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Dual-Reactive Hyperbranched Polymer Synthesis through Proton Transfer Polymerization of Thiol and Epoxide Groups

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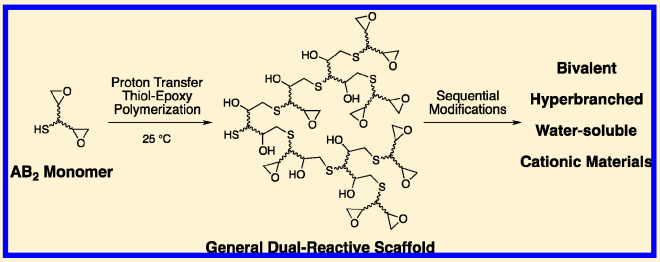
Supporting Information

ABSTRACT: A new synthesis of hyperbranched polymers through proton transfer polymerization of thiol and epoxide groups is presented. For this, an AB_2 monomer bearing two epoxides and a thiol groups is synthesized. Base-catalyzed proton transfer polymerization of this monomer led to the formation of a polythioether-based hyperbranched polymer with a 65−69% degree of branching and carrying about 2% of disulfide-based structural defects. This polymer contained two reactive sites, a hydroxyl group and an epoxide unit, distributed throughout the branched scaffold. The epoxide groups could be employed in anchoring an alkyl, aryl, or ethylene oxide chain through a thiol−epoxy reaction, while the hydroxyl groups produced during the polymerization and the first functionalization reactions could be engaged in attaching positively charged primary ammonium groups to the branched backbone. These sequential postpolymerization modifications transformed the general dual-reactive scaffold into dual-functionalized hyperbranched materials with potential utility in the arena of gene delivery applications.



INTRODUCTION

Since Flory's theoretical work in 1952, the field of hyperbranched polymers has flourished.[1−9] Elegant synthetic approaches have been developed, effects of the branched architecture on the material properties have been elucidated, self-assembling properties have been considered, and these unique architectures have been demonstrated to be of considerable utility in a wide range of applications.[2−9] Despite these developments, heterodual-functionalization approaches of the hyperbranched scaffold remain relatively few.[9] This limitation is noteworthy, as capability of heterofunctionalization will allow for development of a functionalized materials platform suited for targeting sophisticated applications. For example, in the biomedical arena, introduction of a long alkyl chain for cell permeation[10,11] or an ethylene oxide chain for stealth properties[12] along with a complexation site (such as a chemically charged ammonium group)[13] can give rise to well-defined bifunctional materials with potential applicability in the arena of siRNA delivery.[10c,11,14] In this regard, a recent study has shown that linear polymers carrying an ammonium group and a lipophile (an alkyl/aryl moiety) were capable of forming supramolecular complexes with siRNA and delivering it to human colon carcinoma cells (HT-29-luc).[11] In this design, the positively charged ammonium groups interacted with the negatively charged siRNA and the lipophilic chains allowed the formed complex to cross the cell/endosome membrane. This study, along with other works,[10,15,16] underlines the importance of developing new synthetic pathways to dual-functional soft materials. Toward this end, in the present work, we present development of a new synthesis to hyperbranched polymers (Scheme 1). This synthesis is based upon proton transfer polymerization of thiol and epoxide groups. The resulting polymers represent a general and dual-reactive scaffold that can be functionalized in a precise fashion with two distinctly different functionalities.

RESULTS AND DISCUSSION

The concept of proton transfer polymerization was elegantly illustrated by Fréchet and co-workers in 1999.[8a] In this work, the ring-opening reaction of an epoxide group by the phenol nucleophile was employed as the polymerization process. In this system, it was established that after initiation with a catalytic amount of a hydroxide ion (70 °C), the generated alkoxide anion does not undergo propagation but rather a thermodynamically driven proton exchange reaction with the phenol group. The phenolate anion created by this proton transfer reaction then becomes active and propagates the epoxy ring-opening (polymerization) reaction. In a later report, acid groups were used instead of a phenol to obtain hydrolyzable polyesters.[8b] We envisaged that the thiol-epoxy reaction[16] could also be employed for the preparation of the hyperbranched polymers through a similar proton transfer mechanism (Scheme 1). Since this reaction operates under ambient conditions, the polymerization in this system could be carried out at room temperature. Furthermore, the resulting polymers would differ from Fréchet's polyethers as the sulfur atom

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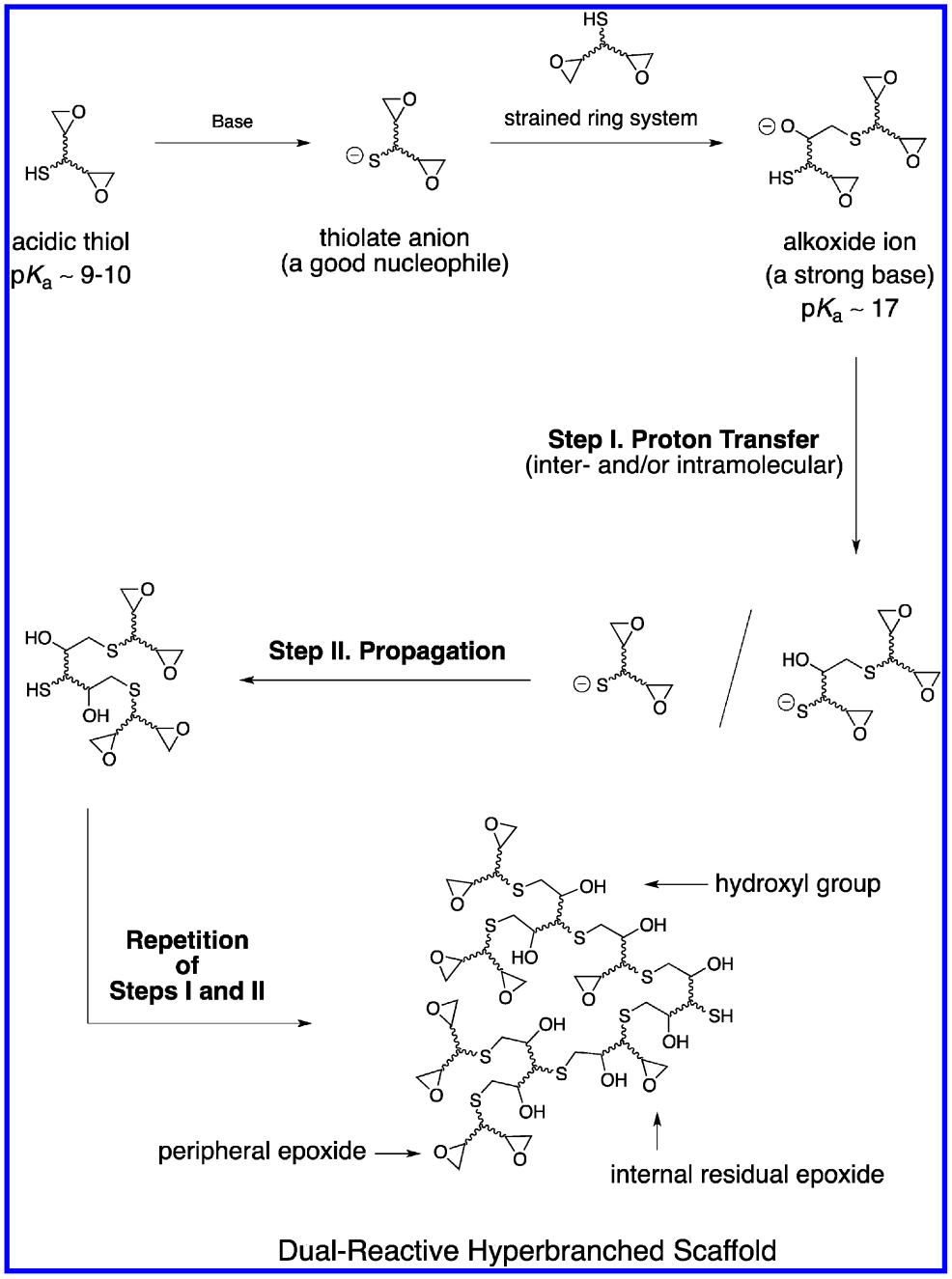
Scheme 1. Schematic Representation of the Proton Transfer Polymerization of Thiol and Epoxide Groups[a]



[a]The wavy lines do not represent chemical bonds and are used to simplify the structure and the underlying concept.

present within the polymer backbone may also, if required, be oxidized, functionalized, and degraded under mild conditions or used as an adhesion promoter.[17] These polymers would carry epoxide and hydroxyl reactive groups. Alteration of these moieties through thiol-epoxy and esterification reactions would then lead to the formation of a bifunctionalized polythioether-based hyperbranched polymer.

Monomer Synthesis. To test this hypothesis, an AB_2 monomer carrying two epoxide groups and a thiol moiety was synthesized in two steps (Scheme 2). In the first step, commercially available olefin, **1**, was partially epoxidized using *m*-chloroperbenzoic acid. The resulting diepoxide, **2**, was then subjected to a photoinitiated free-radical coupling reaction with a dithiol molecule **3**, yielding the desired AB_2 monomer **4**, in a highly reproducible manner and in an isolated yield of 80−85%. The free-radical chemistry was chosen for the last step as it offered a chemically neutral environment. This attribute was deemed essential in gaining synthetic access to a molecule that carried thiol and epoxide groups placed on the same molecule. This is due to the fact that reactions operating under acidic or basic conditions may have resulted in premature opening of the epoxide groups. The free-radical coupling reaction could be monitored with the help of ^{1}H NMR spectroscopy as the olefin proton resonances of **2** located in the region of 5−6 ppm (designated "e' and 'f" in Figure 1) disappeared after the reaction and new signals for the newly formed methylene groups in **4** could be observed (designated "e' and 'f" in Figure 1). In addition to these, the monomer showed typical proton

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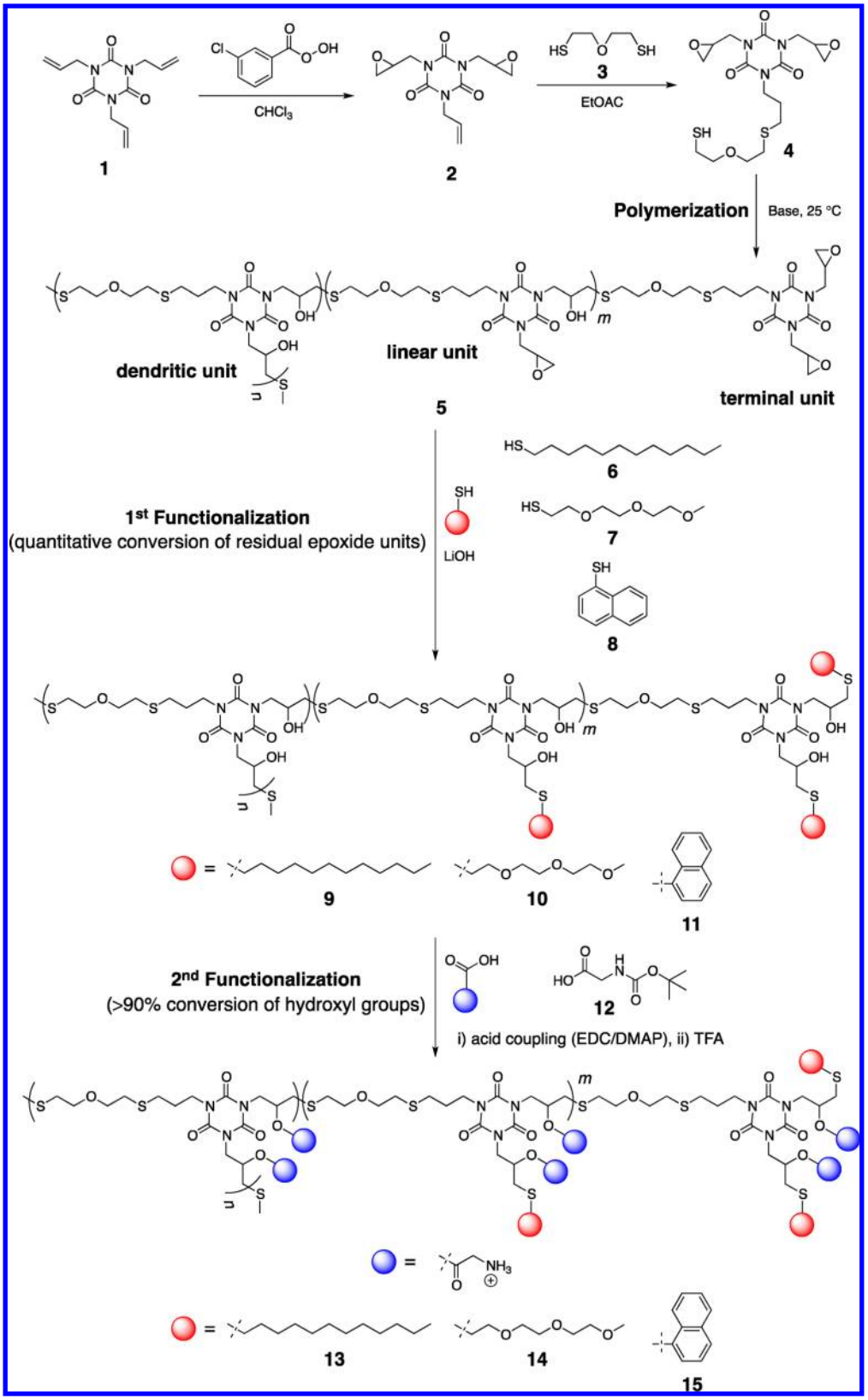
Scheme 2. Synthesis of Bi-Functionalized Hyperbranched Polymers



resonances of the epoxide units in the range of 2−4 ppm while a triplet from the thiol proton could be observed at 1.6 ppm (Figure 1). The purity of monomer **4** could also be verified with the help of elemental analysis, which showed that the theoretical ratio of elements (C, H, O, N, and S) were in good agreement to the experimentally determined values (Figure S1, Supporting Information). The monomer was stored in dilute organic solutions, at low temperatures, and under inert atmosphere as material gelation was observed upon its storage in pure form under ambient conditions.

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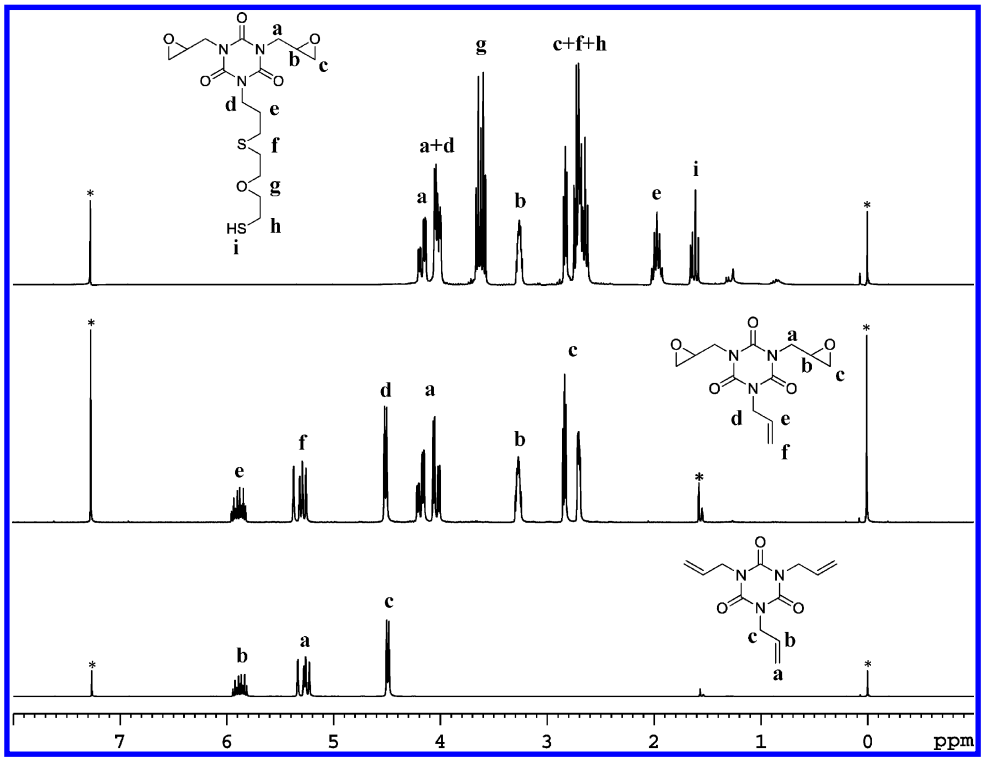

Figure 1. ^{1}H NMR of precursors **1** and **2**, and monomer **4**. For an emphasis on the 1−5 ppm area (monomer **4**), please see Figure 10

Table 1. Polymerization of Monomer 4

entry	catalyst (mol %)	T (°C)	time (h)	solvent	M_n (g/mol)	M_w (g/mol)	PDI (M_w/M_n)	yield (%)
1	TEA (7)	25	23	THF	–	–	–	–
2	TEA (14)	25	23	THF	–	–	–	–
3	TBAF (7)	25	23	THF	6000	13 100	2.16	80
4	TBAF (14)	25	23	THF	6100	14 000	2.29	78
5	LiOH (7)	25	23	THF/H_2O	6700	15 700	2.34	80
6	LiOH (14)	25	23	THF/H_2O	6900	15 900	2.30	84
7	LiOH (7)	25	48	THF/H_2O	7000	13 400	1.91	80

Plausible Polymerization Mechanism. In the present system, the thiol group of an AB_2 monomer could be deprotonated by catalytic amounts of a base and the resulting thiolate nucleophile would attack the less hindered site of the epoxide unit as established in numerous small molecular as well as polymeric systems (Scheme 1).[16,18,19] The alkoxide unit thus formed will be rapidly protonated due to its high basicity ($pK_a \sim 17$)[20] by either the aliphatic thiol group ($pK_a \sim 9-10$)[21] through inter- or intramolecular proton transfer or by the typical wet/protic nature of the reaction medium or by the water generated during the reaction (e.g., while using a hydroxide base). This thermodynamically driven proton transfer step is critical in quenching the alkoxide anion and its potential to start an anionic ring-opening polymerization of the epoxides. The proton transfer step would either result in the formation of another thiolate anion directly or regeneration of the catalyst (e.g., a hydroxide anion). Thus, newly formed thiolate anion would be ready for attacking another epoxide ring and creation of a second alkoxide anion. Repetition of these two steps: (i) thiolate formation by the alkoxide anion or the catalyst present in the system, and (ii) epoxide ring-opening reaction by the thiolate anion, would result in the formation of a polymeric product. Since the monomer carries two-epoxide units, the polymerization reaction would proceed with branching, yielding a hyperbranched architecture.

Scaffold Synthesis. To confirm the aforementioned hypothesis, polymerization of monomer **4** was carried out in the presence of a catalytic amount of triethylamine (TEA) in tetrahydrofuran (THF) and in an argon atmosphere at room temperature. This reaction, however, did not produce any polymer. This result is not surprising considering that pK_a of TEA and aliphatic thiols are in a similar range. Hence, it is likely that TEA fails to act as an efficient base at room temperature in THF. Therefore, the polymerization catalyst was then changed to tetrabutylammonium fluoride (TBAF). TBAF is soluble in a variety of organic solvents as well as water, and known to be a good catalyst for the thiol-epoxy reaction.[16e,18] This reaction produced polymers with molecular weights ranging from 6 to 7 kDa at room temperature (Table 1). To further investigate the polymerization reaction, lithium hydroxide (LiOH) was used as the polymerization catalyst. This catalyst has been used with significant success for the thiol−epoxy coupling reaction in small molecular[19] as well as polymeric[16] systems. This change, however, did not alter the outcome of the polymerization reaction. Moreover, using a higher catalyst loading and increasing the polymerization time did not result in any significant changes in the average molecular weight of the

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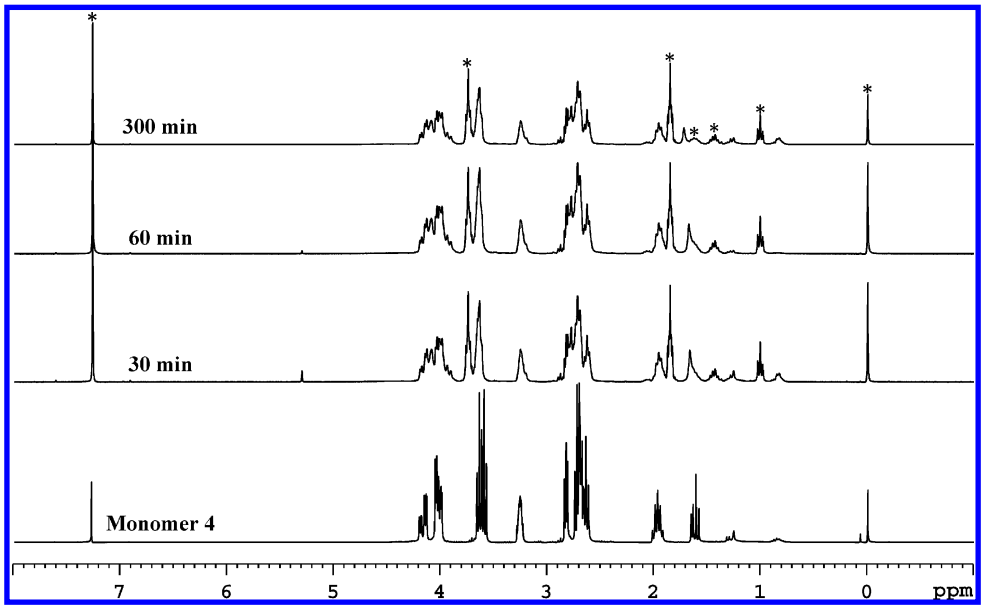

Figure 2. ^{1}H NMR of the polymerization mixture as a function of time. Signals from TBAF, THF, tetramethylsilane (TMS), and chloroform are marked with an asterisk. For a focus on 1−5 ppm area (polymer **5**), please see Figure 11

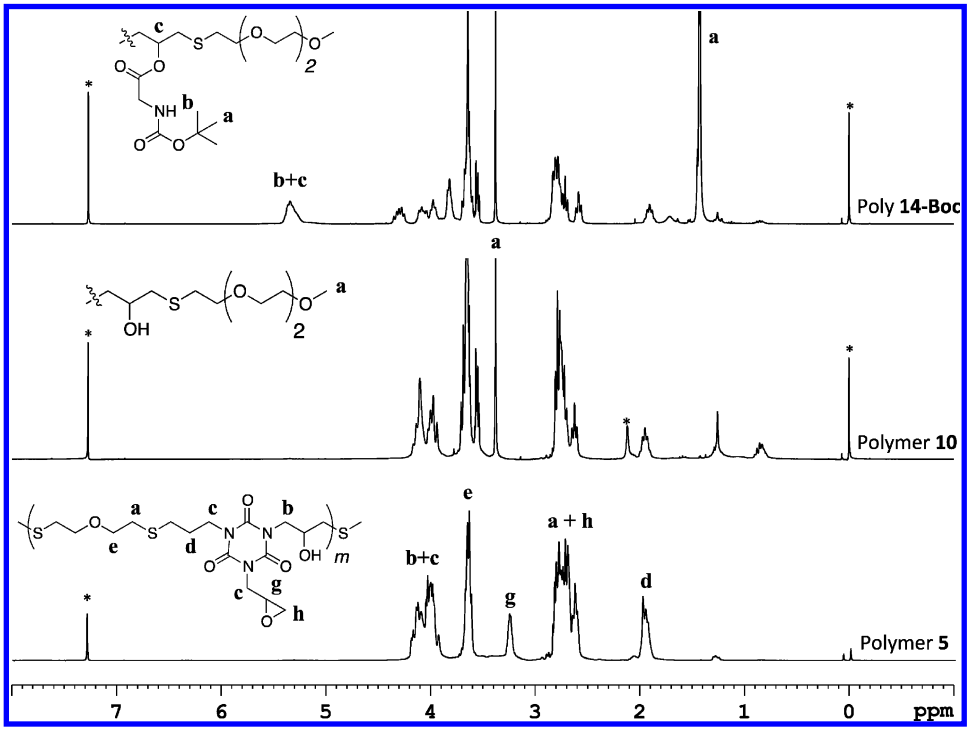

Figure 3. ^{1}H NMR of polymers **5**, **10**, and **14**-Boc (also see Figures S3 and S4). For an emphasis on the 1−5 ppm area (polymer **5**), please see Figure 11

obtained materials (Table 1). Presumably, the steric hindrance to the nucleophilic focal point increases with the progression of the reaction and leads to an intrinsic limitation of the achievable molar mass. It is clear that more experiments are necessary to investigate this aspect. Therefore, the polymerization data presented here should be considered preliminary. However, it should be mentioned that the polymerization reaction could be repeated in a reproducible manner. Figure 2 shows a series of ^{1}H NMR spectra obtained from the polymerization mixture as a function of polymerization time. Compared to the sharp signals of the monomer, the polymer signals were broadened (Figure 2). IR spectroscopy confirmed that the carbonyl stretch at 1670 cm^{-1} of the monomer **4** remained unperturbed under the polymerization conditions (Figure S2). A broad band belonging to the newly generated hydroxyl groups could be located at 3400 cm^{-1}. The dual-reactive scaffold was observed to become insoluble upon storage in its dry state. Therefore, after synthesis, the polymer was stored in an organic solution at low temperatures. The functionalized polymers (discussed henceforth), however, were perfectly stable in dry state and at room temperature.

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Scaffold Bifunctionalization. The epoxide groups in polymer **5** could be subjected to a functionalization reaction with a thiol-functionalized long alkyl chain (**6**), an ethylene oxide chain (**7**), or an aromatic naphthalene unit (**8**). The alkyl/aryl chains are known to endow membrane permeation properties[10,11] whereas the ethylene-oxide chains are known to provide water solubility and stealth properties.[12] The functionalization reactions could be examined with the help of ^{1}H NMR spectroscopy (Figures 3 and S3–S4). This study indicated complete consumption of the epoxide units and appearance of the proton resonances belonging to the triethylene glycol and dodecyl groups in the range of 0.9–1.4 and 3.3–3.7 ppm, in polymers **9** and **10**, respectively. In case of polymer **11**, aromatic resonances could be observed in the range of 7–8.5 ppm. These polymers were found to be insoluble in water but soluble in a range of common laboratory solvents including THF, chloroform, dichloromethane, and dimethylformamide (DMF). A complete consumption of the residual epoxides (^{1}H NMR, Figures 3 and S3 and S4) indicated that the degree of the first functionalization was nearly quantitative. The second functionalization was achieved through esterification of the secondary hydroxyl groups of the hyperbranched scaffold **9**, **10**, and **11** with the *t*-butoxycarbonyl (Boc)-protected acid molecule **12**. A successful second functionalization was evident by the appearance of a signal at 5.3 ppm from the proton located adjacent to the newly formed ester group and the proton resonance signal of the Boc unit at 1.3 ppm (Figures 3 and S3 and S4). On the basis of this, the degree of second functionalization was calculated to be over 90% through area integration analysis in ^{1}H NMR spectroscopy. Finally, the Boc groups could be removed under acidic conditions. In deuterated dimethyl sulfoxide (DMSO-d_6), the ammonium signal could be observed at 8.4 ppm (Figures 4 and S5 and S6). These bifunctionalized cationic hyperbranched polymers (**13**–**15**) were completely soluble in water. Therefore, ^{1}H NMR study could also be carried out in deuterated water (D_2O), which confirmed that the signal at 8.4 ppm in DMSO-d_6 belonged to the ammonium group as it could no longer be observed in D_2O due to a fast exchange with deuterium. The first functionalization reaction did not change the polydispersity of the materials significantly as could be observed in the gel permeation chromatograms of the precursor polymer and its functionalized structures (Figures 5 and S7 and S8). However, some changes are observed after the second functionalization. This is most likely due to an increased solubility of the esterified products and solubilization of the oligomers in diethyl ether. Thermal analysis of the polymers suggested that the glass transition temperature (T_g) of the reactive scaffold decreased upon introduction of alkyl and ethylene oxide chains and increased with the introduction of the aromatic groups in the polymeric structure (Figures 6 and S9 and S10, Table 2). The T_g increased further upon substitution with the Boc-protected and positively charged glycine units.

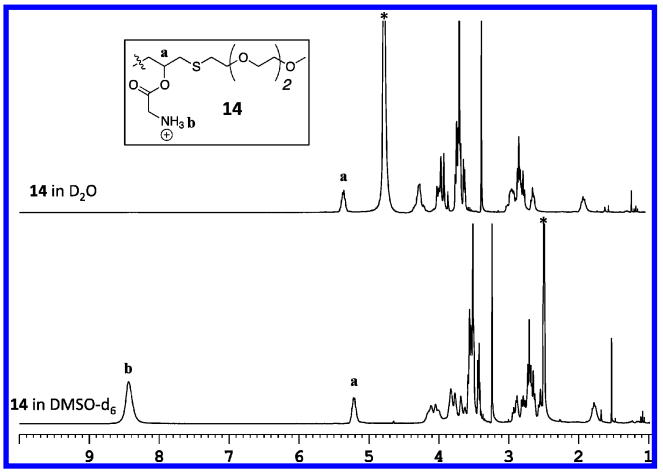

Figure 4. ^{1}H NMR of dual-functionalized polymer **14** in DMSO-d_6 and D_2O (also see Figures S5 and S6).

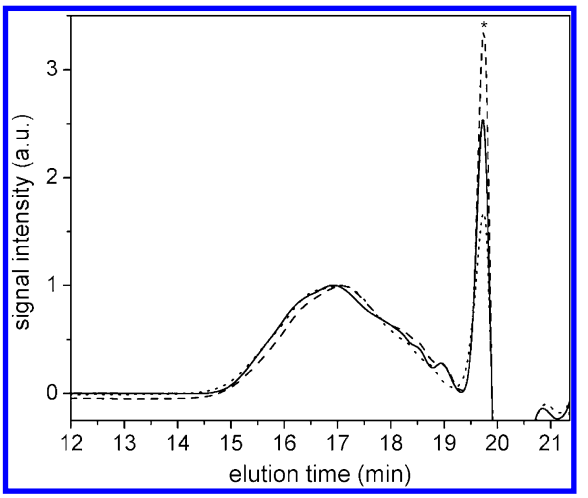

Figure 5. GPC traces of polymer **5** (solid line), **9** (dash line), and **13**-Boc (dot line) (also see Figures S7–8).

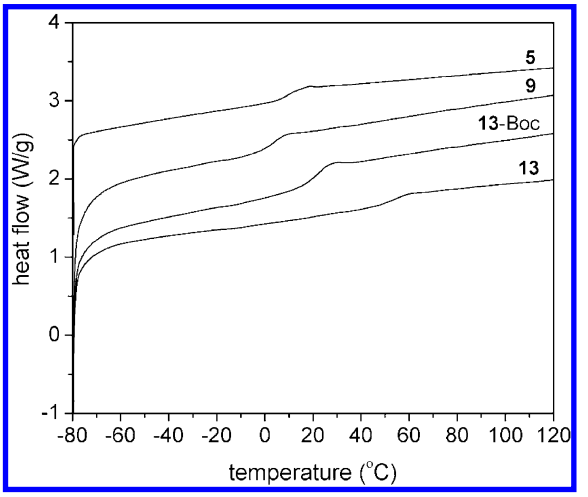

Figure 6. DSC traces of polymers **5**, **9**, **13**-Boc, and **13** (also see Figures S9 and S10).

Determination of Degree of Branching. To investigate the degree of branching in present polymers, model compounds mimicking the linear, terminal, and dendritic units of the hyperbranched scaffold were synthesized. Figure 7 shows the ^{1}H NMR of these compounds. Because of the overlapping of signals and presence of residual epoxide groups, ^{1}H NMR data could not be used to assign the linear, terminal, and dendritic units in polymer **5**. Therefore, signals arising from the carbonyl groups were used for the assignment and area integration analysis.[3a,22] Figure 8 shows the ^{13}C NMR (^{13}C frequency of 176 MHz) of the model compounds and polymer

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Table 2. Glass Transition Temperature of the Prepared Polymers

polymer	5	9	10	11	13-Boc	14-Boc	15-Boc	13	14	15
T_g (°C)	10	4	−21	42	23	24	58	51	47	85

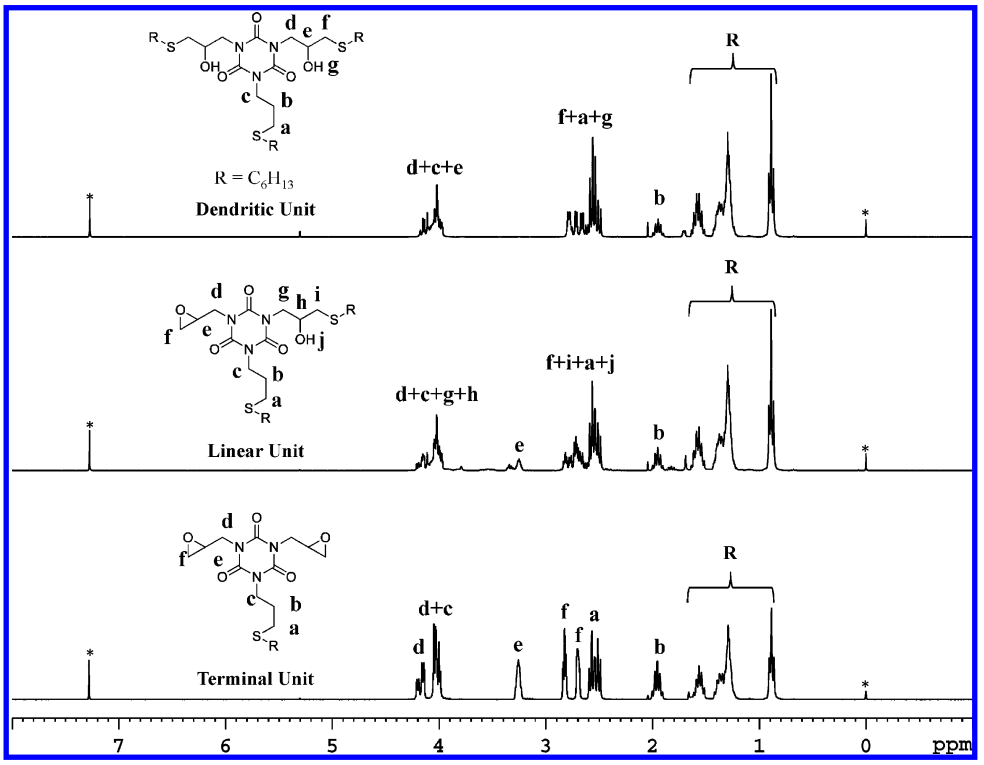

Figure 7. ^{1}H NMR of the model compounds mimicking the linear, dendritic, and terminal structures.

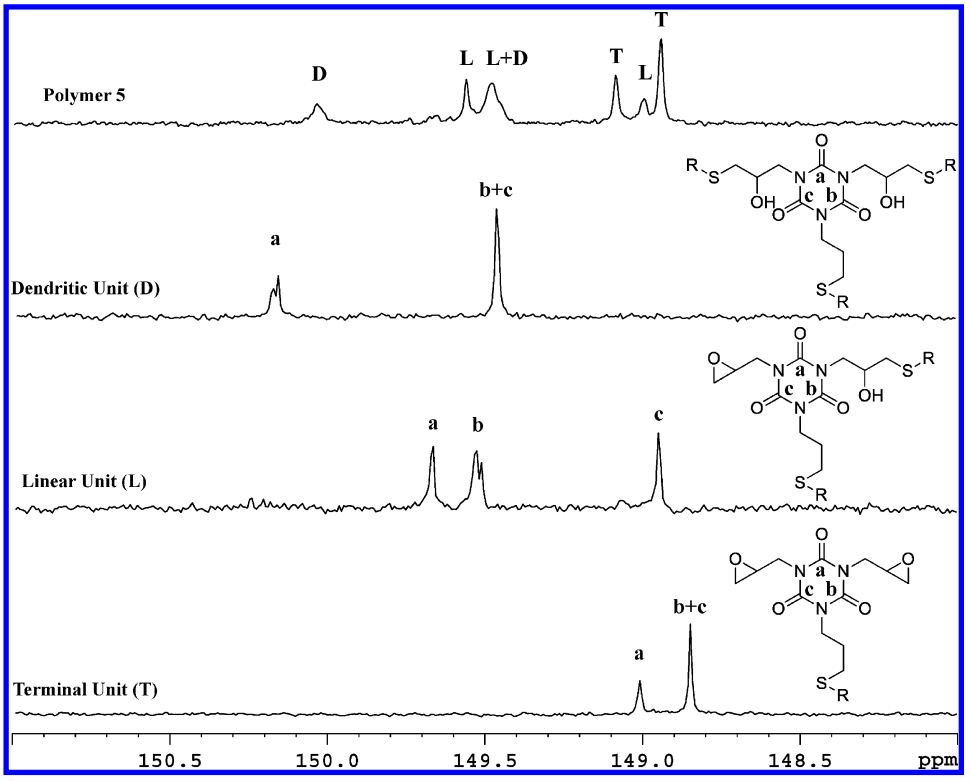

Figure 8. ^{13}C NMR (^{13}C frequency of 176 MHz) of the model compounds and polymer **5**.

5. As expected, the carbonyl groups in ^{13}C NMR, assigned as a, b, and c in Figure 8, had different identities depending upon the substitution pattern. In hydroxy-substituted compounds, signal splitting was observed presumably due to the interaction of the

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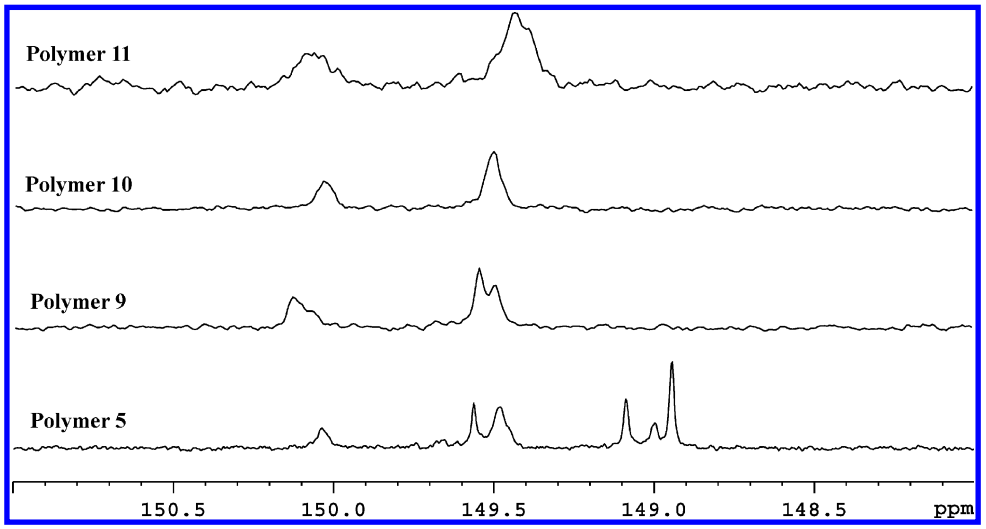


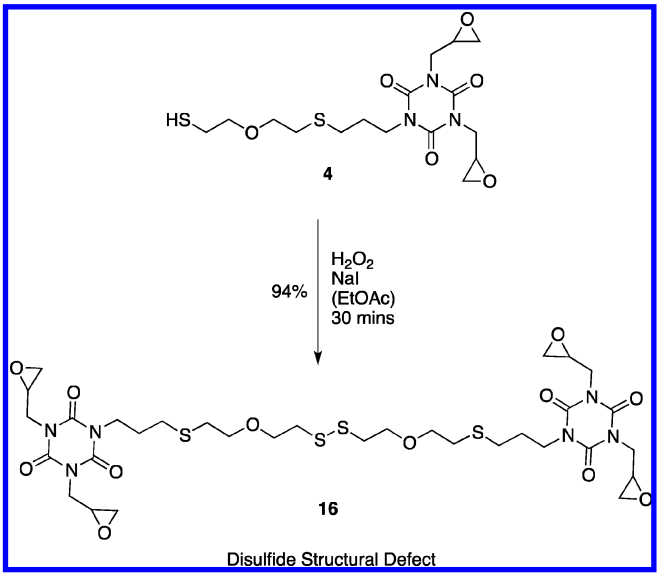
Figure 9. ^{13}C NMR (^{13}C frequency of 176 MHz) of precursor polymer **5**, and functionalized polymers **9**, **10**, and **11**.

carbonyl with the proton of the hydroxyl unit through hydrogen bonding interaction. With the help of these compounds, the ^{13}C-signals of the carbonyl groups in polymer **5** could be assigned to terminal, linear, and dendritic structures. It was observed that the signals were shifted by 0.2−0.3 ppm in the case of polymer. Nonetheless, separation of the signals allowed for area integration analysis to be performed (Figure S11). However, in order to account for the nuclei's different relaxation times, a pulse delay of 20 s was given to record the ^{13}C NMR spectrum. Through area integration analysis and input of these values into the equation described by Hawker, Lee, and Fréchet,[3a] the degree of branching in the present polymers could be calculated to be about 69% (please see the Supporting Information for further information). However, given the relatively low molecular weight of the present polymers, application of the equation given by Hölter, Burgath, and Frey[23] indicated a degree of branching of 65%.

The assignment to the linear, terminal, and dendritic unit was further confirmed by recording the ^{13}C NMR of polymers **9**, **10**, and **11** (Figure 9). These polymers had been subjected to the first functionalization reaction in which all the epoxide groups were consumed. Therefore, the triazine ring in these polymers represented the substitution pattern of a dendritic unit. ^{13}C NMR of these polymers exhibited lack of signals in the vicinity of 149 ppm, indicating that assignment of these signals to the terminal and linear units was correct.

Studying the Disulfide-Originated Structural Defects. A potential issue in the present synthesis may be the formation of disulfide-based structural defects. To examine this aspect, monomer **4** was oxidized with the help of sodium iodide in the presence of hydrogen peroxide to afford the corresponding disulfide dimer **16** (Scheme 3). A ^1H NMR examination of the prepared disulfide dimer revealed that the methylene group located adjacent to the disulfide defect resonated at a different position then the methylene group located adjacent to a thiol or a thio-ether moiety (Figure 10). This signal could also be observed in the ^1H NMR of polymer **5**. An area integration analysis revealed that the content of such disulfide-originated structural defects amounted to about 2% (Figure 11). To further study this aspect, the prepared polymers were subjected to reducing conditions known to break the disulfide linkages in synthetic polymers.[24] For this, dithiothreitol (DTT) was used as the reducing agent in THF at room temperature. Initially,

Scheme 3. Preparation of Disulfide Dimer 16



dimer **16** was subjected to DTT treatment in THF (23 h). However, epoxide rings of this molecule were observed to be consumed under these conditions. In light of this, functionalized polymers **10** and **11** (having no residual epoxide units) were subjected to DTT in THF for 23 h. The reaction mixture was then subjected to a GPC analysis. If the disulfide defects were present in a significant amount then the polymer is expected to be broken-down into smaller entities. The GPC analysis, however, did not show any significant change in the molecular weight distribution or the signal intensity profile of polymers **10** and **11** after subjecting them to the reducing conditions (Figure 12 and Figure S12). This indicated that the content of the disulfide defects, as corroborated by the ^1H NMR study, would be low in the prepared polymers.

CONCLUSIONS

In conclusion, a new synthesis of hyperbranched polymers is developed. In this scheme, proton transfer polymerization of an AB_2 monomer, carrying two epoxide and a thiol units, produced a double-reactive and general hyperbranched scaffold at room temperature. The degree of branching in these

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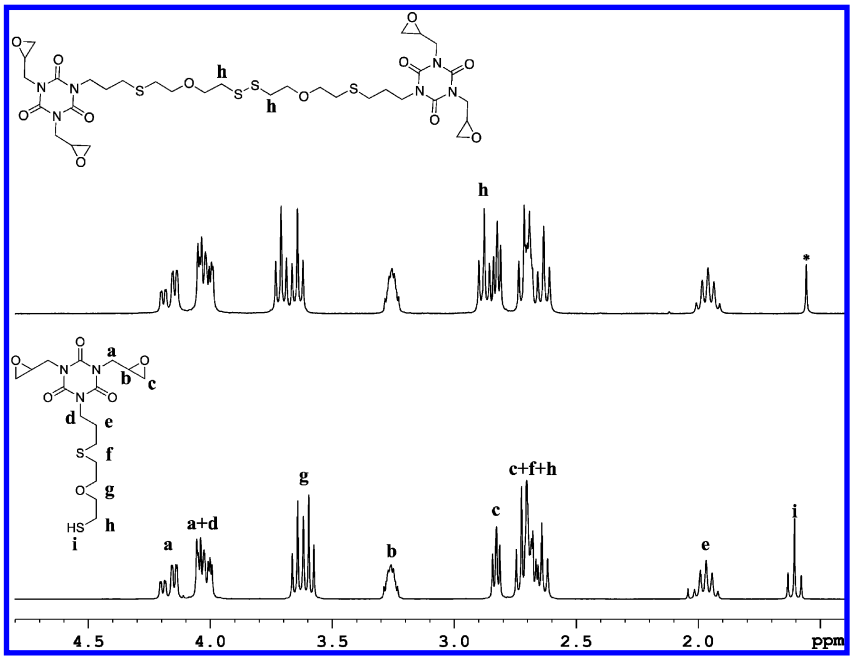

Figure 10. ^{1}H NMR of monomer **4** and disulfide dimer **16**.

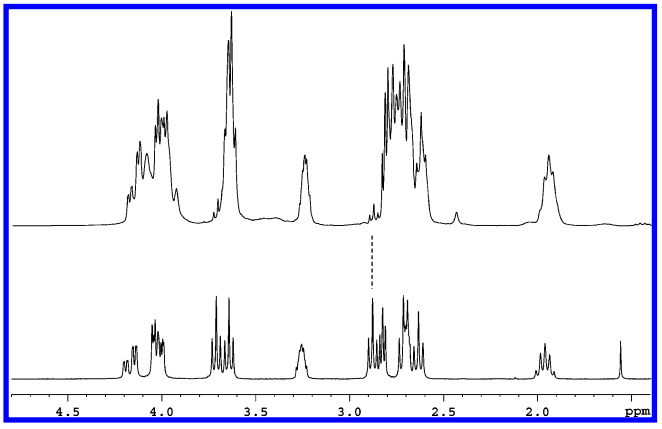

Figure 11. ^{1}H NMR of polymer **5** and disulfide dimer **16**. The dashed line indicates the signal originating from the disulfide defect.

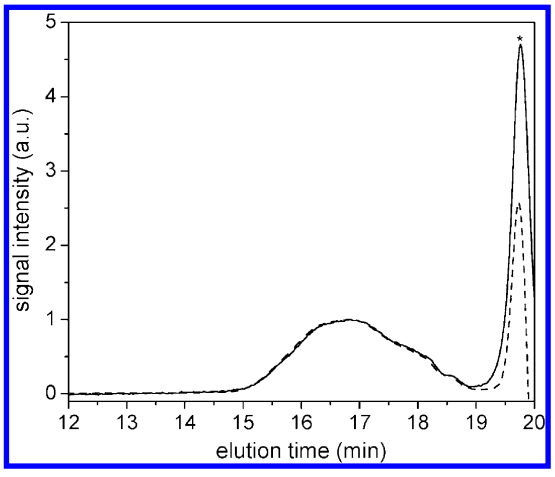

Figure 12. GPC traces of polymer **10** before (solid line) and after (dashed line) treatment with DTT (please also see Figure S12 for polymer **11**).

polymers was calculated to be 65−69% based upon the ^{13}C NMR studies. While a carefully carried out model compound study suggested the presence of about 2% structural defects originating from the formation of disulfides. The epoxide units of these polymers could be modified with lipophilic alkyl or phenyl groups, known for their membrane penetration properties, or with ethylene oxide chains, known for their stealth properties. These polymers were also subjected to a second functionalization reaction. This reaction allowed for installation of a positively charged primary ammonium site, known for its complexation capability with a siRNA molecule, into the polymer structure. Therefore, bivalent materials, of interest to the gene delivery applications, could be obtained starting from a general and novel dual-reactive polythioether-based hyperbranched scaffold obtained through a newly developed proton transfer polymerization between thiol and epoxide groups.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthesis and characterization details. 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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