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High-Throughput Synthesis of Nanoscale Materials: Structural Optimization of Functionalized One-Step Star Polymers

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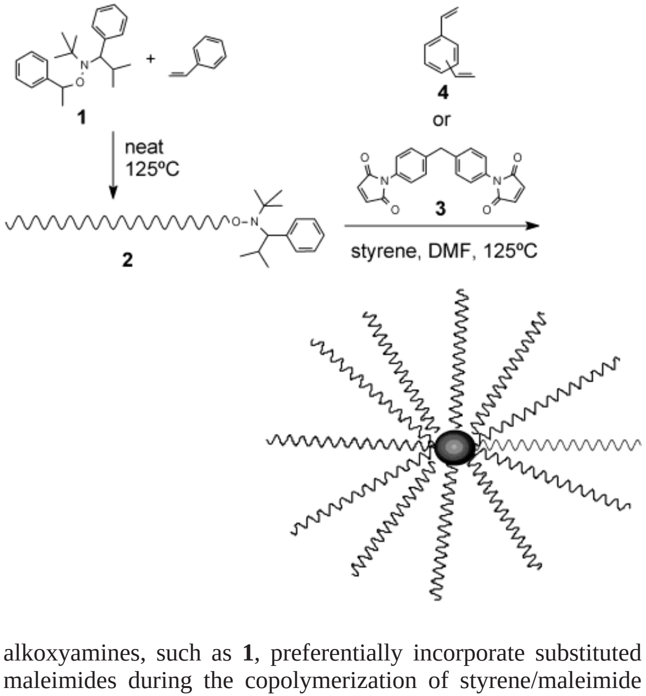
The development of techniques for the controlled preparation of functionalized nanoscale materials has rapidly become a vigorous research topic.[1−4] The accompanying interest in highly branched star polymers is driven by their synthetic accessibility and promise as nanoscopically tailored materials with controllable topology and functional group placement.[5] While multiarm star polymers have previously been prepared by living anionic procedures,[6] the approach is impractical for functionalized materials due to its experimental demands. Recent reports have demonstrated the potential of Living Free Radical Polymerization for the preparation of star polymers but the large number of variables in these systems severely limited the authors' ability to optimize and understand structural control in these systems.[7−9] In this report, we describe the development of high-throughput techniques for the rapid screening and optimization of the reaction space for the synthesis of functionalized, well-defined, 3-dimensional star polymers by living radical techniques.[10−12] Whereas combinatorial approaches have proven their value in the search for new bioactive compounds,[13] catalysts, and inorganic materials,[14,15] the feasibility of this approach in the development and analysis of new soft materials has received limited attention.[16−17]

When the general strategy for the one-step synthesis of star polymers is considered, it is apparent that a large number of variables have a significant influence on the final structure of the star polymer (Scheme 1). These include the following: (1) molecular weight (MW) of the linear arms of the star; (2) amount of difunctional cross-linking reagent; (3) the nature of the cross-linker; (4) use of a comonomer; and (5) the nature of solvent and concentration. Key to our concept is the fact that α-hydrido-based alkoxyamines, such as **1**, preferentially incorporate substituted maleimides during the copolymerization of styrene/maleimide mixtures.[18] Consequently, when a polystyrene-based macroinitiator, **2**, is used to initiate the polymerization of a mixture of 1,1′-(methylenedi-4,1-phenylene)bismaleimide (BMI, **3**) and styrene, the BMI produces a cross-linked BMI nodule with random styrene spacers, which effectively knits together the polymeric arms of the macroinitiator leading to formation of a soluble star polymer (Scheme 1).

Scheme 1



Given the multiplicity of variables and lack of precedent, our initial attempt to perform this reaction could only be based on chemical intuition. Therefore a polystyrene macroinitiator, **2** (5.5 kDa, polydispersity (PD) = 1.09), BMI (2.5 equiv), and styrene (10.0 equiv) were dissolved in DMF (10 wt %) and heated at 125 °C. ^{1}H NMR and SEC analysis showed that the consumption of the BMI cross-linker is almost complete after 15 min, while analysis of the product reveals that small star polymers are initially formed and eventually condense to give larger stars until further coupling essentially stops after 2 h (Figure 1). Given the high polydispersity of the product, **5** (PD = 14.0), and the fact that a significant amount of macroinitiator remained unreacted, it is clear that the conditions chosen for this reaction were unsuitable and did not provide sufficient control over the structure of the final product.

As a result of the number of variables in this system, a serial approach to optimization is not practical and a high-throughput strategy was therefore adopted to explore the parameter space of interest. Four 96-element libraries exploring the main variables were designed and synthesized. The computer-based planning and robotic dispensing of the libraries decreased the time for preparation of each library to ca. 2−4 h depending on the number of components and the complexity of the dispensing protocol (serial

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(19) Regions a−d: primarily linear starting polymer with increasing amounts of oligiomerized, coupled linear chains. Region e and f: primarily oligiomerized stars, low MW, high PD. Region g: high MW, high PD stars. Region h: high MW, low PD stars. Region i: cross-linked gel.

(20) High throughput GPC was performed on a polystyrene-based column with a separating range of 10 K to 3 M, operated at 2 mL/min, and calibrated by polystyrene standards and LS with an absolute calibration.

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Table 1. SEC/Differential Viscometry Data Star-Library[a]

batch:		Star 1[b]	Star 2	Star 3	Star 4	Star 5	Star 6	Star 7[c]
macroinitiator	M_n (kDa):	2.4	3.5	4.4	6.5	9.1	16	42
reactant ratio	(PS/BMI/St)	1/3/4	1/3.5/8	1/3.5/8	1/3.5/10	1/3.5/10	1/4/10	1/4/10
star polymer	abs M_n (kDa)	520	2100	470	350	160	48	58
	M_w/M_n:	2.9	2.3	1.3	1.3	1.2	1.2	1.4

[a] All data were obtained in triplicate after fractional precipitation in 2-propanol/DMF/dichloromethane. [b] Insoluble gel was obtained for a ratio of 1/3.5/8. [c] Reaction product could not be separated from the starting polymer.

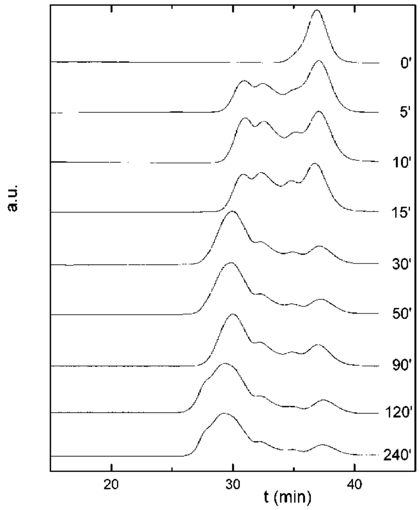

Figure 1. Variation in SEC traces with time (minutes) for the synthesis of polystyrene star polymers using reaction parameters based on an "*educated guess*".

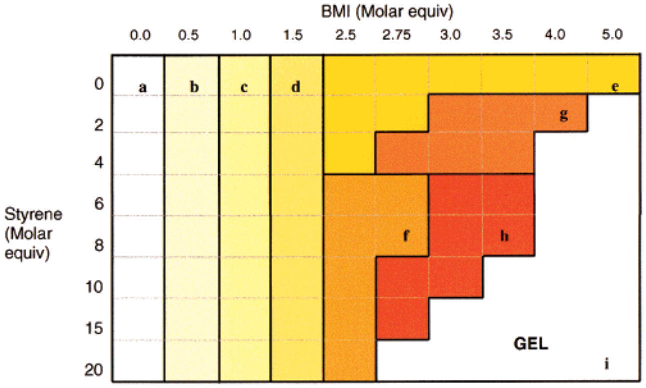

Figure 2. Schematic representation of the 9 different regions present in library 1.

preparation of 4 × 96 reaction mixtures by hand takes ca. 2−3 days). In a typical experimental series, a 96-well library (400−500 μL of reaction mixture per well) was constructed with the ratio of styrene to macroinitiator **2** (5.5 kDa) ranging from 0 to 20 molar equiv and the ratio of BMI to **2** ranging from 0 to 5 molar equivs. After 6 h of stirring at 125 °C qualitative evaluation of the library by high throughput SEC revealed the presence of 9 different regions. When the amount of BMI is low (<2.0 equiv), the relative styrene content is not critical and little star formation is seen (regions a−d, Figure 2).[19] For BMI:**2** ratios of 2.5−3.5 the relative amount of styrene is crucial, and 4 qualitatively different kinds of SEC traces could be observed ranging from oligomerized stars to very high MW macromolecules (regions e−h).[20] From the viewpoint of molecular weight and peak profile best results were obtained in regions g and h of the library. Further focused library evaluation showed that the optimal composition for well-defined, high MW, star formation was the mixture 1/3.5/8 (polystyrene/BMI/styrene). Translation of this finding to larger scale synthesis (>20 g) proved to be successful and in fact led to a slight improvement in the degree of control (lower PD, which was subsequently shown to be a general feature of library scale-up. The one-step polystyrene star was therefore obtained in 87% yield with an absolute M_n of 275 000 and PD = 1.25 (M_n = 250 000; PD = 1.37 prior to precipitation),[21] which corresponds to the controlled knitting of ca. 50−60 linear polymer chains into a single star.

The success achieved in our initial application of high-throughput techniques to polymer synthesis prompted the evaluation of further variables such as MW and the amount of macroinitiator in the overall monomer mixture. A 168-member library was generated around the lead reaction conditions from the initial library. A biased library with 7 different macroinitiators at a concentration of 10 wt % was investigated. For the low MW macroinitiators (2.4, 3.5, 4.4, and 6.8 kDa), the styrene and BMI feeds were varied between 4 and 10 and 2.75−3.5 equiv, respectively. In contrast, the amount of cross-linker was increased to 3.0−5.0 equiv for the 9.1, 16 and 42 kDa macroinitiators. Interestingly, the MW of the macroinitiator was found to have a dramatic effect on star polymer formation. As molecular weight increased, the amount of cross-linker required to give well-defined high molecular weight stars also increased, though not linearly. Table 1 shows the optimal BMI/styrene ratios for each molecular weight and demonstrates that the very low MW macroinitiator, 2.4 kDa, is very prone to cross-linking. In contrast, coupling of the 42kDa macroinitiator to give stars does not occur to any appreciable extent even at high BMI ratios (Table 1). These results indicate that there is also an optimal MW range (3.5−9.1 kDa) for the macroinitiator if well-defined, high MW stars are desired.

The scope of this star synthesis was further investigated with commercial grade divinylbenzene (DVB) as cross-linker. A 96-member library using similar conditions to the initial BMI library (polystyrene 5.5 kDa, styrene 0−20 equiv, actual DVB 0−5 equiv) was constructed. Analysis of the products from this library revealed general trends analogous to the BMI case with one significant variation. The amount of DVB required for optimized star formation was greater by 0.5−0.75 equiv than for BMI. In conclusion, we have presented a new methodology to synthesize multiarm star polymers using nitroxide-mediated "living" radical polymerization. The use of combinatorial techniques has enabled the rapid evaluation of the scope and limitations of this general methodology useful for the preparation of well-defined macromolecules with 3-dimensional architecture.

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Supporting Information Available: Experimental procedures for star formation, library processing, and a photograph of a typical 96-well reactor (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Using optimized procedures, the highly branched stars were typically contaminated with 1−2% of unreacted linear arms.