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Construction of a 3-Miktoarm Star from Cyclic Polymers

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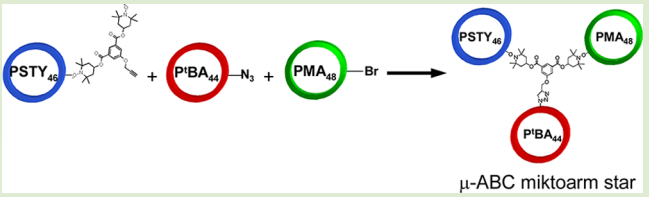
Supporting Information

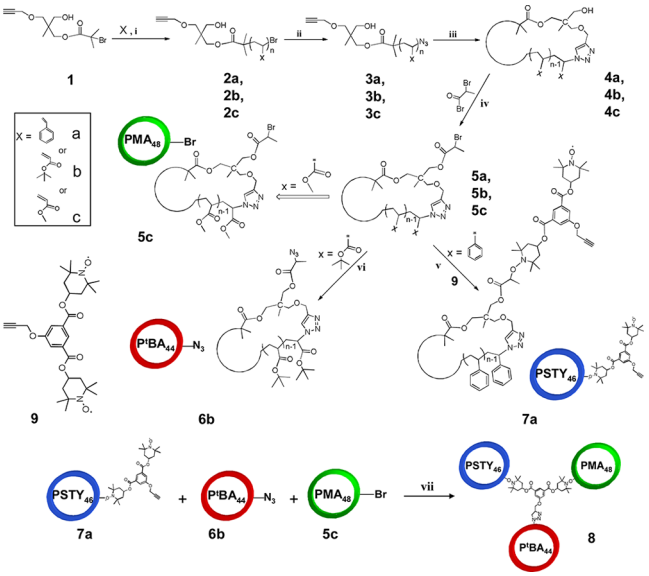
ABSTRACT: Cyclic polymers have intriguing physical properties, including those found in biological membranes for greater temperature, salt and acid stability. Although, many unique and complex synthetic cyclic structures have been prepared, there are no reports of ABC miktoarm stars constructed of three cyclic polymers with very different chemical compositions. We report such a structure in one pot at 25 °C by modulating the copper catalyst activity using combinations of solvents and ligands.



Cyclic polymers have interesting properties compared to their linear counterparts with the same molecular weight.[1,2] In biological systems, cyclolipids often have increased thermal, salt, and acid stability.[3] A characteristic feature of these lipids includes the hydrophobic isoprenoid core connected to a glycerol moiety. This and other features of cyclic lipids in cell membranes allow microorganisms to live in high temperature (hot spring) environments.[4,5] Synthetic cyclic amphiphilic block copolymers mimic this remarkable feature with a much greater cloud point (>40 °C) compared with the linear polymer.[6] This suggests that the self-assembled micelles will maintain their structure even at high temperatures and provide a more robust micelle structure. The self-assembly of AB_2 stars, where block A was a hydrophobic cyclic polystyrene and block B was a hydrophilic linear poly(acrylic acid), gave a similar size (~14 nm) to its linear counterpart but with a 4-fold increase in the aggregation number, resulting in a highly compact hydrophobic core and a densely packed hydrophilic corona.[7] Therefore, the elaboration of synthetic methodologies to generate monodisperse cyclic polymer topologies with different chemical compositions will have broad appeal for a wide range of applications, including micelles for drug and vaccine delivery, high temperature micelles as viscosity modifiers, and as micelle catalysts. Although recent and elegant work showed the construction of 8-shaped, θ-shaped, P-shaped, Q-shaped, and spiro-multicyclic polymers, these cyclic precursors were cyclized under very dilute conditions and with limited chemical variations.[8−10] There have been many reports for the synthesis of cyclic polymers through ring closure[11,12] and ring expansion[13,14] methods, which have been presented in review articles.[12,15−18] There are no reports to our knowledge of the construction of multicyclic polymer structures with different chemical compositions, in which all the polymer building blocks are cyclic.

In this work, we present an efficient and rapid strategy for the synthesis of an μ-ABC tricyclic miktoarm star constructed from three different cyclic polymers using two orthogonal coupling reactions in one pot at room temperature (Scheme 1). The linear polymer precursors to the cyclic polystyrene (c-PSTY), cyclic poly-*tert*-butyl acrylate (c-P^{t}BA) and cyclic polymethyl acrylate (c-PMA) were synthesized using either ATRP (atom

Scheme 1. Synthetic Strategy for the Construction of μ-ABC -tricyclic Miktoarm Star[a]



[a](i) ATRP of STY and SET-LRP for MA and ^{t}BA, (ii) NaN_3 in DMF for 17 h at 25 °C, (iii) cyclization through feeding the polymer into a toluene mixture of CuBr/PMDETA at 25 °C, (iv) TEA in THF at RT for 56 h, (v) **9**, Me_6tren, CuBr, DMSO/toluene (50/50 v/v) for 15 min at 25 °C, (vi) NaN_3 in DMF for 17 h at 25 °C, (vii) **7a**, **6b** (1.5 mol excess to **7a**), **5c** (1.5 mol excess to **7a**), PMDETA, CuBr (×4 equiv to **7a**), toluene for 30 min at 25 °C, addition of DMSO, and further reacted for 1.5 h.

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transfer radical polymerization)[19] or SET-LRP (single electron transfer − living radical polymerization).[20,21] LRP provides a versatile polymerization method to synthesize a wide range of polymers with near uniform chain length (i.e., low polydispersity indexs, PDIs). Therefore, coupling these functional cyclic polymers will result in a monodisperse μ-ABC miktoarm star.

The general strategy to build cyclic polymers and couple them together is given in Scheme 1. The linear P^{t}BA (**2b**) and PMA (**2c**) synthesized by SET-LRP using an unprotected alkyne-functional initiator, **1**, gave number-average molecular weights (M_ns) of 5300 and 4500 and PDI values below 1.12 (Tables S2 and S3, respectively). ATRP of styrene gave l-PSTY (**2a**) with an M_n of 5100 and PDI of 1.09 (Table S1). The Br-groups on the chain-ends of the three polymers were converted to azide groups (**3**), and the linear polymers cyclized using the copper-catalyzed azide−alkyne cycloaddition (CuAAC)[22] reaction. The polymer, dissolved in toluene, was fed into a toluene solution of an excess of Cu^{I}Br and PMDETA at a feed rate of 1.24 mL min^{-1} at 25 °C over 8 min and then stirred for 3 h, following a procedure shown to be highly effective in producing monocyclic polymer.[23] The reason for using the [Cu^I(PMDETA)Br] complex to activate the CuAAC reaction in toluene is that the complex forms a neutral, distorted square planar structure and is more soluble and thus more reactive in toluene than other ionized and partially soluble copper complexes.[24] The monocyclic polymers (c-PSTY−OH (**4a**), c-P^{t}BA−OH (**4b**), and c-PMA−OH (**4c**)) under these feed conditions gave conversions of 85, 81, and 91%, respectively, as determined using the log-normal distribution (LND) model.[25] This is shown in the molecular weight distributions (MWDs) given in Figure 1A for PSTY and Figures S8 and S11 for P^{t}BA and PMA, respectively. A comparison before and after cyclization for the SEC chromatograms based on a linear polystyrene calibration curve (denoted here as RI detection) shows the characteristic decrease in hydrodynamic volume (0.75[26]) after transformation into a cyclic polymer. Fitting a log-normal distribution model using a Gaussian function allowed us to determine the purity of the monocyclic polymer formed after cyclization. The excellent fit of the LND to l-PSTY **3a** (comparing curves a and b in Figure 1A) using the M_n and PDI values in Table S5 highlight that this method is quite accurate. The monocyclic PSTY **4a** (curve c) was fit using the same M_n and PDI values above but with a hydrodynamic volume change of 0.76 (see Table S5). This result further supports the loss of all l-PSTY and formation of monocyclic, which is well separated from the higher molecular weight multiblock polymer. The same method was used to analyze c-P^{t}BA and c-PMA (see Figures S8 and S11 and Table S5). The crude monocyclic polymers were then purified through preparative SEC, as shown in Supporting Information, to remove all polymers with greater hydrodynamic volume (i.e., high molecular weight multiblock polymer).

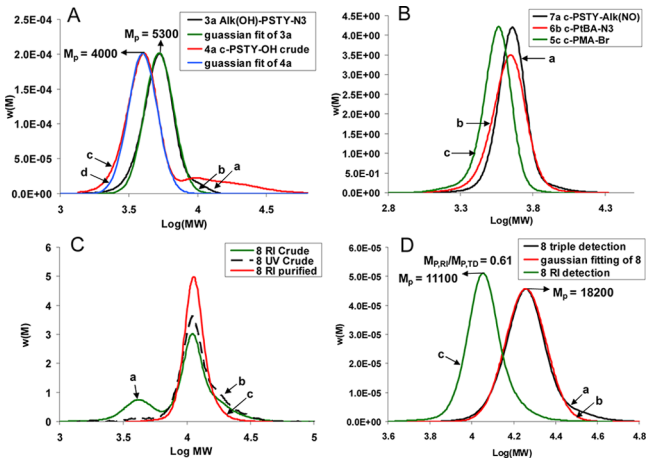

Figure 1. Molecular weight distributions (MWDs) for starting polymers and products (A) Before and after cyclization of PSTY using RI (PSTY calibration) SEC (a) linear ≡(OH)-PSTY-N$_3$, **3a**; (b) Log-normal distribution (LND) simulation of **3a**; (c) After cyclization of **3a** to form c-PSTY−OH, **4a**; and (d) LND simulation of **4a** with hydrodynamic volume change of 0.76. (B) MWDs of cyclic precursors to ABC miktoarm **8** (a) c-PSTY-(≡)NO, **7a**; (b) c-P^{t}BA-N$_3$, **6b**; (c) c-PMA-Br, **5c**. (C) MWDs of product **8** (a) SEC RI trace of crude ABC miktoarm **8**; (b) SEC UV trace (262 nm) of crude ABC miktoarm **8**; and (c) SEC RI trace of purified ABC miktoarm **8** by preparative SEC. (D) MWDs of **8**: (a) SEC absolute triple detection, (b) LND simulation of **8**, and (c) SEC RI of **8**.

Copper-catalyzed NRC[27] and CuAAC reactions can work in parallel to allow the one-pot synthesis of complex polymer architectures in a rapid and efficient manner.[24,28] The copper activity can be modulated to significantly enhance the rate of CuAAC coupling over NRC and vice versa through the choice of solvent and ligand. The NRC reaction is significantly faster in high ratios of DMSO solvent with Me$_6$tren ligand due to the disproportionation[20] of Cu^I to Cu(0) and the subsequent higher activation from both Cu(0) and [Cu^I(Me$_6$tren)Br].[29] In toluene and PMDETA, the CuAAC reaction becomes significantly faster for the reasons described above, and in an equal mixture of DMSO and toluene with PMDETA the CuAAC and NRC reaction rates were similar (a parallel process). Initial attempts to synthesize the μ-ABC-tricyclic miktoarm star **8** using toluene and PMDETA (the CuAAC first strategy) afforded rapid rates for the CuAAC reaction but due to the very slow NRC reaction rate gave incomplete formation of 3-arm star even after 17 h (expts 1 and 2 in Table 2). A simulation of the molecular weight distributions using the LND model, allowed us to determine the maximum peak molecular weight (M_p) for the formation of the 3-arm star (see Figure S13). Even after 17 h, the reaction was not complete as shown from the much lower M_p compared to $M_{p,cal}$ (Table 2). By changing the solvent to an equal mixture of DMSO and toluene (parallel process), the reaction reached full conversion after 17 h (expts 3−6 in Table 2). This is surprising, especially considering that the synthesis of other complex polymer architectures formed through the parallel process under similar conditions were complete in less than 30 min.[30]

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Table 1. Molecular Weight Data for Synthesis of ABC Miktoarm Stars 8, 16, and 17

	UV detection	RI detection				triple detection			
structures	consumption of PSTY[a] (%)	M_n	M_p[b] (g/mol)	PDI	$M_{p(theory)}$[c] (g/mol)	M_n	M_p (g/mol)	PDI	$M_{p(theory)}$[d] (g/mol)
7a (1.0 equiv)		4100	4400	1.09		5900	6200	1.06	
6b (1.5 equiv)		4200	4500	1.08		6100	6600	1.09	
5c (1.5 equiv)		3400	3600	1.07		5000	5400	1.08	
8	96	8200	11100	1.38	11200	17800	18200	1.08	18200
14 (1.0 equiv)		3400	3460	1.06		2900	3000	1.09	
10 (1.3 equiv)		2800	3100	1.12		3400	3800	1.12	
11 (1.3 equiv)		2800	2870	1.05		2200	2300	1.07	
16	93	5540	8700	1.30	8500	8250	8400	1.03	9100
15 (1.0 equiv)		2850	2950	1.07		3800	4000	1.06	
10 (1.3 equiv)		2840	3100	1.12		3400	3800	1.12	
11 (1.3 equiv)		2820	2870	1.05		2200	2300	1.07	
17	97	4645	8200	1.36	8000	9700	9900	1.02	10100

[a]Determined by dividing the area of the product SEC peak at 262 nm absorbance over the total area of all peaks from the SEC at 262 nm (using a weight distribution). [b]M_p is the peak maximum of the product SEC peak. [c]$M_{p(theory)}$ was calculated based on M_ps of starting polymers and then multiplying by 0.9 (a hydrodynamic volume change determined from 3-arm star formation from linear polymer precursors).[32] [d]$M_{p(theory)}$ was calculated based on M_ps of starting polymers.

Table 2. Summary of Small Scale Reactions of c-PSTY(≡)NO• (7a) with c-P^{t}BA-N$_3$ (6b) and c-PMA-Br (5c) under Different Solvent Conditions

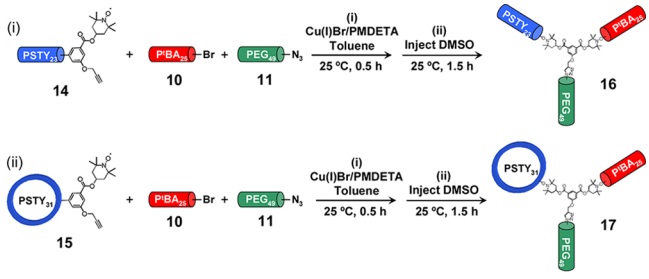
	reaction vessel		product	
expt	solvent conditions	reaction time (h)	$M_{P,exp}$[c]	$M_{P,calcd}$[d]
1	toluene	0.5	8600	11120
2	toluene	17	9400	11120
3	toluene/DMSO (mix)[a]	4	10500	11120
4	toluene/DMSO (mix)	6	10800	11120
5	toluene/DMSO (mix)	10	11100	11120
6	toluene/DMSO (mix)	17	11200	11120
7	toluene/DMSO (inject)[b]	1	10700	11120
8	toluene/DMSO (inject)	2	11100	11120
9	toluene/DMSO (inject)	4	11100	11120

[a]Toluene and DMSO were mixed at the beginning of the reaction (50/50 v/v). [b]DMSO was injected after 30 min into the reaction (to make up DMSO/toluene 50/50 v/v). [c]$M_{p'(exp)}$ was obtained from SEC (RI detector using linear PSTY calibration curve). [d]$M_{p'(theory)}$ was calculated based on M_ps of starting polymers (RI detector, PSTY calibration curve). The final value was multiplied by a factor of 0.9 to account for the hydrodynamic volume of a star polymer.[32]

To overcome the slow parallel reaction, we advantageously modulated the copper activity via the addition of a cosolvent. The reaction was first carried out in toluene/PMDETA such that the CuAAC reaction would be first, and then an equal amount of DMSO was added to induce a rapid NRC reaction, resulting in a sequential reaction. The functional cyclic polymers **5c**, **6b**, **7a**, and PMDETA were dissolved in toluene, and Cu^{I}Br was then added to start the reaction, facilitating a rapid CuAAC reaction. After 30 min, an equal volume of DMSO was added to toluene. It was found that the μ-ABC-tricyclic miktoarm star **8** was complete after a further 1.5 h (see Figure 1C and Table 2). There was full consumption of the c-PSTY (from the UV trace, curve b in Figure 1C) and high conversion of 3-arm formation. Purification of the crude 3-arm star through preparative SEC removed all starting cyclic polymers as shown in curve c in Figure 1C. Curve a in Figure 1D shows the SEC trace based on RI detection (i.e., PSTY calibration curve) with an M_p of 11200, which increased to 18200 when analyzed using triple detection (i.e., absolute MWD) SEC, as shown in curve b. This significant difference in hydrodynamic volume is a consequence of the change in hydrodynamic volume from the combination of individual cyclic polymers and the formation of a 3-arm star, resulting in a hydrodynamic shift of 0.61. The LND model was used to fit the absolute MWD (curve c) with an M_p of 18140 and PDI of 1.05. The fit was excellent suggesting that **8** was pure with no remaining starting or dicyclic polymers. The μ-ABC-tricyclic miktoarm star was stable (i.e., showed no degradation) after 5 months being stored at 8 °C and also showed no degradation after 110 h at 40 °C (see Figure S36 in Supporting Information)

The versatility of this strategy (i.e., addition of DMSO after 30 min) was further elaborated with the construction of other ABC 3-miktoarm stars (Scheme 2). In comparison to the formation of **8**, both products **16** and **17** could be formed in high yields in 2 h using the sequential strategy (see Table 1).

Scheme 2. Construction of μ-ABC Miktoarm Stars from a Combination of Linear and Cyclic Polymers



In conclusion, we have demonstrated a rapid and efficient method for the construction of monodisperse ABC miktoarm stars. Modulating the copper activity allows difficult or slower reactions to be significantly more rapid and efficient. The synthesis of 3-miktoarm stars from a variety of cyclic polymer precursors can be made on much greater scales than other procedures. The P^{t}BA can be readily converted to poly(acrylic acid), resulting in an ABC miktoarm star with a hydrophilic arm. This synthetic methodology can allow such architectures to be used in a variety of applications (e.g., temperature, salt

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and acid stable micelles for drug and vaccine delivery[31]), some of which are yet to be discovered.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, and supporting figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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