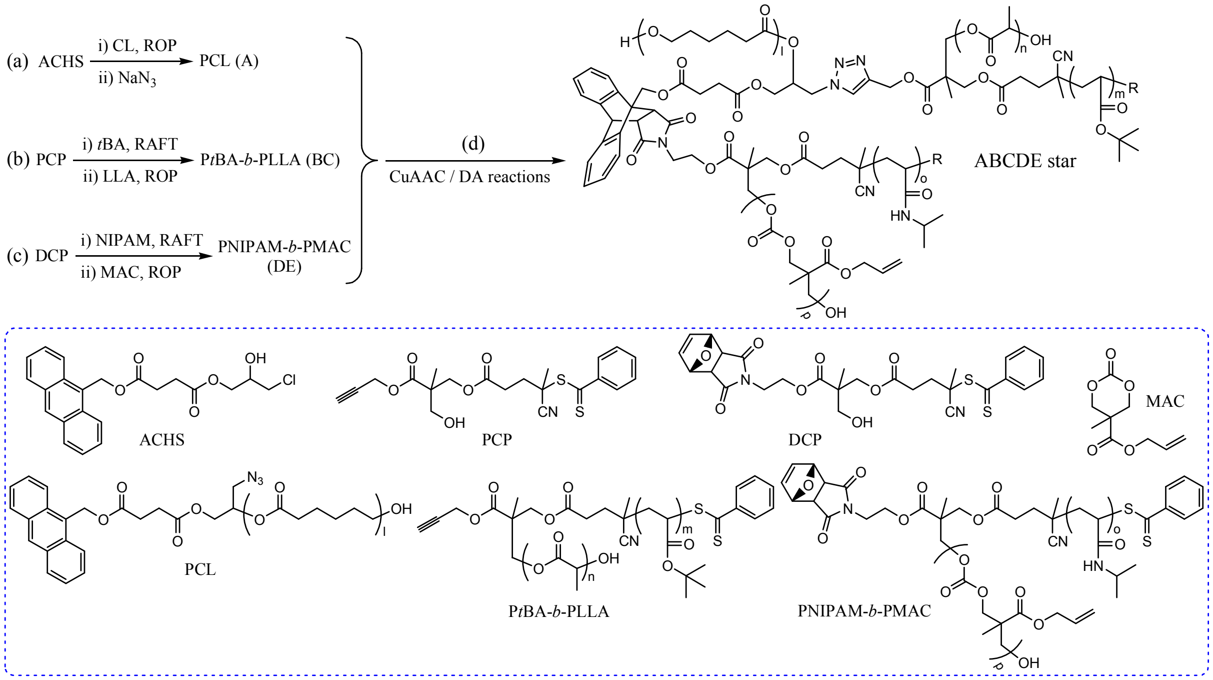

Scheme 1 Synthesis of couplable PCL-P*t*BA-PLLA-PNIPAM-PMAC (ABCDE) star copolymer by one-pot copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) and Diels-Alder (DA) reactions.

construct copolymers with increasing compositions and functions. Thus far, modular technique has been extended to construct some star copolymers such as ABCD-[25–30] and ABCDE-type[39,40] miktoarm stars, and orthogonal chemistry has been applied to generate some ABC-type covalent[20,21] and supramolecular[71–73] star terpolymers. To our surprise, ABCDE-type star quintopolymers have not been achieved by combination of modular and orthogonal synthesis strategies which are extremely promising in facile construction of multicomponent copolymers.

In this study, orthogonal chemistry is chosen to address the limitations remaining in the traditional modular “1+2+2” strategy[39] using the same type of ligation method. To this end, an alternative approach involving tandem CuAAC and Diels-Alder (DA) click reactions is developed to prepare multifunctional ABCDE stars (Scheme 1). The target star comprises poly(ε-caprolactone) (PCL, A), poly(*tert*-butyl acrylate) (P*t*BA, B), poly(L-lactide) (PLLA, C), poly(*N*-isopropylacrylamide) (PNIPAM, D) and poly(5-methyl-5-allyloxycarbonyl-1,3-dioxane-2-one) (PMAC, E) segments. Among them, PCL and PLLA are biodegradable and crystallizable, PNIPAM is responsive to temperature, P*t*BA can be converted into pH-sensitive poly(acrylic acid) (PAA, B’), and PMAC is a biodegradable polycarbonate suitable for thiol-ene reaction.[76–79] The integration of multiple segments endows star copolymer with some unique properties involving biodegradability, stimuli-responsiveness, and versatile postmodification. The success of this study reveals the great potential of modular and orthogonal strategy in synthesis of functional miktoarm stars. In addition, various booming orthogonal reactions potentially enable us to further generalize this concept to construct various types of covalent, dynamic, and supramolecular miktoarm stars with tunable composition and rich topology.

Results and discussion

Synthesis of PCL-PAA-PLLA-PNIPAM-PMAC star and its precursors

To perform the modular synthesis, three kinds of polymers, namely, *α*-anthracene-*α*-azide-functionalized PCL, alkyne-mid-functionalized P*t*BA-*b*-PLLA, and furan-protected maleimide-mid-functionalized PNIPAM-*b*-PMAC, were initially synthesized by ROP and RAFT polymerization (Scheme 1). On this basis, they acted as building blocks to construct the target star via orthogonal CuAAC and DA click reactions. The detailed syntheses were described below.

First, end-functionalized PCL (A) was synthesized by combination of ROP and end group transformation (run 1 of Table 1). To this end, (anthracen-9-yl)methyl 3-chloro-2-hydroxypropyl succinate (ACHS, Scheme S1 in the Supporting Information) was synthesized by one-pot two-step reactions (Fig. 1a and Fig. S1). ROP of CL initiated with ACHS was performed in dry toluene, and the isolated PCL was further subjected to azidation. After precipitation into methanol, dual-end-functionalized PCL was obtained in 97.0% yield. In ^{1}H NMR spectrum (Fig. 2), characteristic signals appeared at 7.4-8.6 (Ar*H*), 6.19 (ArC*H*$_2$O), 3.8-4.5 (C*H*$_2$O of PCL, C*H*$_2$O and C*H*O), 3.65 (terminal C*H*$_2$OH), 3.42 (C*H*$_2$N$_3$), 2.31 (C*H*$_2$CO of PCL), 1.65 (C*H*$_2$CH$_2$C*H*$_2$CH$_2$CO of PCL), and 1.38 ppm (CH$_2$CH$_2$C*H*$_2$CH$_2$CO of PCL). The integrated area at 3.42 (C*H*$_2$N$_3$) agreed well with that at 6.19 ppm (ArC*H*$_2$O), corresponding to quantitative azidation process. By comparing the integrated signal areas at 2.31 (C*H*$_2$CO of PCL) and 6.19 ppm (ArC*H*$_2$O), polymerization degree and molecular weight ($M_{n,NMR}$) were calculated as 30 and 3830 g mol^{-1}, respectively. The molecular weight given by ^{1}H NMR analysis was similar to the theoretical value ($M_{n,th}$ = 3720 g mol^{-1}). The GPC trace exhibited monomodal distribution, with relatively low polydispersity (PDI =

1.09, Fig. 3). In IR spectrum (Fig. S3a), typical absorptions of various moieties appeared at 2100 (ν_{N3}), 1725 ($\nu_{C=O}$), 840, 733 and 708 cm^{-1} (ν_{C-H} of anthracenyl moiety).

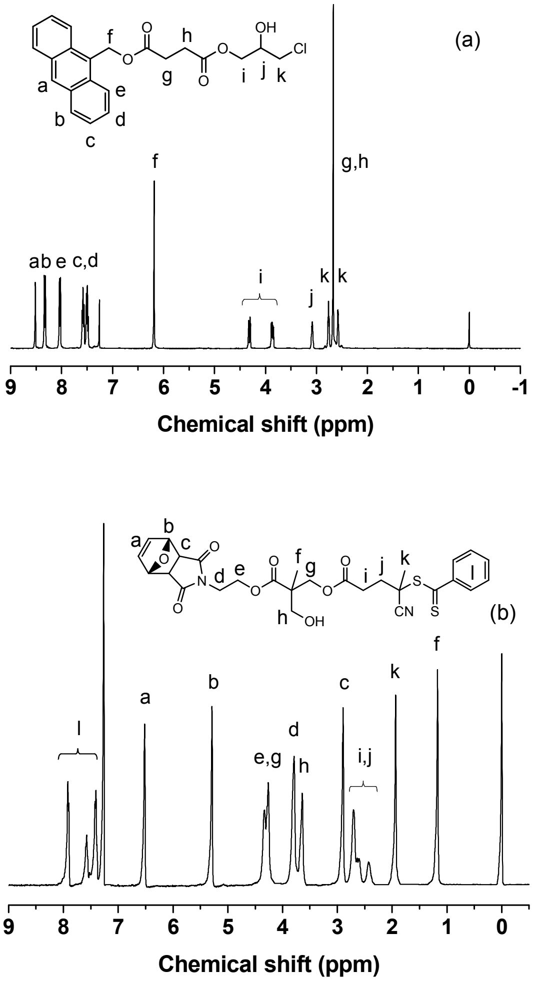

Fig. 1 ^{1}H NMR spectra of ACHS (a) and DCP (b).

Second, alkyne-mid-functionalized P*t*BA-*b*-PLLA (BC) diblock copolymer was prepared via two-step polymerizations using propargyl 5-cyano-5-phenylthiocarbonylsulfanylpentanoyloxy-2-hydroxymethyl-2-methylpropanoate (PCP)[39] as a multifunctional agent (runs 2 and 3 of Table 1). PCP mediated RAFT polymerization of *t*BA gave α-alkyne-α-hydroxyl-terminated P*t*BA (B, Fig. 4a), and followed by ROP of LLA to generate alkyne-bearing BC copolymer. In ^{1}H NMR spectrum of P*t*BA-*b*-PLLA (Fig. 4b), typical signals appeared at 7.3-8.0 ($\mathrm{Ph}\mathit{H}$), 5.17 ($\mathrm{C}\mathit{H}$ of PLLA), 4.72 ($\mathrm{CH{\equiv}CC}\mathit{H}_2\mathrm{O}$), 2.50 ($\mathrm{C}\mathit{H}\mathrm{{\equiv}CCH_2O}$), 2.23 ($\mathrm{C}\mathit{H}$ of P*t*BA), 1.59 ($\mathrm{C}\mathit{H}_3$ of PLLA), and 1.44 ppm ($\mathrm{C}\mathit{H}_3$ of P*t*BA). After LLA polymerization, the signal at 3.71 ppm ($\mathrm{CC}\mathit{H}_2\mathrm{OH}$, e of Fig. 4a) was completely disappeared, and a new signal corresponding to terminal $\mathrm{C}\mathit{H}\mathrm{OH}$ of PLLA block (e' of Fig. 4b) was quantitatively observed at 4.37 ppm, confirming the highly efficient ROP process. Polymerization degrees were determined to be 48 ($DP_{PtBA} = 2I_{2.0\text{-}2.4}/I_{4.72} - 2$) and 38 ($DP_{PLLA} = I_{5.17}/I_{4.72} + 0.5$) by ^{1}H NMR analysis, and the $M_{n,NMR}$ values of B and BC were in good accordance with the expected values. The GPC trace of BC copolymer wholly shifted to higher molecular weight side as compared with its precursor B (Fig. 3), and their polydispersity indices were in the range of 1.06-1.08.

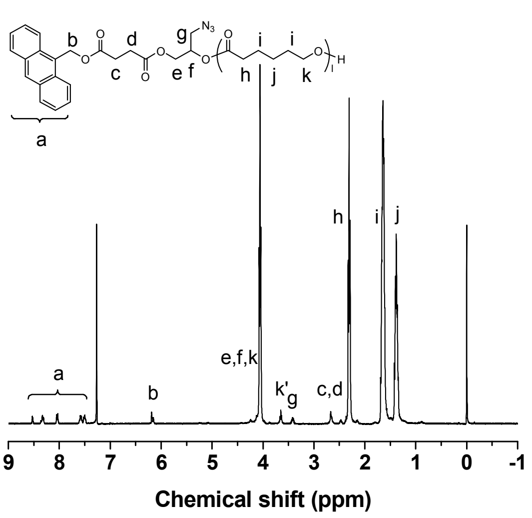

Fig. 2 ^{1}H NMR spectrum of α-anthracene-α-azide-terminated PCL, in which k' denotes terminal $\mathrm{C}\mathit{H}_2\mathrm{OH}$.

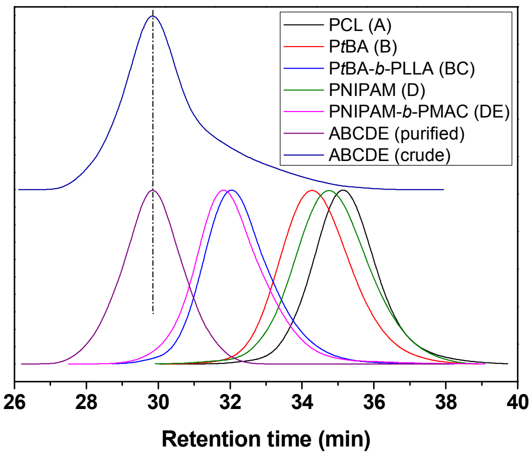

Fig. 3 GPC traces of various linear (co)polymers and PCL-P*t*BA-PLLA-PNIPAM-PMAC (ABCDE) star copolymers before (crude) and after (purified) reaction with surface-functionalized silica particles.

Third, furan-protected maleimide-mid-functionalized PNIPAM-*b*-PMAC (DE) diblock copolymer was generated using a specially designed agent 2-(3,5-dioxo-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)ethyl 5-cyano-5-phenylthiocarbonylsulfanylpentanoyloxy-2-hydroxymethyl-2-methylpropanoate (DCP, Fig. 1b and Fig. S4). DCP mediated RAFT polymerization of NIPAM gave PNIPAM (D, Fig. 5a), and followed by 1,8-diazabicycloundec-7-ene (DBU) catalyzed ROP of MAC to afford DE copolymer. In ^{1}H NMR spectrum of PNIPAM-*b*-PMAC (Fig. 5b), signals originating from the initiator appeared at

Table 1 Results for synthesis of PCL (A), P*t*BA (B), P*t*BA-*b*-PLLA (BC), PNIPAM (D), PNIPAM-*b*-PMAC (DE), and ABCDE star[a]

run	polymer	I[b]	M	DP_0	C/Y[c]	$M_{n,th}$[d]	$M_{n,GPC}$[e]	PDI[e]	$M_{n,NMR}$ (DP_{PM})[f]
1	A	ACHS	CL	30	0.970	3720	5650	1.09	3830 (30)
2	B	PCP	*t*BA	100	0.505	6910	7320	1.06	6590 (48)
3	BC	P*t*BA	LLA	50	0.764	12100	12800	1.08	12100 (38)
4	D	DCP	NIPAM	80	0.648	6440	6300	1.08	6240 (50)
5	DE	PNIPAM	MAC	80	0.479	13900	13700	1.11	13400 (36)
6	ABCDE	—	—	—	0.851	29300	24200	1.08	29600 (—)

[a] Reaction conditions: $[M]_0$ = 3.0 mol L^{-1} (runs 1-5), $[CL]_0:[ACHS]_0:[Sn(Oct)_2]_0$ = 30:1:0.2, in toluene at 90 °C for 20 h, and then followed by azidation (run 1); $[tBA]_0:[PCP]_0:[AIBN]_0$ = 100:1:0.1, in toluene at 60 °C for 20 h (run 2); $[LLA]_0:[PtBA]_0:[Sn(Oct)_2]_0$ = 50:1:0.2, in toluene at 90 °C for 20 h (run 3); $[NIPAM]_0:[DCP]_0:[AIBN]_0$ = 80:1:0.2, in dioxane at 70 °C for 18 h (run 4); $[MAC]_0:[PNIPAM]_0:[DBU]_0$ = 80:1:0.5, in dioxane at 70 °C for 18 h (run 5); $[A]_0:[BC]_0:[DE]_0:[Cu(PPh_3)_3Br]_0$ = 1:1.1:1.1:1, $W_{polymer}:V_{DMF}$ = 0.10 g mL^{-1} (run 6). [b] Initiator (runs 1, 3 and 5) or RAFT agent (runs 2 and 4). [c] Monomer conversion (C, runs 1-5) or yield (Y, run 6) determined by gravimetry. [d] Theoretical molecular weight (g mol^{-1}). [e] Apparent molecular weight (g mol^{-1}) and polydispersity estimated by GPC. [f] Number-average molecular weight ($M_{n,NMR}$, g mol^{-1}) and degree of polymerization (DP_{PM}) determined by ^1H NMR analysis.

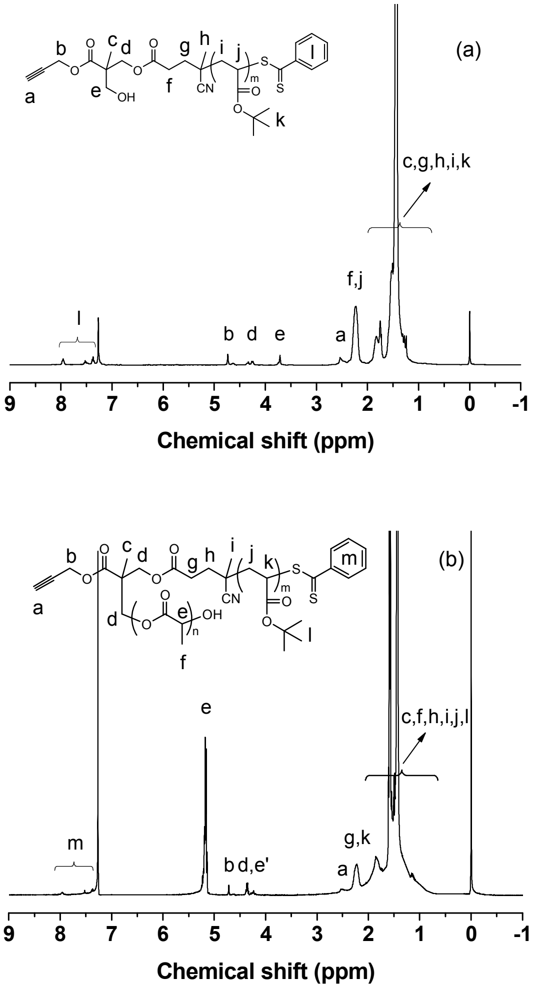

Fig. 4 ^1H NMR spectra of P*t*BA (a) and P*t*BA-*b*-PLLA (b), in which e' indicates terminal $CH(CH_3)OH$.

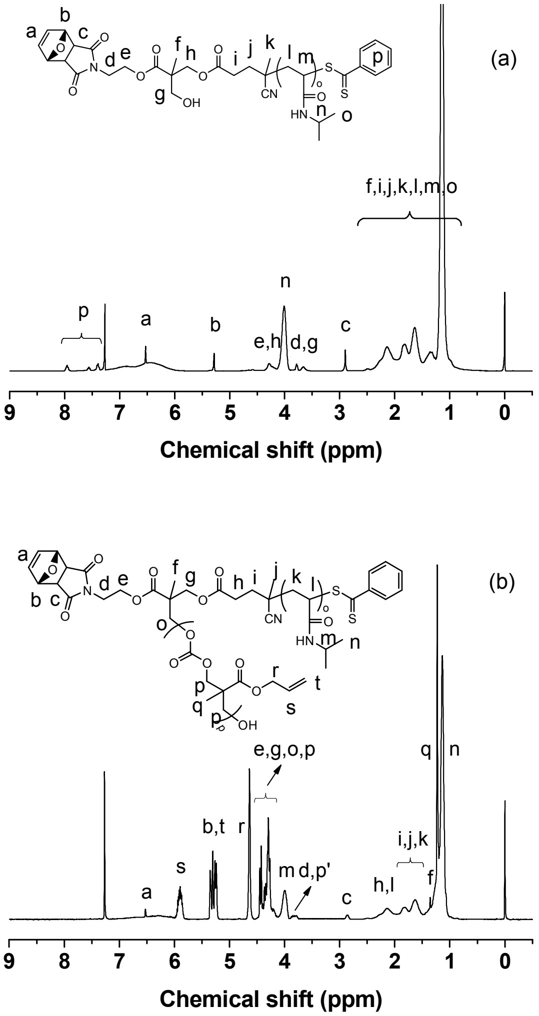

Fig. 5 ^1H NMR spectra of PNIPAM (a) and PNIPAM-*b*-PMAC (b), in which p' means terminal CH_2OH.

about 6.52 (C*H*=C*H*), 5.29 (C*H*O), 3.78 (NCH_2) and 2.86 ppm (C*H*CON), signals ascribing to PNIPAM block appeared at 4.00 (C*H*NH), 2.08 (C*H*CO) and 1.14 ppm (CH_3), and signals corresponding to PMAC block were noted at 5.8-6.0 (C*H*=CH_2), 5.2-5.4 (CH=CH_2), 4.64 (OCH_2CH=CH_2), 4.1-4.5 (CH_2O), and 1.23 ppm (CH_3). After MAC polymerization, the signal of original CCH_2OH (g of Fig. 5a) was completely absent in ^{1}H NMR spectroscopy, and new signals were noted at around 4.1-4.5 (CCH_2O connecting with PMAC) and 3.85 ppm (terminal CH_2OH of PMAC, p' of Fig. 5b). By comparing the integrated signal areas at 1.14 (CH_3 of PNIPAM), 4.64 (OCH_2CH=CH_2 of PMAC) and 2.86 ppm (C*H*CON of furan-protected maleimide unit), DP_{PNIPAM} ($I_{1.14}/(3I_{2.86})$) and DP_{PMAC} ($I_{4.64}/I_{2.86}$) were determined to be 50 and 36, respectively. The $M_{n,NMR}$ and $M_{n,th}$ values of D and DE were roughly comparable, and their GPC traces exhibited unimodal distribution, with polydispersity indices around 1.1 (Fig. 3).

Last, PCL (A), P*t*BA-*b*-PLLA (BC), and PNIPAM-*b*-PMAC (DE) were utilized as building blocks to construct amphiphilic ABCDE star via orthogonal reactions, and PCL-PAA-PLLA-PNIPAM-PMAC (AB'CDE) star was obtained by selective hydrolysis. Considering the compatible conditions of CuAAC and DA reactions, one-pot strategy using slightly excess BC and DE was adopted, and the mixture bearing $Cu(PPh_3)_3Br$ catalyst was stirred in DMF at 110 °C for 48 h. In GPC trace of crude product (Fig. 3), the higher molecular weight fraction could be ascribed to the target star, and the notable tailing corresponded to unreacted diblock copolymers and/or 3-arm star terpolymers. The impurities with low-component polymers may be removed by fractional precipitation at the cost of reduced yield. In this study, the heterogeneous graft reaction was used as an alternative and general method to isolate the desired star, in which the impurities comprising reactive functionalities were grafted onto silica particles and readily removed by filtration. To this end, various reactive moieties were bound to the surface of silica particles via alkoxysilane-hydroxyl coupling reaction and postmodification (Scheme S3), and the loadings (with unit of mmol per g silica) of surface-functionalized silica particles were around 0.612 (azide moiety), 0.398 (alkyne moiety), 0.320 (anthracene functionality) and 0.537 (maleimide functionality) given by TGA analysis (Fig. S6). As surface-functionalized silica particles were added to the mixture, the click reactions were further conducted for 20 h. After purification, ABCDE star was isolated in 85.1% yield.

In ^{1}H NMR spectrum of ABCDE star (Fig. 6), characteristic signals originating from the coupling reactions appeared at 7.71 (C*H*N, e), 7.0-7.5 (Ar*H*, m), 5.4-5.7 (CH_2O originating from click reactions, f and j), and 3.32 ppm (COC*H*C*H*CON, k), and typical signals of various arms were noted at 5.91 (C*H* of PMAC, s), 5.17 (C*H* of PLLA, h), 4.06 (broad, CH_2O of PCL and C*H* of PNIPAM, a and n), 1.44 (broad, CH_3 of P*t*BA and CH_2CH_2CH_2CO of PCL, c and i), 1.23 (CH_3 of PMAC, q) and 1.14 ppm (CH_3 of PNIPAM, o). If we assumed that star quintopolymer and its linear precursors had same chemical compositions, the theoretical composition was PCL_{30}-$PtBA_{48}$-$PLLA_{38}$-$PNIPAM_{50}$-$PMAC_{36}$ (the subscript denotes the polymerization degree of each block). By using the signal at 5.91 ppm (C*H*=CH_2 of PMAC, DP_{PMAC} = 36) as the internal standard, the chemical composition was calculated as PCL_{30}-$PtBA_{48}$-$PLLA_{39}$-$PNIPAM_{51}$-$PMAC_{36}$ by comparing the integrated signal areas at 5.0-5.4 (CH=CH_2 of PMAC and C*H* of PLLA), 3.90-4.19 (CH_2O of PCL and C*H*NH of PNIPAM), 1.31-1.53 (CH_2CH_2CH_2CO of PCL and CH_3 of P*t*BA), and 1.0-1.31 ppm (CH_3 of PMAC and PNIPAM). Considering the experimental error (normally within ±5%) and partial overlapping of some signals, the theoretical and experimental compositions of ABCDE star were in good accordance. The apparent molecular weight and polydispersity as estimated by GPC analysis were 24200 g mol^{-1} ($M_{n,GPC}$) and 1.08 (PDI), and the GPC trace notably shifted to higher M_n side than its precursors. GPC-MALLS analysis revealed that the number-average molecular weight and polydispersity of ABCDE star were 29800 g mol^{-1} ($M_{n,LS}$) and 1.09 (PDI). The $M_{n,th}$ (29300 g mol^{-1}), $M_{n,NMR}$ (29600 g mol^{-1}) and $M_{n,LS}$ values were similar, suggesting lack of significant change in weight composition after double click reactions. In IR spectrum (Fig. S7), the characteristic absorption of azide at 2100 cm^{-1} was absent, and the absorbance peaks of various segments were noted at 1759 ($\nu_{C=O}$ of PLLA and PMAC), 1734 ($\nu_{C=O}$ of PCL and P*t*BA), and 1649 cm^{-1} ($\nu_{C=O}$ of PNIPAM).

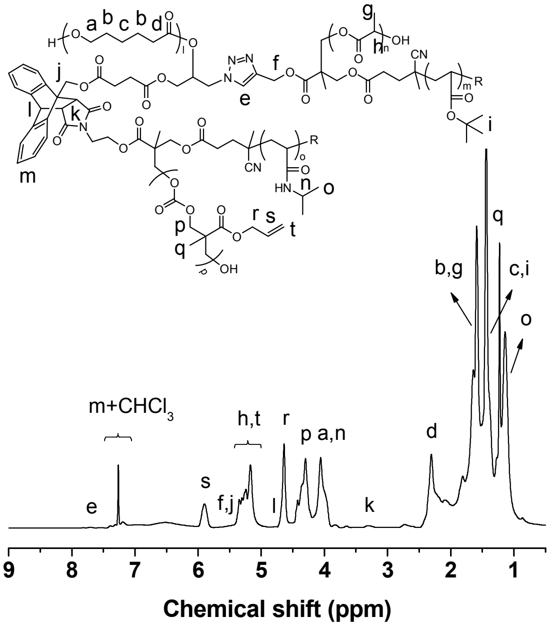

Fig. 6 ^{1}H NMR spectrum of PCL-P*t*BA-PLLA-PNIPAM-PMAC star.

Meanwhile, the P*t*BA segment of ABCDE star was readily converted into pH-sensitive PAA (B') segment via selective hydrolysis. The signal at 1.44 ppm (CH_3 of P*t*BA, as labelled with dashed line in Fig. S8) disappeared in ^{1}H NMR spectrum of AB'CDE star, confirming the efficient hydrolysis of P*t*BA chain. The chemical compositions of A, C, D and E arms were similar to those noted in ABCDE star, revealing lack of significant degradation of PCL, PLLA and PMAC segments during hydrolysis.

These results indicated the combination of orthogonal reactions and surface graft reaction based purification technique could afford the desired star quintopolymers with well-controlled molecular weight and precise composition. Since a wide range of functional monomers can be controllably polymerized via ROP and RAFT process, it can act as a robust and versatile method to construct various types of ABCDE stars and their derivatives.

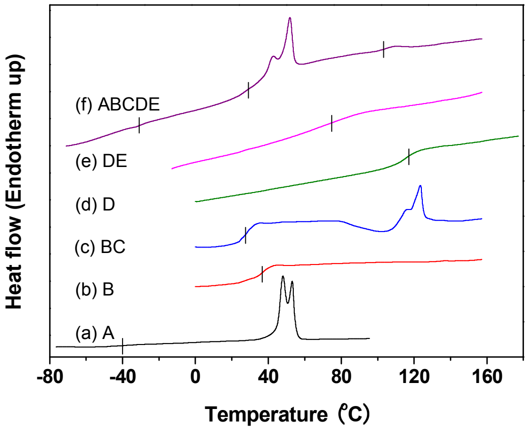

Fig. 7 DSC curves of ABCDE star and its precursors, in which the T_gs are identified using solid lines.

DSC analysis

DSC measurement was performed to further understand the compatibility, chain relaxation and melting behaviors of ABCDE star and its precursors (Fig. 7). PCL exhibited a glass transition temperature (T_g = -40.5 ^{o}C) and two melting peaks (T_m = 48.1, 53.2 ^{o}C), and the degree of crystallinity (X_c) was calculated as 54.1% by using the equation $X_c = (\Delta H_m - \Delta H_c)/(\Delta H_m^0 \times f_{w,PCL})$ in which the enthalpy of fusion of perfectly crystalline PCL (ΔH_m^0) was 136.4 J/g, and the weight percent of PCL ($f_{w,PCL}$) was 89.3%. The glass transition of P*t*BA homopolymer appeared at 36.4 ^{o}C. One T_g (28.5 ^{o}C) and two melting peaks (T_m = 116.3, 123.3 ^{o}C) were noted in DSC curve of P*t*BA-*b*-PLLA, and the X_c value was about 15.6% (ΔH_m^0 = 93.6 J/g, $f_{w,PLLA}$ = 45.2%), in which the reduced $T_{g,PtBA}$ in diblock copolymer indicated that P*t*BA and PLLA segments were partly compatible. The glass transition of PNIPAM homopolymer was observed at 116.5 ^{o}C, and only one obvious T_g appeared at 75.2 ^{o}C for PNIPAM-*b*-PMAC, revealing both segments were compatible. In Fig. 7e, ABCDE star exhibited three notable glass transitions resulting from PCL, P*t*BA and PNIPAM segments and two melting peaks of PCL segment ($T_{m,PCL}$ = 42.5, 52.1 ^{o}C). As compared with their homopolymer precursors, $T_{g,PCL}$ increased from -40.5 ^{o}C to -30.8 ^{o}C, $T_{g,PtBA}$ decreased from 36.4 ^{o}C to 28.8 ^{o}C, and $T_{g,PNIPAM}$ reduced from 116.5 ^{o}C to 103.4 ^{o}C, suggesting these segments were partly compatible when they were covalently connected to a central core. On the basis of $f_{w,PCL}$ (11.6%) and enthalpy of fusion, $X_{c,\ PCL}$ was estimated to be 24.2%. No melting peak was noted for PLLA segment, and $X_{c,PCL}$ of ABCDE star was significantly lower than that of PCL homopolymer (54.1%). This phenomenon could be attributed to restricted crystallization behaviors originating from topological effect dependent on chain length and chemical composition.

Self-assembly and stimuli-triggered morphological transition

Owing to the presence of pH-sensitive PAA segment and thermo-responsive PNIPAM segment, the star copolymers can exhibit stimuli-adjustable physicochemical properties and multipurpose applications. In this study, self-assembly of both star copolymers in aqueous solution was preliminarily investigated. The copolymer aggregates were prepared by dissolving star copolymer in DMSO and followed by addition of water at a constant temperature (T = 25 or 37 ^{o}C). After dialysis, the aggregates obtained were characterized by TEM and DLS, in which the average hydrodynamic diameter (D_h), peak size with the highest intensity (D_{peak}) and particle size distribution (PD) of various aggregates were given by DLS analysis.

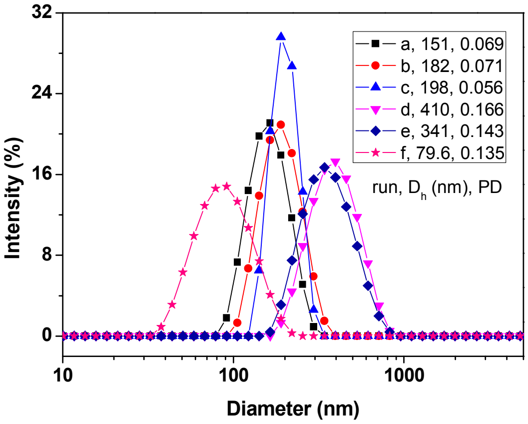

Fig. 8 DLS plots of copolymer aggregates (c = 0.50 mg mL^{-1}) formed from PCL-P*t*BA-PLLA-PNIPAM-PMAC (a and b) and PCL-PAA-PLLA-PNIPAM-PMAC (c-f) stars at 25 ^{o}C (a, c, e and f) and 37 ^{o}C (b and d): pH = 7.0 (a-d), 3.0 (e) and 10.0 (f).

ABCDE star aggregates formed at 25 and 37 ^{o}C were of monomodal distribution in DLS plots (a and b of Fig. 8), and their apparent particle parameters (D_h, D_{peak}, and PD) were obtained as 151 nm, 162 nm, 0.069 (T = 25 ^{o}C), 182 nm, 195 nm, 0.071 (T = 37 ^{o}C). TEM images revealed that the aggregates were vesicles, and the thicknesses of the membrane were about 16 nm (T = 25 ^{o}C, Fig. 9a) and 42 nm (T = 37 ^{o}C, Fig. 9b). The thicker membrane of vesicles obtained at 37 ^{o}C could be ascribed to the enhanced hydrophobicity of PNIPAM segment beyond its lower critical solution temperature. Owing to the potential shrinkage of various aggregates during the dryness, the sizes of copolymer aggregates estimated by TEM were smaller than those given by DLS analysis.

Different from thermo-sensitive ABCDE aggregates, AB'CDE star aggregates could exhibit thermo and pH dual-tunable morphological transitions. At 25 ^{o}C, AB'CDE star tended to form spherical micelles (Fig. 9c), and the particle parameters were 198 nm (D_h), 202 nm (D_{peak}) and 0.056 (PD). As temperature increased to 37 ^{o}C, the formed aggregates exhibited increased particle size (D_h = 410 nm) and broadened distribution (PD = 0.166), and TEM study revealed the micellar structure corresponding to aggregation and/or fusion of spherical micelles due to the strong intermicellar interactions (Fig. 9d).[80] In addition, pH-adjusted self-assembly at 25 ^{o}C was also attempted. Under different pH conditions, the sizes of aggregates varied from 198 nm (pH 7.0) to 341 nm (pH 3.0) and 79.6 nm (pH 10.0), and the morphologies corresponded to large compound micelles (pH 3.0) and spherical micelles (pH 10.0), respectively. The pH-dependent morphologies could be attributed to increasing hydrophobicity of PAA segment under acidic condition and hydrophilicity of poly(sodium acrylate) segment formed under basic condition. Therefore, the change in hydrophobic/hydrophilic balance caused the variable microenvironment and further induced the formation of copolymer aggregates with distinct morphologies.

These preliminary results indicated the self-assembled structures could be efficiently adjusted by control over external stimuli. Since both of them can be widely tuned, different types of nanoobjects are expected to be obtained through self-assembly of these functional star copolymers.

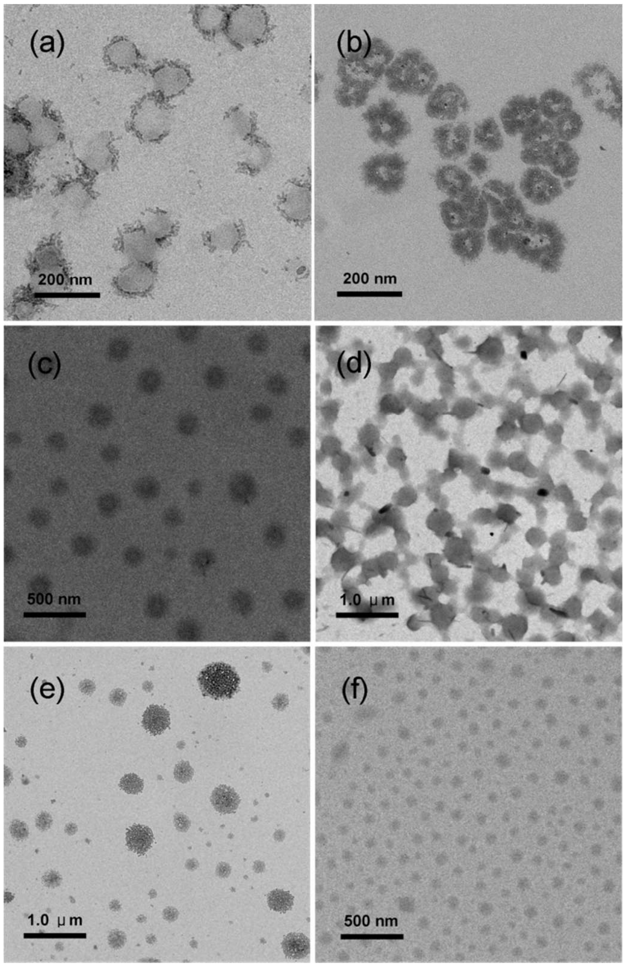

Fig. 9 TEM images of PCL-P*t*BA-PLLA-PNIPAM-PMAC (a and b) and PCL-PAA-PLLA-PNIPAM-PMAC (c-f) star copolymer aggregates formed in aqueous solution (c = 0.50 mg mL^{-1}) at 25 °C (a, c, e and f) and 37 °C (b and d): pH = 7.0 (a-d), 3.0 (e) and 10.0 (f).

Conclusions

We have demonstrated modular synthesis and orthogonal click reactions could be efficiently used to construct multifunctional ABCDE-type star quintopolymers. As heterophase surface graft reactions were applied for the straightforward purification, well-defined target miktoarm stars could be readily achieved in high yield, as evidenced from GPC-MALLS and ^{1}H NMR analysis. DSC results confirmed the polymer segments were partly compatible. The resultant amphiphilic star copolymers were liable to self-assemble into rich morphologies which could be tuned by control over external stimuli. Considering that two and more compositions can be involved in each arm via random copolymerization and chain extension polymerization, increasing compositions and functional units are potentially integrated into the five-arm star copolymers. In addition, various thiol-bearing compounds and polymers can be tethered to the side chain of PMAC segment via thiol-ene click reaction, which allows us to convert a single star into many examples of star copolymers with on-demand stimuli-responsiveness and amphiphilicity. Therefore, this one-pot “1+2+2” strategy can act as a robust and versatile method to generate multicomponent stars with tunable compositions, functions and chain length. The success of this study has opened a novel window to easily achieve ABCDE stars and their derivatives with a great potential as multiphase functional materials.

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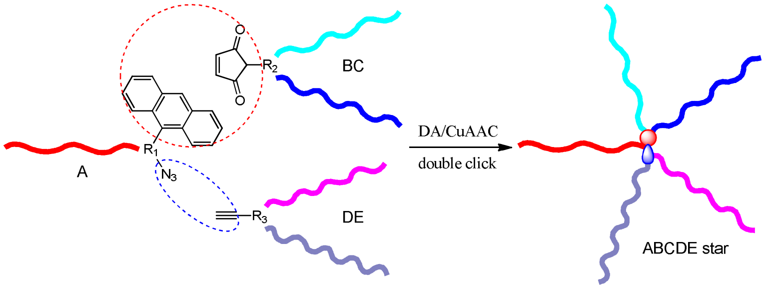
Graphical Abstract:

Synthesis and properties of couplable ABCDE star copolymers by orthogonal CuAAC and Diels-Alder click reactions

Huanhuan Liu, Weidong Pan, Min Tong and Youliang Zhao



Well-defined ABCDE star quintopolymers generated by modular and orthogonal strategy could self-assemble into intriguing nanoobjects sensitive to thermo and pH stimuli.