Alternative o-Quinodimethane Cross-Linking Precursors for Intramolecular Chain Collapse Nanoparticles

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Alternative *o*-Quinodimethane Cross-Linking Precursors for Intramolecular Chain Collapse Nanoparticles

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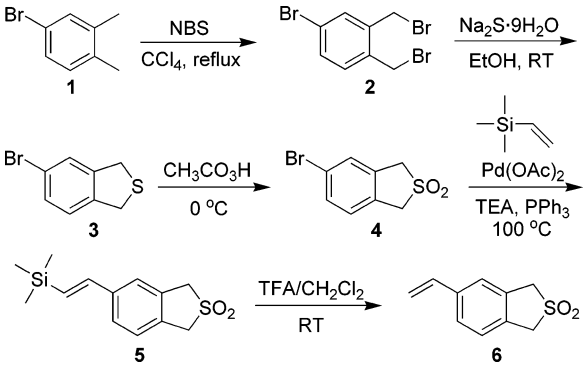
The construction of polymeric architectures with refined structures and their broad utility has created an ever-increasing need for simplified methodologies and strategies to further control the nanoscopic scale.[1] In particular, methods to synthesize polymeric architectures in the 5−20 nm size range have been highly desirable. While dendritic macromolecules have dominated this nanoscopic size range with dimensions of 1−10 nm, more recently an intramolecular chain collapse process allowed facile access to larger quantities of 3-D architectures in the 5−10 nm range.[2] This technique relies on two critical factors: one, the incorporation of thermally activated cross-linking moieties into linear polymer backbones, and two, their rapid activation during the continuous addition process to guarantee intramolecular irreversible coupling reactions leading to collapsed single-molecule nanoparticles. Polystyrene nanoparticles produced in this fashion have been ideal to study the relaxation dynamics and processes of high molecular mass polymer melts as the cross-linked structure discourages entanglements.[3] Mixed into linear polymers, further studies revealed that the blend viscosity was found to decrease with the change of free volume rather than with the decrease in entanglements.[4] Although the unusual physicochemical behavior of collapsed nanoparticles in dispersions has been recognized, their contributions to other areas of interest such as biomedical research are only beginning to be exploited. The critical contribution of the incorporated cross-linking unit to the controlled intramolecular chain collapse process motivated our efforts to develop a novel cross-linking unit which proceeds through the same *o*-chinodimethane intermediate and is prepared by a more convenient synthetic pathway. Benzocylobutene derivatives are difficult to obtain and are associated with multistep synthetic pathways, complicated purification steps, and low yielding intermediates. In view of the desirable *o*-quinodimethane derivative, we investigated benzothiophene dioxide derivatives as potential *o*-quinodimethane precursors with the ability to be incorporated as comonomers into linear polymer backbones and exhibit similar cross-linking characteristics as benzocyclobutene derivatives.

Benzothiophene derivatives are well-known structures which form *o*-quinodimethanes upon heating at 250 °C under the loss of SO_2 and can be prepared in a number of different ways as described in the literature.[5,6] In the designed synthetic pathway, we converted a bromine-substituted benzothiophene dioxide derivative, **4**, into the desired cross-linking monomer unit, 5-vinyl-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (VBS), **6**, allowing for its incorporation as a comonomer in living free radical polymerization (LFRP) processes. In particular, we implemented a practical procedure in which a modified Heck coupling reaction provides the necessary vinyl functionality from its bromine derivative in one step and proved to be critical to achieve a simplified synthesis for *o*-quinodimethane precursors. Furthermore, the ease of the chemical conversion offers the synthesis of vinyl monomers with demanding functional groups for further utilization in macromolecules. The cross-linking unit, **6**,[7] was shown to be compatible with standard nitroxide-mediated living free radical polymerization[8] conditions, and the intramolecular chain collapse process of both polystyrene and acrylate polymers gave well-defined monodisperse nanoparticles in the 5−10 nm size dimension.

Scheme 1. Synthesis of Vinylbenzosulfone Monomer, 6



The synthetic method for the preparation of the cross-linking unit consists of a five-step pathway which requires only two purification steps. Following the bromination of commercially available 4-bromo-*o*-xylene with *N*-bromosuccinimide, the purified product 4-bromo-1,2-bis(bromomethyl)benzene, **2**, is converted to 5-bromo-1,3-dihydrobenzo[*c*]thiophene, **3**, through a reaction of **2** with sodium sulfide in ethanol at room temperature.[6] Prior methods to maintain ring closure forming cyclic sulfides required reflux temperatures or in-situ preparation of sodium sulfide using solid sodium and hydrogen sulfide in an ethanol solution. The oxidation of **3** was achieved with peracetic acid in an overnight reaction to afford 5-bromo-1,3-dihydro-2-benzo[*c*]thiophene 2,2-dioxide, **4**, in quantitative yields from the crude starting material. In order to introduce the vinyl functionality in a rapid and high yielding process, we introduced a trimethylsilane-protected vinyl group utilizing a Heck-type reaction described by Hallberg and Westerlund.[9] The very simple procedure merits attention because no pressure vessels are needed and vinyltrimethylsilane is used as an ethylene equivalent. Whereas the original method was aimed to maximize conversion of the halogen derivative to the free vinyl while minimizing the formation of the trimethylsilane (TMS)-protected byproduct, for our approach the vinyl functionality in its protected form was recognized as a vital attribute to prevent any premature polymerization of the benzosulfone cross-linking unit during the Heck reaction. A series of experiments to optimize reaction conditions for the preparation of the VBS cross-linking monomer, **6**, were employed. A significant increase in the yield of the TMS-protected product, **5**, was observed when the reaction was performed at 100 °C, the reaction time was extended to 18 h, and an additional 4 equiv of vinyltrimethylsilane and $Pd(OAc)_2$ catalyst were added. After reaction, the crude product was deprotected and purified before being investigated as cross-linking unit in *o*-chinodimethane-mediated reactions. Traditional trimethylsilane deprotection reagents such

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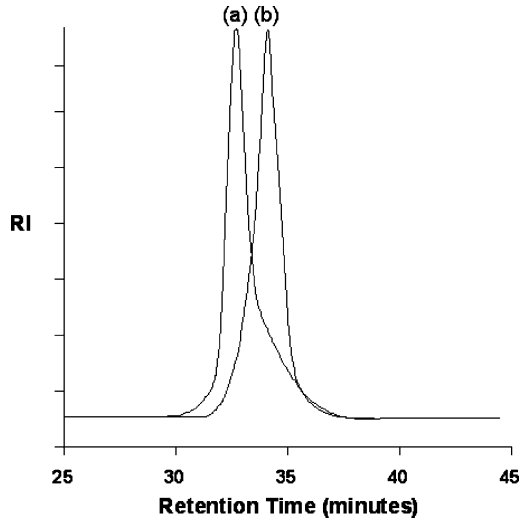

Figure 1. Overlay of GPC traces for (a) the starting linear polymer, M_w = 30 600 and PDI = 1.20, and (b) nanoparticles with 10% VBS incorporation.

as tetrabutylammonium fluoride (TBAF) caused the base labile benzosulfone derivative to degrade; thereby, the exploration of an alternative deprotection method was crucial. A mild deprotection of the TMS group was accomplished with a 60 wt % trifluoroacetic acid (TFA) solution in methylene chloride, allowing for high conversion to the final vinyl product, **6**.

The vinylbenzosulfone cross-linking monomer proved to be compatible with living free radical polymerization methods such as nitroxide-mediated polymerization procedures. Random copolymers of 90% styrene and 10% vinyl benzosulfone (90:10 Sty/VBS) were synthesized with high control over molecular weight and low polydispersity in the presence of α-hydrido alkoxyamine[10] (M_w = 30 600 amu, PDI = 1.20). After successful incorporation of the novel *o*-chinodimethane precursor into polystyrene, the ability to transform linear polymer structures into defined, three-dimensional architectures was compared to linear polymer precursors with the reported benzocyclobutene cross-linker.[2] Differential scanning calorimetry (DSC) of the 90:10 styrene/VBS random copolymer precursor confirmed reports that benzosulfone derivatives form *o*-quinodimethane intermediates at temperatures around 250 °C based on the exothermic maximum of the DSC curve relating to the opening of the sulfone ring. Thus, we could investigate the intramolecular chain collapse process in dibenzyl ether and chose for the first experiment optimized conditions of the ultradilute drop-in technique described for the benzocyclobutene cross-linking unit.[2] Under these conditions, the continuous addition strategy of a concentrated solution of the same linear polymer with a VBS concentration of 0.07 M gave a final cross-linking concentration of 0.003 M in dibenzyl ether after addition. Evidence of the conformational change from random coil linear polymers to intramolecular collapsed nanoparticles was deter-

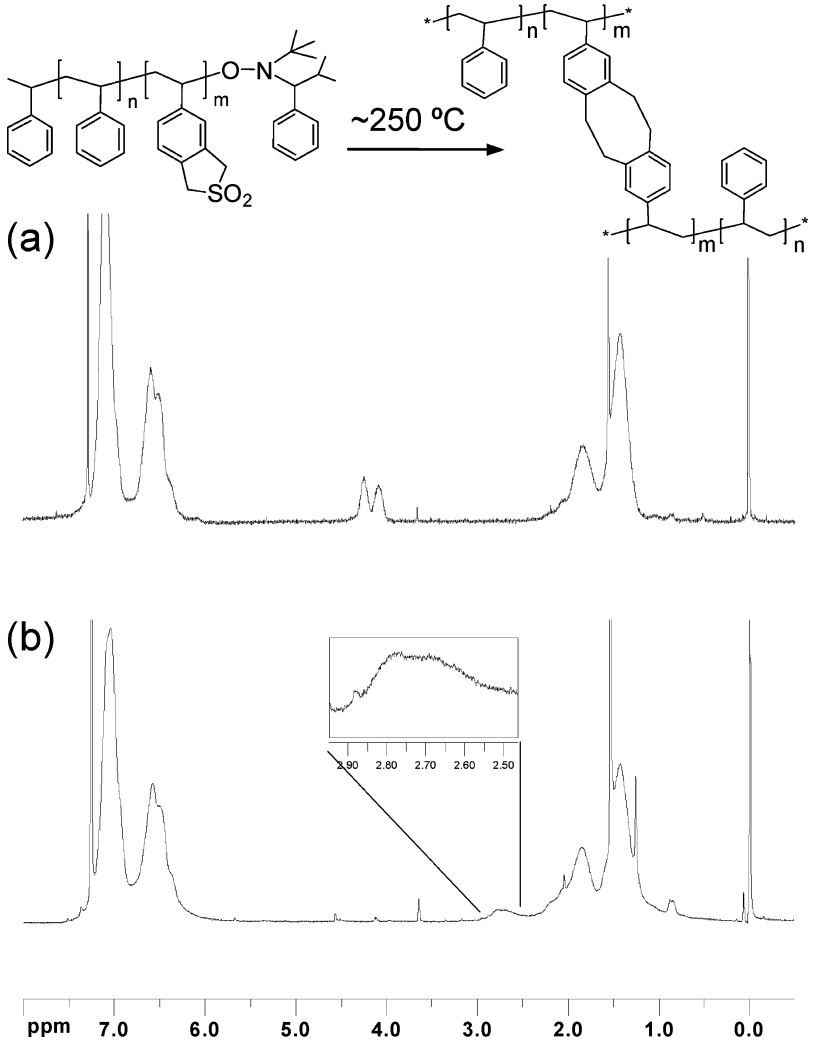

Figure 2. Comparison for the ^{1}H NMR spectra for (a) the starting linear polymer, 90/10 Sty/VBS, M_w = 30 600, and PDI = 1.20, and (b) the resulting nanoparticle, M_w = 19 000 and PDI = 1.18.

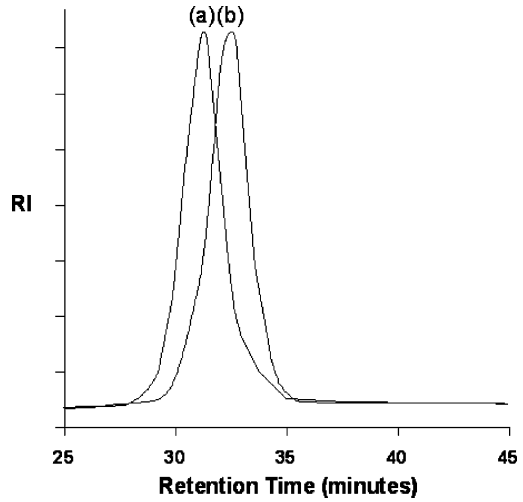

Figure 3. Overlay of GPC traces for (a) the starting linear polymer, M_w = 68 000 and PDI = 1.28, and (b) nanoparticles with 5% VBS incorporation.

mined through an apparent molecular weight decrease from 30 600 to 19 000 amu for the two respective architectures (Figure 1).

Furthermore, NMR studies showed that the two sets of aliphatic protons of the incorporated benzosulfone ring observed at 4.0−4.3 ppm disappeared after collapse while a broad resonance structure at 2.6−3.1 ppm is formed. These results are consistent with the collapse of linear polymers containing the benzocyclobutene−*o*-quinodimethane precursor to form dibenzocyclooctadiene units after the intramolecular chain collapse process with a broad resonance between 2.0 and 3.0 ppm[2] (Figure 2).

After the first indication that the cross-linking unit provided an alternative to the benzocyclobutene unit, we explored the implementation of the novel benzosulfone derivative into acrylate backbones and its performance during the intramolecular chain collapse process. The key to investigate collapsed nanoparticles in a biological environment requires compatibility in physiological conditions. To meet these demands, the copolymerization of benzyl acrylate monomers with benzosulfone cross-linking units has been proposed. While poly(benzyl acrylate) is very well soluble in dibenzyl ether, the deprotection of the carboxylic acid groups via hydrogenation maintains hydrophilic discrete particles for applications in biological systems. The linear random copolymer is synthesized from 95% benzyl acrylate and 5% benzosulfone cross-linker, **6** (95:5 BA/VBS), employing nitroxide-mediated polymerization in the presence of α-hydrido alkoxyamine (M_w = 68 000, PDI = 1.28 following fractional precipitation). After an intramolecular chain collapse process under the same experimental conditions as demonstrated for the 90:10 styrene/VBS random copolymers, the resulting purified nanoparticles were analyzed with GPC and ^{1}H NMR. It was found that no indication of intermolecular cross-linking was observed, and the GPC trace shifted to lower

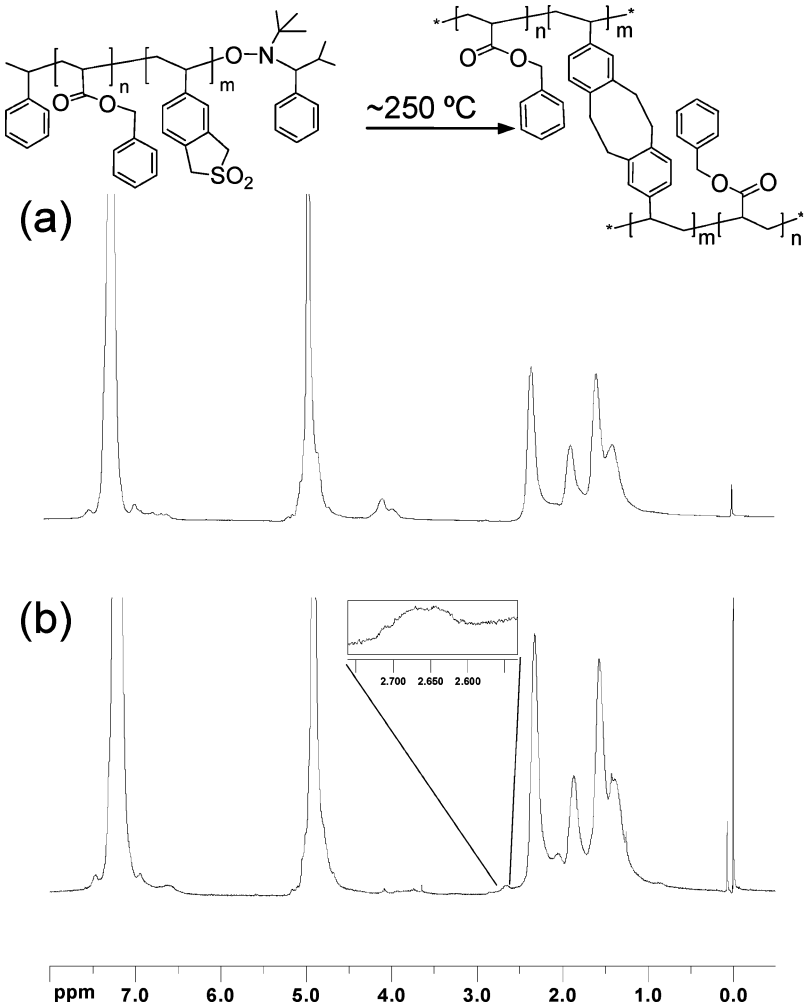

Figure 4. Comparison for the ^{1}H NMR spectra for (a) the starting linear polymer, 95/5 BA/VBS, M_w = 68 000, and PDI = 1.28, and (b) the resulting nanoparticle, M_w = 42 000 and PDI = 1.26.

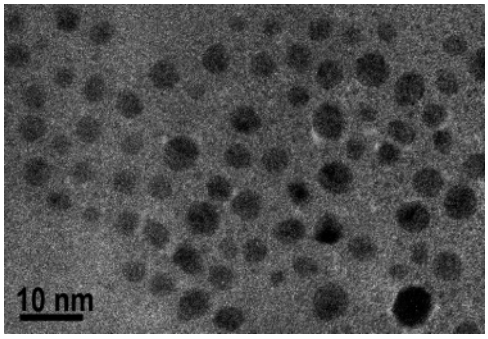

Figure 5. TEM image of benzyl acrylate nanoparticles.

molecular weights of M_w 42 000 amu with a slightly lower polydispersity than the linear precursor (Figure 3).

^{1}H NMR studies showed again the disappearance of the characteristic aliphatic protons of the benzosulfone derivative at 4.0−4.3 ppm parallel to the formation of the dibenzocyclooctadiene unit with broad resonance peaks at 3.1 ppm (Figure 4). Further evaluation of the collapsed nanoparticles with transmission electron microscopy (TEM) confirmed the controlled cross-linking process of linear precursors into defined 3-D architectures with the mean diameter of 6.52 ± 1.7 nm (Figure 5). In order to achieve the transformation into a hydrophilic nanoparticle with free carboxylic acid groups for further modifications, the nanoparticles were hydrogenated with Pd/C in a THF mixture for 48 h.[11] The complete removal of the benzyl protecting groups was confirmed in ^{1}H NMR measurements and yielded hydrophilic nanoparticles soluble under physiological conditions.

In this report, we have demonstrated the practical synthesis of 5-vinyl-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (VBS) as an *o*-chinodimethane precursor to facilitate controlled cross-linking of linear polymers utilizing an intramolecular chain collapse process. The novel cross-linking unit was compatible with nitroxide-mediated polymerization procedures that allowed the incorporation into polystyrene and poly(benzyl acrylate) backbones. Intramolecular chain collapse procedures confirmed the fidelity of this *o*-quinodimethane precursor as a viable alternative to traditional benzocyclobutene cross-linking units and gave distinct nanoparticles in the dimensions of 6−10 nm. In particular, the deprotected hydrophilic acrylate-based nanoparticles are attractive vectors as their application in the biomedical arena will be further investigated.

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Supporting Information Available: Experimental details for synthetic procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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