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Facile access to internally functionalized dendrimers through efficient and orthogonal click reactions†

Taegon Kang,[ab] Roey J. Amir,[a] Anzar Khan,[a] Kaoru Ohshimizu,[cd] Jasmine N. Hunt,[ac] Kulandaivelu Sivanandan,[a] Maria I. Montañez,[e] Michael Malkoch,[e] Mitsuru Ueda[d] and Craig J. Hawker*[abc]

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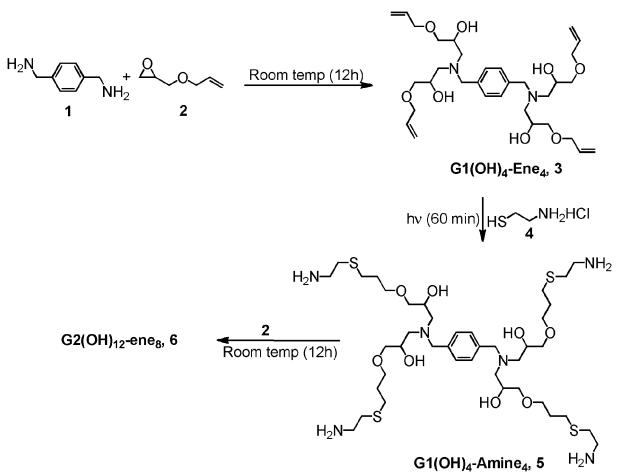
A simple synthetic strategy has been developed for accessing internally functionalized dendrimers. The key feature of this approach is the use of two orthogonal and efficient reactions—'epoxy–amine' and 'thiol–ene' coupling—for rapid growth of the dendritic scaffold. This sequence of reactions allows for the introduction of reactive hydroxyl groups at each dendritic layer.

Traditionally, the chemical identity of dendritic macromolecules[1,2] originates from the presence of functionalities at the periphery[3] and/or core[4] with few studies investigating the influence of functional groups placed at internal repeat units.[5] The synthetic difficulty and increased level of sophistication required to prepare these internally functionalized dendrimer[6] have hindered research in this field even though the number of internal functional groups can exceed the number of chain ends.

The potential influence of internal functional groups can be gauged from the related field of hyperbranched macromolecules where the added versatility of readily available and internal functional groups has been exploited by a wide range of researchers.[7] For hyperbranched macromolecules, a direct consequence of their one-step synthetic strategy is the presence of linear sequences throughout the structure which provides for reactive handles, typically of the same nature as the chain ends.[8,9] The increased availability of internally functionalized dendrimers would permit the optimized placement of catalytically active moieties,[10] creation of energy gradients—allowing for cascade processes to occur,[11] while also increasing the drug loading capacity of dendrimers *via* internal anchor groups.[12]

Herein, we demonstrate that by employing two robust and highly efficient orthogonal reactions—'epoxy–amine' and 'thiol–ene' coupling—it is possible to efficiently synthesize dendrimers containing unprotected internal functional groups. The orthogonal nature and modularity of this approach is exemplified by carrying reactive hydroxyl functionalities through all synthetic steps in an unprotected form (Scheme 1).

The choice of epoxy–amine and thiol–ene chemistries was governed by two factors: the efficiency of both reactions and their potential for orthogonality. As has been previously demonstrated, 'epoxy–amine' coupling possesses many of the attributes of a click reaction. The reaction is highly efficient, can proceed at room temperature in the absence of a catalyst and tolerates a number of functional groups. Importantly for the synthesis of internally functionalized dendrimers, ring opening of the epoxy group leads to the formation of a secondary alcohol. This secondary alcohol can serve as a point of attachment for various kinds of functionalities, while at the same time being orthogonal to subsequent epoxy–amine reactions. As a partner reaction to 'epoxy–amine' chemistry, 'thiol–ene' coupling has been exploited in the construction of dendrimers, modification of polymer backbones/chain ends, fabrication of thin-film and hydrogel materials.[13] The high efficiency, simplicity, and functional group tolerance of 'thiol–ene' chemistry makes it an ideal reaction to be used in combination with an 'epoxy–amine' strategy for the accelerated growth of internally functionalized dendrimers from readily available starting materials in a limited number of steps.



Scheme 1 General scheme for generation growth using epoxy–amine and thiol–ene chemistry.

[a] *Materials Research Laboratory, University of California, Santa Barbara, CA 93106-5121, USA*
[b] *Materials Department, University of California, Santa Barbara, CA 93106-5121, USA*
[c] *Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106-5121, USA. E-mail: hawker@mrl.ucsb.edu*
[d] *Department of Organic and Polymeric Materials, Tokyo Institute of Technology, 2-12-1, O-okayama, Meguro-Ku, 152-8552, Tokyo, Japan*
[e] *Division of Coating Technology, Fiber and Polymer Technology, KTH, Teknikringen 56-58, SE-10044, Stockholm, Sweden*

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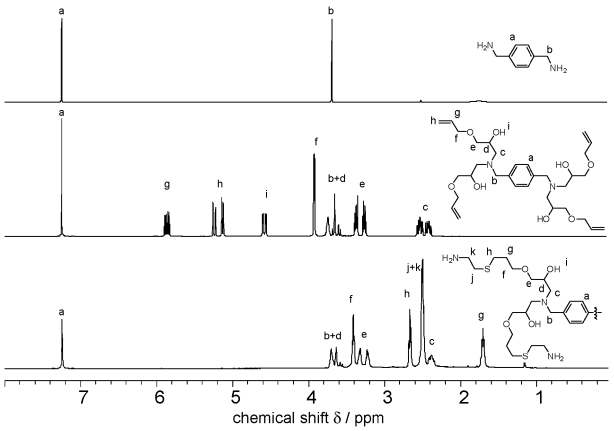

Fig. 1 ^{1}H NMR spectra of the core molecule, 1,4-bis(aminomethyl)-benzene **1** (top), and its product, G1(OH$_4$)-Ene$_4$, **3**, after amine–epoxy coupling reaction (middle), and the next generation dendrimer, G1(OH$_4$)-Amine$_4$, **5**, after subsequent thiol–ene reaction.

The synthetic strategy for generation growth is illustrated in Scheme 1. Starting from 1,4-bis(aminomethyl)benzene, **1**, as the core, reaction with commercially available allyl glycidyl ether, **2**, results in branching and the introduction of 4 secondary alcohol and 4 terminal alkene units. Significantly, the reaction between **1** and **2** was carried out at room temperature in methanol with complete disappearance of the starting material being observed after 12 hours. The resulting molecule, G1(OH$_4$)-Ene$_4$, **3**, could be easily isolated by precipitation into hexanes and obtained in >95% yield. The ^{1}H NMR spectrum of G1(OH$_4$)-Ene$_4$ is shown in Fig. 1 and shows unique signals for repeat units derived from **1** (7.22 ppm—aromatic protons) and **2** (4.6–6.0 alkene protons) with integration values verifying the attachment of four dendritic arms to the core molecule. An enabling feature of the epoxy–amine reaction between **1** and **2** is that the first generation dendrimer, **3**, is obtained in excellent yield without the need for chromatographic purification and, more importantly, with a high degree of purity.

The terminal alkene functionalities were then exploited for further dendrimer growth by the reaction of G1(OH$_4$)-Ene$_4$, **3**, with the commercially available cysteamine hydrochloride, **4**, under thiol–ene conditions. Exposure to 365 nm light in the presence of trace amounts of photoinitiator (2,2-dimethoxy-2-phenylacetophenone) was shown to result in complete consumption of the starting material and formation of the corresponding G1(OH$_4$)-Amine$_4$, **5**, after neutralization. As with the epoxy–amine reaction, the yield for this step was high with no detectable impurities. Fig. 1 shows the ^{1}H NMR spectrum of the G1(OH$_4$)-Amine$_4$, **5**, and complete loss of resonances for the terminal alkene units with concomitant appearance of signals diagnostic for thioether units derived from **4**.

Repetition of this stepwise process then produces the second generation dendrimer, **6**, by the reaction of **5** with allyl glycidyl ether, **2**. Significantly, no reaction was observed to occur at the 4 internal secondary alcohol groups which allows for the clean introduction of 8 terminal alkene units. Thiol–ene reaction followed by epoxide ring opening results in the third generation dendrimer, G3(OH$_{28}$)-Ene$_{16}$ **7**, which features twenty-eight internal hydroxyl groups and sixteen terminal alkene moieties. For all steps, the orthogonality and high efficiency of the 'epoxy–amine' and 'thiol–ene' reactions results in a lack of byproducts which allows the dendrimers to be purified by simple precipitation methods with yields greater than 90%. The high degree of functionalization and efficient construction of these dendritic macromolecules necessitated careful characterization of these materials using a variety of techniques such as ^{13}C{^{1}H}-NMR spectroscopy, mass spectrometry, IR spectroscopy, and SEC. As described previously, the ^{13}C{^{1}H}-NMR spectra proved to be diagnostic due to the appearance and disappearance of unique resonances during construction of the dendritic framework. In addition, systematic increases in dendrimer size and monodispersity were observed in the SEC.[14] To confirm the presence of multiple, internal hydroxyl groups, IR and NMR spectra revealed characteristic signals due to the secondary alcohols with MALDI mass spectrometry allowing rigorous identification of the amino and alkene-terminated dendrimers at each generation level. Only at the third generation dendrimer did MALDI reveal any impurities. As can be seen in Fig. 2, the MALDI mass spectrum for the third generation dendrimer, G3(OH$_{28}$)-Ene$_{16}$ **7**, reveals a prominent set of molecular ions correlating to the expected molecular formula of $C_{200}H_{376}N_{14}O_{56}S_{12}$ and a molecular weight of 4258 a.m.u. A minor set of peaks can be observed at *ca.* 4050 a.m.u. (no peaks were observed below 3900 a.m.u.) which likely corresponds to a failure sequence resulting from incomplete alkylation of a terminal amino group in **6** during the reaction with **2**. When compared to other dendrimers prepared by the divergent growth approach, this level of purity is high (*ca.* 90+%; *cf.* 50% for DAB dendrimers) and approaches that observed for convergent strategies involving chromatographic purifications at each step of the synthesis.[14] The final outcome of this synthetic sequence is the preparation of high purity, internally functionalized dendrimers, such as **7**, in just five steps from commercial starting materials.

The presence of internal hydroxyl groups and chain end alkene units opens up the intriguing possibility of performing regiospecific chemical reactions within the same dendritic framework. To demonstrate this potential, the internal hydroxy groups of the G-1, G-2 and third generation dendrimers, G3(OH$_{28}$)-Ene$_{16}$ **7**, were initially esterified with

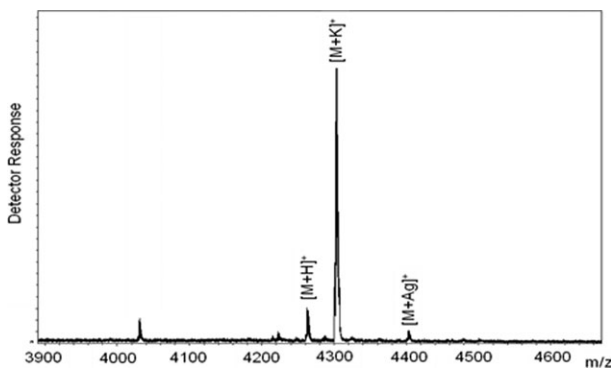

Fig. 2 MALDI-TOF mass spectra of G3(OH$_{28}$)-Ene$_{16}$, **7**.

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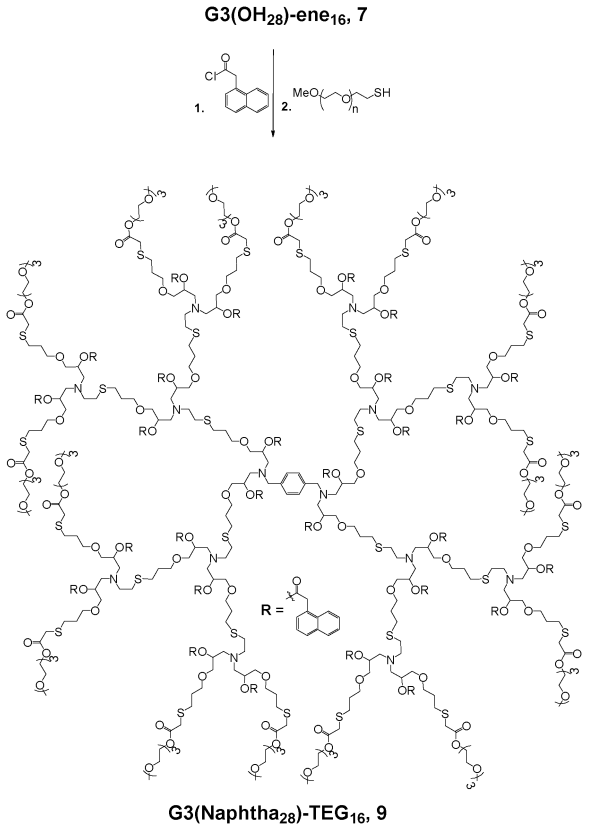

Scheme 2 Internal and chain end functionalization of $G3(OH_{28})$-Ene_{16}, **7**, to give $G3(Naphtha_{28})$-TEG_{16}, **9**.

naphthalene-1-acetyl chloride, resulting in the introduction of 4, 12, and 28 internal naphthalene groups respectively. In a second step, the terminal alkene functionalities were coupled with monomethyl(triethyleneglycol)mercaptan, **8** (TEG), resulting in the formation of amphiphilic dendrimers, such as $G3(Naphtha_{28})$-TEG_{16}, **9**.

A variety of spectroscopic and chromatographic techniques were used to evaluate the extent of internal and chain end functionalization reactions for these dendrimers. At lower generation numbers (G-1 and G-2), MALDI provided strong evidence for full functionalization of both the interior and chain end functional groups with essentially quantitative functionalization being observed. These data were further supported by NMR and UV spectroscopy. For the third generation derivative, **7**, MALDI mass spectral data could not be obtained reproducibly and so ^{1}H NMR spectroscopy was employed for structural characterization. While not providing quantitative conformation of full functionalization, the presence of unique resonances for **9** (*i.e.* four protons for the dendritic core at 7.05 ppm, naphthalene aromatic resonances at 7.25–8.00 ppm and resonances for the tri(ethylene glycol) units at *ca.* 4.05 ppm) allowed these regions to be integrated and high levels of functionalization at both the internal and chain end functional groups (*ca.* 90 + %) demonstrated (Scheme 2).

In conclusion, the successful synthesis and functionalization of internally functionalized dendritic macromolecules demonstrate the power of combining click reactions for the rapid and facile construction of traditionally challenging macromolecular structures. Starting from readily available precursors, the combination of epoxy–amine and thiol–ene chemistry allows for the introduction of reactive hydroxyl groups at each dendritic layer while also allowing the chain end alkene groups to be regiochemically functionalized.

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