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Multiply Functionalized Dendrimers: Protecting-Group-Free Synthesis through Sequential Thiol-Epoxy 'Click' Chemistry and Esterification Reaction

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Multiply functionalized dendrimers: Protective-group-free synthesis through sequential thiol-epoxy 'click' chemistry and esterification reaction

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A modular synthetic strategy is described for the preparation of multiply functionalized dendrimers. In this strategy, thiol-epoxy 'click' chemistry is employed for installation of functional groups, and the hydroxyl group produced upon completion of this process is utilized for the growth of the dendritic scaffold through an esterification reaction. Due to the sequential nature of the two involved processes, the developed synthetic pathway remains free from the typical protection/deprotection requirements of dendrimer synthesis. Furthermore, the present strategy allows for placement of chemically different moieties at different dendritic layers.

Synthesis of dendrimers[1-9] featuring spatial functional group distribution[10] is a challenging task that has been receiving increasing attention in the past few years.[11-23] The driving force behind such efforts is the realization that dendrimer multifunctionalization will enhance the range of possible applications as well as performance of this unique class of macromolecules. For example, in the biomedical arena, molecular structures that possess multiple functional groups for tissue targeting, cell entry, delivery, and imaging, in an all-in-one system are highly desired.[24-25] Dendrimers displaying a layered arrangement of functional groups can fit this profile in an excellent manner. However, such sophisticated monodisperse structures remain strikingly rare.[11-12] In this regard, we report a modular synthetic pathway that allows for the preparation of dendrimers carrying multiple functionalities (Scheme 1). The practicality of the present strategy is due to the application of the thiol-epoxy coupling reaction.[26-28] This reaction, in the present context, proceeds to completion in a few minutes at 0 °C, in a solvent mixture of tetrahydrofuran and water, and in the presence of catalytic amounts of lithium hydroxide. Due to the high efficiency of the reaction and absence of byproducts, the dendritic thio-ethers are isolated simply by precipitation into a non-solvent. Importantly, the thiol-epoxy reaction results in the formation of a secondary hydroxyl unit. This hydroxyl group is used as an attachment site *via* an esterification reaction for further dendrimer growth processes. In this way, in the absence of the typical protection/deprotection requirements, a third generation dendrimer having three different functionalities (one kind in each layer) is obtained in 5 synthetic steps. The synthetic ease, complexity of the molecular structures produced, and modularity of the approach represent a unique example in the field of dendrimer synthesis. This progress underlines the potential of cascade reactions in macromolecular synthesis.[26-29]

The synthetic strategy for dendrimer growth is illustrated in Scheme 1. The reaction between tri-epoxide **1** and thiol **2** was carried out at 0 °C for 20 minutes in the presence of LiOH (0.2 equivalents/thiol). A variation of the thiol/epoxy ratio suggested that 1.1 equivalents of thiol per epoxide unit were necessary for completion of the reaction (Figure S1-S2). A simple water washing and precipitation of the reaction in a mixture of diethylether and heptane afforded mono-functional first generation dendrimer **3**. The isolated product yield ranged from 90-95%. The hydroxyl groups of **3** allowed for installation of a branching unit, **4**, *via* an esterification reaction. This reaction resulted in 40% isolated yield of monofunctional second generation dendrimer **5**. The epoxide units of this molecule could be opened by a thiol molecule, **6**, carrying a second type of functionality, a naphthalene unit. Again, the same reaction conditions were applied as described for the synthesis of dendrimer **3**. Precipitation into a diethylether/heptane mixture gave rise to the second generation bifunctional dendrimer **7** in isolated yield of 90%. The dendrimer growth *via* the esterification reaction, followed by the layer functionalization using thio-glycerol afforded third generation dendrimer **9**. Once again, the thiol-epoxy reaction afforded high yields (80%) and the esterification reaction remained low yielding (10%). The final dendritic structure **9** carried 3 anisole units (first layer), 6 naphthalene units (second layer), and 24 secondary and 12 primary hydroxyl units in the dendrimer periphery. The sequence of reactions could be followed by ^{1}H-NMR spectroscopy (Figure 1 and Figure S3-S8). In dendrimers **1**, **5**, and **8**, the epoxy proton at the stereogenic center (shown with an arrow in Figure 1) resonated at 3.30 ppm. Upon opening of the epoxide ring, this proton resonance shifted to 4.00 ppm in dendrimers **3**, **7**, and

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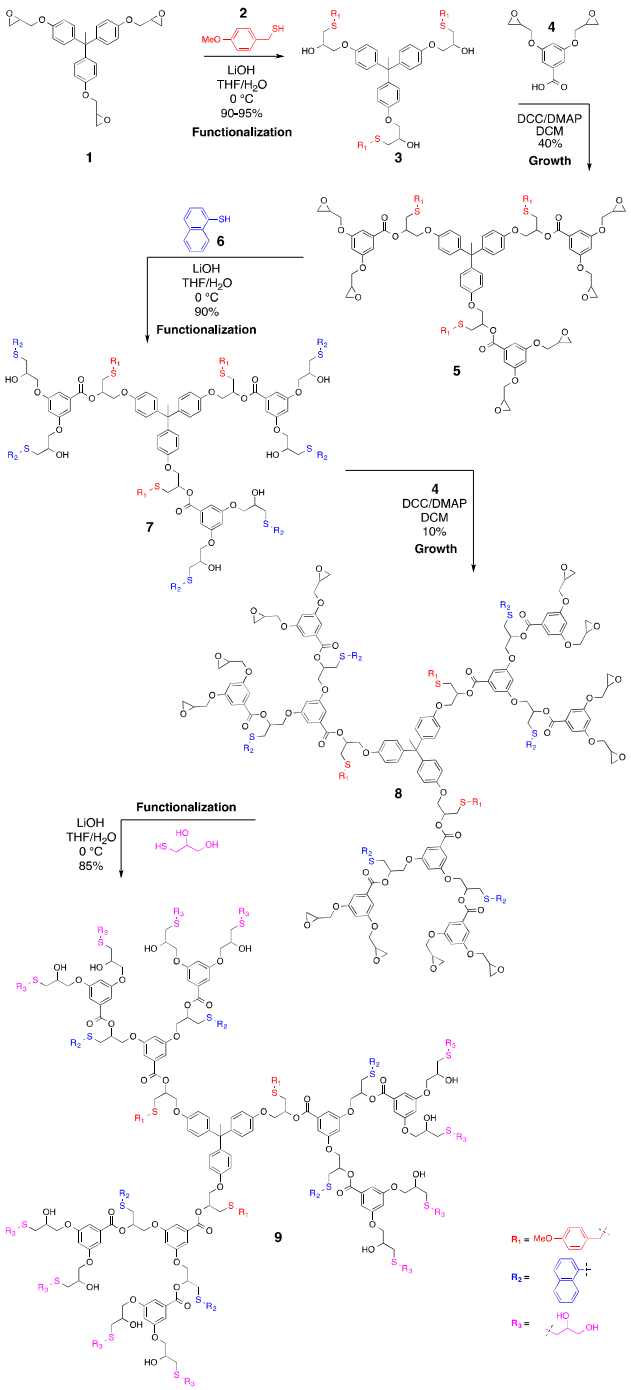

Scheme 1. Synthesis strategy involving a sequential thiol-epoxy and esterification reaction to generate multiply functionalized dendrimers.

9. Upon esterification reaction, due to conversion of the secondary hydroxyl group into an electron withdrawing ester moiety, this proton signal shifted further downfield to about 5.45 ppm in dendrimers **5** and **8**. The area integration analysis in the ^{1}H-NMR spectroscopy established 90% and higher compound purity for the

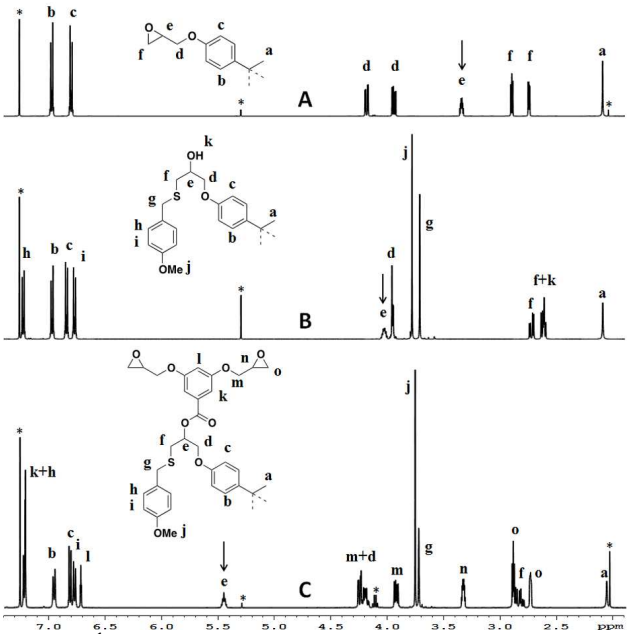

Figure 1. ^{1}H-NMR of dendrimers **1** (A), **3** (B), and **5** (C) in $CDCl_3$. Tetramethylsilane was used as an internal standard. The solvent signals are shown with an asterisk.

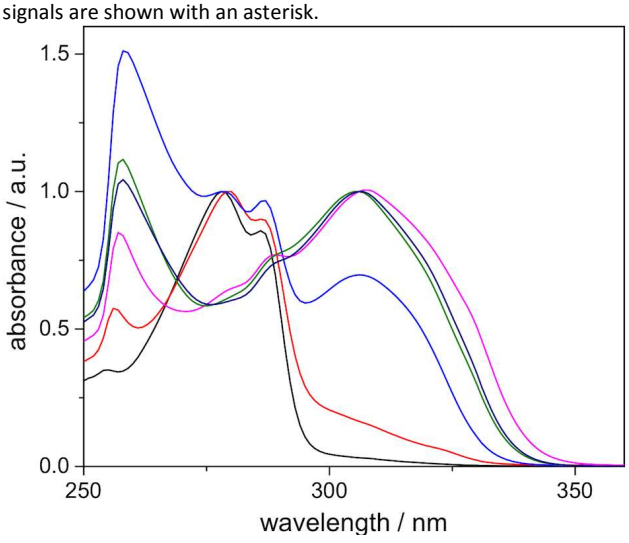

Figure 2. UV/Vis absorption spectra of **1** (black), **3** (red), **5** (blue), **7** (magenta), **8** (green), and **9** (navy blue) in DMSO.

complete dendritic series, which is remarkable for dendritic materials prepared through a divergent growth method.[30]

The UV/Vis absorption spectrum of dendrimer **3** displayed three absorption peaks at 256, 280, and 287 nm with tailing of the

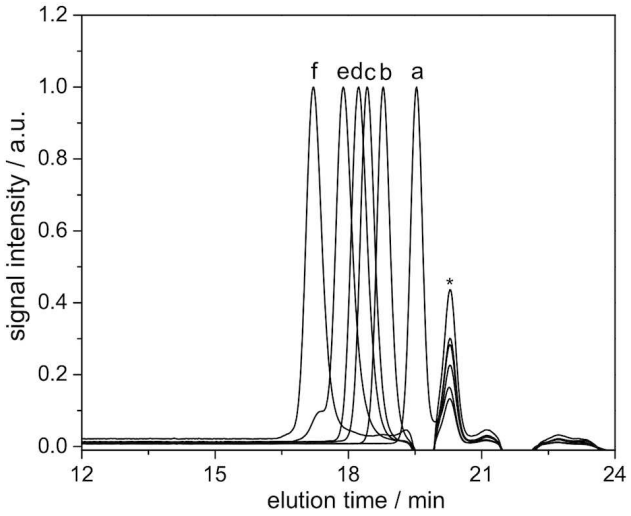

Figure 3. GPC traces of dendrimers **1** (a), **3** (b), **5** (c), **7** (d), **8** (e), and **9** (f) in DMF. Signal from LiBr is shown with an asterisk.

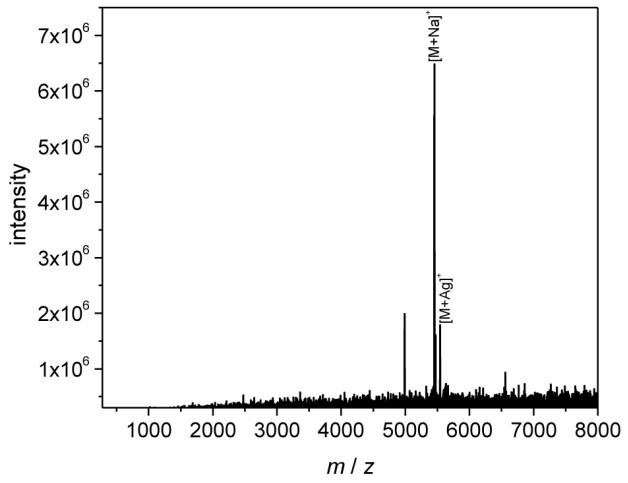

Figure 4. MALDI mass spectra of dendrimer **9**.

absorption band up to 340 nm (Figure 2). Dendrimer **5**, due to incorporation of the aromatic units from the branching unit, **4**, showed an increase in the intensity of the absorption band at 258 nm. Interestingly, a well-defined absorption band was observed centered at 306 nm. Absorption from the naphthalene group dominated the UV/Vis spectrum of dendrimer **7**. In dendrimers **8** and **9**, the absorption peaks remained at similar positions as in the case of **7**. However, intensity of the band at 257 nm increased due to an increase in the number of aromatic repeat units. In IR spectroscopy (Figure S9-S10), dendrimers **1**, **5**, and **8** exhibited the C-O stretching band from the epoxide group at 910 cm^{-1}. Upon opening of the epoxy ring by a thiol molecule, this band disappeared in dendrimers **3**, **7**, and **9**. Dendrimer growth through the esterification reaction was also evident from the appearance of a C=O stretching band of the ester group at 1715 cm^{-1} and disappearance of the OH stretch at 3400 cm^{-1}. In size exclusion chromatograms, a systematic increase in dendrimer size and monodispersity were observed (Figure 3), except in the case of **8**, which showed a high molecular weight shoulder. MALDI mass spectrometry revealed strong signals for molecular ions (as Na^+, K^+, and Ag^+ adducts) of all the prepared branched structures. For example, dendrimer **9** revealed a prominent set of molecular ions corresponding to the expected molecular formula of $C_{266}H_{312}O_{78}S_{21}$ and a molecular weight of 5425 a.m.u. (Figure 4). A minor set of peaks could be observed at 4988 a.m.u., which corresponds to a structurally defective dendrimer resulting from incomplete esterification of a terminal hydroxyl unit in **7** during the reaction with **4**.

Conclusions

In summary, efficiency of the thiol-epoxy reaction can be used to install chemical functionalities on a branched scaffold. Upon completion, such a functionalization process produces a hydroxyl unit. Such reactive moieties can be used for further dendrimer growth through an esterification reaction. Therefore, through application of the thiol-epoxy reaction for dendrimer functionalization, and esterification reaction for the dendrimer growth, multiply functionalized dendrimers can be obtained in a few synthetic steps. However, it is clear that low yields of esterification reaction remains a concern in the present synthetic strategy. Nonetheless, due to the sequential nature of the two involved processes, the designed synthetic strategy is free from any functional group protection/deprotection requirements of organic synthesis. The versatility and practicality of the present approach is expected to give access to a wide range of structurally complex yet chemically precise multiply functionalized dendritic materials.

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