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Synthesis of 3-Miktoarm Stars and 1st Generation Mikto Dendritic Copolymers by "Living" Radical Polymerization and "Click" Chemistry

Michael R. Whittaker, Carl N. Urbani, and Michael J. Monteiro*

Australian Institute of Bioengineering and Nanotechnology, School of Molecular and Microbial Sciences, University of Queensland, Brisbane QLD 4072, Australia

Received June 28, 2006; E-mail: m.monteiro@uq.edu.au

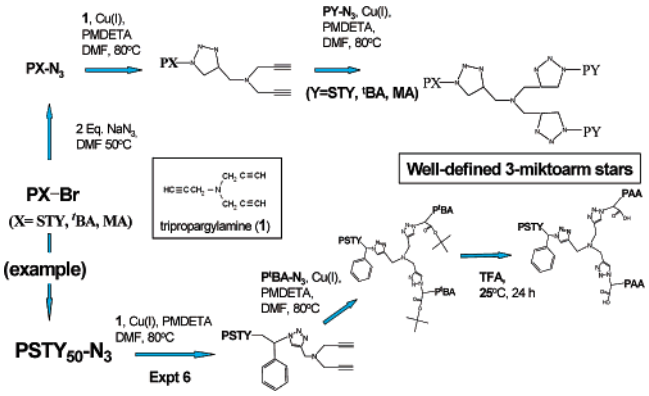
In this communication, we demonstrate the facile and versatile synthesis of 3-miktoarm star polymers (Scheme 1) and 1st generation mikto polymeric dendrimers (Scheme 2) using atom transfer radical polymerization (ATRP) and "click" chemistry. ATRP was used to synthesize near uniform polymers with Br chain ends, which were easily converted into azido groups. These polymer chains were then attached to a trifunctional alkyne molecule (tripropargylamine) using click reactions[1] in a variety of ways to make a range of well-defined and statistical 3-miktoarm stars and 1st generation dendrimers.

Miktoarm star polymers are polymers where the arms are of different chemical composition.[2] This leads to very different aggregation behavior in selective solvents[3] and applications in drug delivery,[4] diagnostic assays, nanopatterned structures,[5] and photonics.[6] Many methods have been used to synthesize miktoarm stars, ranging from combinations of ring-opening, ATRP, nitroxide-mediated, anionic polymerization, and the "in-out" ATRP method.[7] However, there are no reports of the synthesis of miktoarm stars using a combination of ATRP and click chemistry. Gao and Matyjaszewski[8] have recently showed that they could synthesize 3- and 4-arm polystyrene (PSTY) stars in one pot using this methodology. Importantly, they showed that the yields were high for 3-arm stars, and any side reaction of the azido groups on the polymer chain ends did not participate in further ATRP reactions. Although click reactions have been shown to proceed with high specificity in quantitative yields, the yields for the 3- and 4-arm PSTY stars (83 and 90%, respectively) could not implicitly be attributed only to dead polymer formed during the ATRP process. There could be the added difficulties in diffusion of the azido polymer chain ends to the alkyne molecules, especially when one or more polymers are already attached to the alkyne core molecule. Molecular weight of the polymer chains will also play a role; the greater the molecular weight, the slower the diffusion.

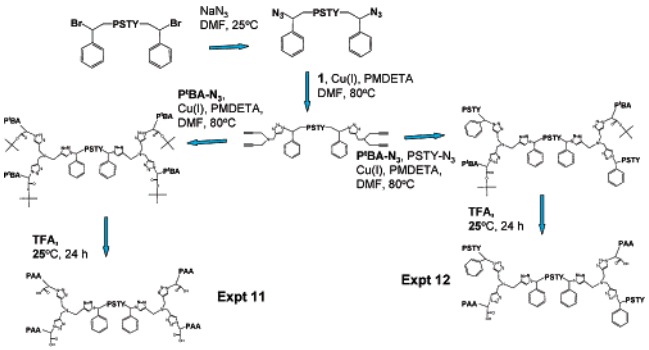
In this study, we tested a variety of techniques from one-pot reactions through to feeding the trialkyne compound via a syringe pump. The latter process was used to kinetically enhance the coupling of three azido polymers to the trialkyne compound, and thus strongly favored formation of exclusively 3-arm stars. Utilizing this procedure, we attempted the synthesis of 3-miktoarm star copolymers consisting of PSTY, poly(*tert*-butyl acrylate) (P^{t}BA), poly(acrylic acid) (PAA), poly(methyl acrylate) (PMA), and a 1st generation miktoarm dendrimer (Scheme 2). It should be noted that all ATRP reactions were carried out in the presence of $CuBr_2$ and conversions taken to approximately 50% to minimize the amount of dead polymer and enhance the amount of PX−Br (where X = STY, MA, or ^{t}BA).

The results of "clicking" PSTY−N_3 (purified through precipitation and washing) to tripropargylamine in a one-shot/one-pot reaction at 80 °C for 19 h to give 3-arm star homopolymers are given in Table 1 (Expt 1, Figure 1A). The yield of the 3-arm star

Scheme 1. Synthesis of 3-Miktoarm Stars Using ATRP and "Click" Reactions



Scheme 2. Synthesis of 1st Generation Miktoarm Polymeric Dendrimers Using ATRP and "Click" Reactions



(M_n is close to theory and PDI low at 1.05) is low (75%) even though the reaction temperature was high in order to increase the diffusion rate constants for the polymer chains. Feeding a solution of tripropargylamine in DMF via a syringe pump into the reaction mixture containing purified PSTY−N_3 increased the yield to 78% (Expt 2). The next experiment used unpurified PSTY−N_3 (i.e., use of the solution mixture directly after azidation−2 equiv of NaN_3 for 24 h at 50 °C) with a slow feed of tripropargylamine (Expt 3). It can be seen that the yield of the 3-arm star increased to 86%, a much better result, and more importantly the residual NaN_3 did not influence the click reactions onto the tripropargylamine core molecule. Homoarm stars of ^{t}BA (Expt 4) and MA (Expt 5) were also synthesized using this methodology and gave near uniform 3-arm stars with yields of 87 and 88%, respectively.

Well-defined 3-miktoarm stars were synthesized by first coupling tripropargylamine (in large excess) to PSTY−N_3 to form PSTY−(-≡)$_2$ (Expt 6, Figure 1B). A solution of this polymer in DMF was then added via a syringe pump to a solution of P^{t}BA−N_3 in DMF at 80 °C. The resulting yield of the 3-miktoarm star after addition of all PSTY−(-≡)$_2$ was 88% (6 h), and further increased to 92%

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Table 1. Size Exclusion Chromatographic Data for the Synthesis of 3-Miktoarm Stars and 1st Generation Dendrimers Using ATRP and "Click" Reactions

Experiment	Starting arms		3-arm stars	M_n	PDI	Yield[d] %
3-homoarm stars						
1[a]	STY_{50}-N_3	(M_n=4974, PDI=1.09)	$(PSty_{50})_3$	13192	1.05	75 (19 h)
2[b]	STY_{50}-N_3	(M_n=4974, PDI=1.09)	$(PSty_{50})_3$	13873	1.04	78 (3.5 h)
3[c]	STY_{50}-N_3	(M_n=4974, PDI=1.09)	$(PSty_{50})_3$	14906	1.03	86 (3.5 h)
4	P^tBA_{54}-N_3	(M_n=6895, PDI=1.08)	$(P^tBA_{54})_3$	19943	1.05	87 (3.5 h)
5	PMA_{65}-N_3	(M_n=5557, PDI=1.06)	$(PMA_{65})_3$	15539	1.04	88 (3.5 h)
Well-defined 3-miktoarm star	**1Eq**	**2Eq**				
6	$PSTY_{50}$-(≡)$_2$ (M_n=4974, PDI=1.09)	P^tBA_{54}-N_3 (M_n=6895, PDI=1.08)	$P[(^tBA_{54})_2$-$(Sty_{50})_1]$	18415	1.03	92 (19 h)
7	$PSTY_{50}$-(≡)$_2$ (M_n=4974, PDI=1.09)	PMA_{65}-N_3 (M_n=5557, PDI=1.06)	$P[(MA_{65})_2$-$(Sty_{50})_1]$	14740	1.05	82 (5 h)
8	P^tBA_{54}-(≡)$_2$ (M_n=6895, PDI=1.08)	STY_{50}-N_3 (M_n=4974, PDI=1.09)	$P[(Sty_{50})_2$-$(^tBA_{54})_1]$	16365	1.04	88 (5 h)
9	P^tBA_{54}-(≡)$_2$ (M_n=6895, PDI=1.08)	PMA_{65}-N_3 (M_n=5557, PDI=1.06)	$P[(MA_{65})_2$-$(^tBA_{54})_1]$	15869	1.05	82 (5 h)
10	PMA_{65}-N_3 (M_n=5557, PDI=1.06)	P^tBA_{54}-N_3 (M_n=6895, PDI=1.08)	$P[(^tBA_{54})_2$-$(MA_{65})_1]$	16059	1.07	75 (5 h)
1st Generation dendrimer						
11	(≡)$_2$-$PSTY_{25}$-(≡)$_2$ (M_n=2639, PDI=1.09)	P^tBA-N_3 (M_n=6895, PDI=1.08)	$P[(STY_{25})_1$-$(^tBA_{54})_4]$	26628	1.08	80 (6 h)
12	(≡)$_2$-$PSTY_{25}$-(≡)$_2$ (M_n=2639, PDI=1.09)	P^tBA_{54}-N_3 (M_n=6895, PDI=1.08) STY_{50}-N_3 (M_n=4974, PDI=1.09)	$P[(STY_{50})_2$-$(STY_{25})_1$-$(^tBA_{54})_2]$	22497	1.10	70 (6 h)

[a] One-pot reaction. [b] Slow addition of tripropargylamine to $PSTY_{50}$−N_3. [c] Slow addition of tripropargylamine to in situ generated $PSTY_{50}$−N_3. [d] Determined from weight distribution.

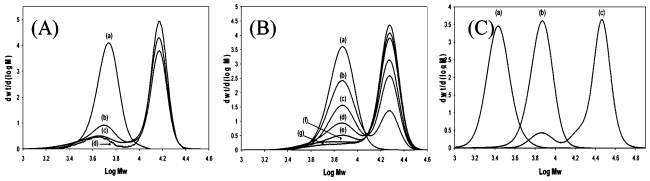

Figure 1. Size exclusion chromatograms for the formation of 3-homoarm star, 3-miktoarm star, and 1st generation polymer dendrimer. (A) $(PSTY_{50})_3$ star (Expt 1): curve (a) PSTY−N_3 (M_n = 4974, PDI = 1.09), (b) 30 min, (c) 90 min, and (d) 150 min reaction with tripropargylamine. (B) 3-miktoarm star $P[(STY_{50})_1$−$(^tBA_{54})_2]$ (Expt 6): curve (a) P^tBA_{54}−N_3 (M_n = 6895, PDI = 1.08), (b) 1 h, (c) 2 h, (d) 3 h, (e) 4 h, (f) 5 h, and (g) 24 h reaction with tripropargylamine. (C) 1st generation dendrimer $P[(STY_{25})_1$−$(^tBA_{54})_4]$ (Expt 11): curve (a) (≡)$_2$$PSTY_{25}$−(≡)$_2$ (M_n = 2639, PDI = 1.09), (b) P^t-BA_{54}−N_3 (M_n = 6895, PDI = 1.08), and (c) after 5 h.

after a reaction time of 19 h. The M_n was around 18 k (which is close to that calculated). It was found that this M_n was greater than that for a statistical 3-miktoarm star (Expt S14 in Supporting Table S4; M_n = 17 141 and PDI = 1.06), suggesting that in Expt S14 there is a small amount of copolymer composition drift favoring attachment of PSTY−N_3 over P^tBA−N_3. However, as the PDI is very low, this is more possibly due to the shorter reaction time and lower yield. The range of well-defined 3-miktoarm stars was prepared from combinations of PSTY, P^tBA, and PMA, in which the PDIs were very low (below 1.07) and % yields greater than 75% (Expts 6−10). In addition, statistical 3-miktoarms stars were prepared (Supporting Table S4) with % yields, M_n, and PDIs similar to those of their well-defined counterparts. The facile conversion of the P^tBA arms to PAA with trifluoroacetic acid (TFA) also afforded 3-miktoarm stars consisting of hydrophobic and hydrophilic portions. Hydrolysis was confirmed by ^1H NMR.

The synthesis of a 1st generation polymeric dendrimer was carried out with a difunctional PSTY (i.e., Br−PSTY−Br), converted to a tetrafunctional (≡)$_2$−PSTY−(≡)$_2$, and using the click reactions, P^tBA-N_3 or equal ratio of PSTY−N_3 and PtBA−N_3 were coupled, Expts 11 (Figure 1C) and 12, respectively. The latter can be considered as a 1st generation mikto polymeric dendrimer. The yields for both dendrimers were high (greater than 70%), and the PDIs were below 1.10. In addition, we converted our PSTY−P^t-BA dendrimers to their corresponding PSTY−PAA polymers using TFA.

In summary, we have shown for the first time that 3-miktoarm star and dendrimers with miktoarm compositions consisting of PSTY, P^tBA, PMA, and PAA can be easily synthesized using a combination of ATRP and click reactions. Feeding in the trialkyne compound afforded exclusively 3-arm stars and gave the greatest yields (>80%). In all reactions, the star and dendrimer structures were well-defined with PDIs lower than 1.09. This is the first step in the synthesis of well-defined high ordered polymer structures, and we are currently designing polymer nanostructures with specific functions for a variety of applications, including drug and vaccine delivery devices. These devices will require that each polymer chain plays a role and be engineered: either for stability, charge, sites of attachment of peptides, and even the attachment of important biomacromolecules.[9]

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Supporting Information Available: Experimental procedures for the synthesis and size exclusion analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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