Selective Convergent Synthesis of Aliphatic Polyurethane Dendrimers

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Polyurethane homodendrimers have proved difficult to synthesize, and very few successful syntheses have been reported. Hyperbranched polyurethanes were first reported by Spindler and Fréchet[1a] and required the synthesis of a thermally degradable AB_2 monomer which liberated a reactive hydroxy diisocyanate that would spontaneously polymerize. More recently, Bruchmann et al. have developed a commercialy viable process using self-cross-linking isocyanates to form hyperbranched polyurethanes on an indusrial scale.[1b] Ideal branching in dendrimers requires the control of monomer reactivity and stable functional groups that aid the minimization of side reactions. For polyurethane dendrimer synthesis this provides specific challenges due to the highly reactive chemistries that are generally used to form linear materials of this class. Arguably the most successful polyurethane dendrimer synthesis has been reported by Taylor and Puapaiboon[2] using a modified Curtius reaction, with dendrimers of MW = 9588 Da being produced. These materials possess an aromatic branching unit with aliphatic spacer groups.

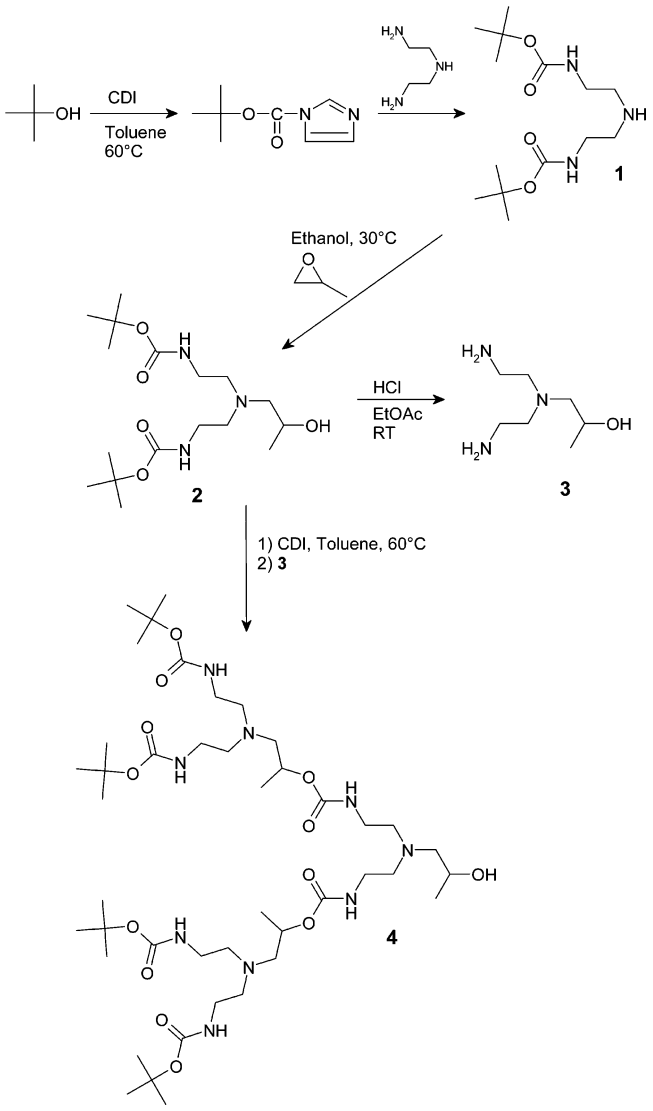
To the best of our knowledge, Clark et al.[3] have published the only report of an all aliphatic polyurethane homodendrimer. Only the first-generation dendrimer was reported due to the complex divergent synthesis used.

Our recent reports of reactions with carbonyl imidazole containing compounds have demonstrated the highly selective formation of urethanes, carbonates, and amides without the need to use protection/deprotection strategies.[4] These techniques have successfully been used to synthesize aliphatic polyamide[5] and polycarbonate dendrimers.[6] In this study we report the first convergent aliphatic polyurethane homodendrimer synthesis to high molecular weight, using selective reactivity.

During polycarbonate dendrimer synthesis we have relied upon the use of an AA'_2 branched triol, 1-[*N*,*N*-bis(2-hydroxyethyl)amino]-2-propanol (HEAP),[6] containing one secondary and two primary hydroxyl groups. Imidazole carboxylic esters derived from the reaction of secondary or tertiary alcohols with 1,1′-carbonyl diimidazole (CDI) react selectively at the primary hydroxyl groups of HEAP.

Our target branching group for convergent polyurethane dendrimer synthesis, 1-[*N*,*N*-bis(2-aminoethyl)-amino]-2-propanol (AEAP), **3**, is analogous to HEAP but differs in that it contains two primary amines and one secondary alcohol. The synthesis of AEAP is shown in Scheme 1 and requires the selective *t*-BOC protection of diethylenetriamine using our previously reported methods,[4] forming the diprotected triamine **1**. This was achieved in a one-pot reaction on a 1.5 L scale, starting from *tert*-butyl alcohol and CDI and yielded 120 g of **1** (80%). Reaction of **1** with a 3-fold excess of propylene oxide was achieved by heating the mixture in ethanol at 30 °C for 20 h, forming the first-generation dendron G1-[*t*-Bu-AEAP]OH (**2**) as a white crystalline solid after purification (89%). Confirmation of the successful formation of **2** was achieved using electrospray mass spectrometry (MH^+ = 361.0), ^1H and ^{13}C NMR spectroscopy, and elemental analysis. Deprotection and the formation of AEAP, **3**, were achieved by stirring at room temperature with a solution of 4 M HCl in ethyl acetate. After evaporation, the amine functionality of AEAP (MH^+ = 162.60) was liberated from the ammonium salts by treatment with basic ion-exchange resin. Vacuum distillation gave the pure, colorless material with an overall yield of 64%.

Scheme 1



Compound **2** was reacted with CDI to form the imidazole carboxylic ester of the secondary alcohol. This

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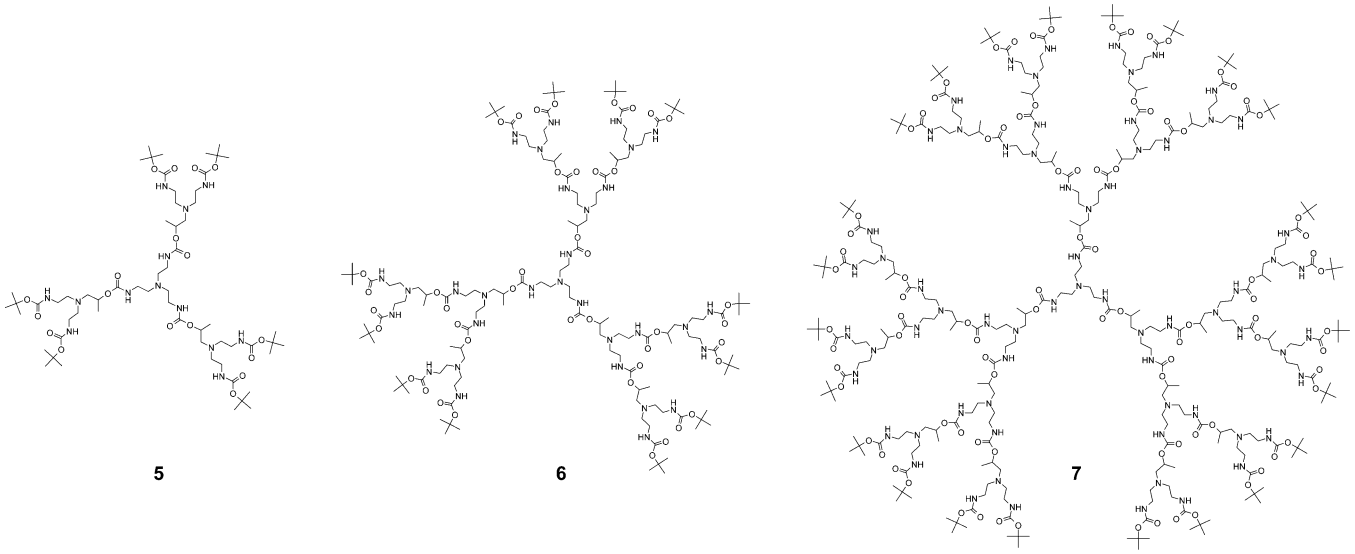

Figure 1. Generation 1−3 polyurethane homodendrimers.

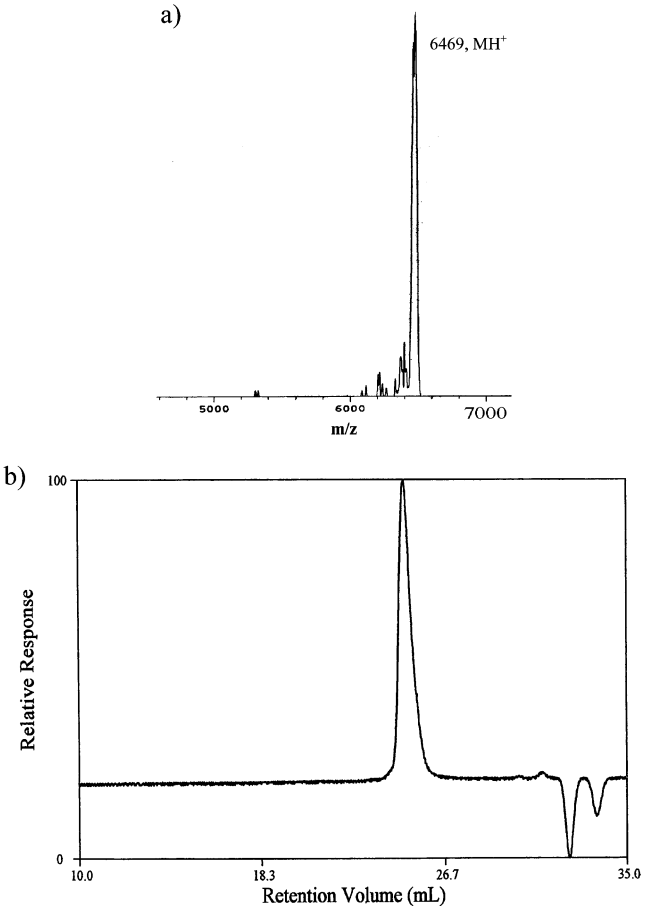

Figure 2. (a) TOF-MALDI spectrum and (b) GPC chromatogram of the G3 dendrimer **7**.

intermediate was not isolated, but the reaction was monitored using NMR to show complete reaction of **2**. When no residual **2** could be detected (approximately 6 h), **3** was added to the reaction mixture and allowed to react for a further 20 h. Purification by aqueous washing and column chromatography produced the pure G2 dendron G2-[*t*-Bu-AEAP$_2$]OH, **4** (50%), as shown by elemental analysis, ^{1}H and ^{13}C NMR spectroscopy, and electrospray mass spectrometry ($MH^+ = 936.0$).

Repetition of this procedure (5 g scale) successfully produced the G3 dendron G3[*t*-Bu-AEAP$_3$]OH (48%) as confirmed by NMR spectroscopy, elemental analysis, and mass spectrometry (TOF-MALDI $MH^+ = 2086$; ES^+ $MNa^+ = 2108.2$).

As the molecular weight of the dendrons increased, it became necessary to use preparative GPC to obtain high-purity samples. Analysis of the dendrons using conventional GPC (polystyrene standards, THF solvent) showed samples with extremely narrow dispersity (PD < 1.02) (Figure 2), and this technique was often unable to sufficiently discriminate between M_n and M_w to give polydispersities greater than 1.00.To synthesize an aliphatic polyurethane homodendrimer, it is important to choose the approriate core molecule. The branching unit AEAP, **3**, has an amine as the branching atom and an ethylene linkage between the branching atom and the reactive amine B groups. Tris(2-aminoethyl)amine, TAEA, is a perfectly complementary core molecule for the AEAP branching unit. By using this core, the order of chemistry from the surface of the dendrimer through to the amine at the center is maintained exactly, producing a true "homodendrimer".

The reaction of each of the G1, G2, and G3 dendrons with TAEA was accomplished following the same procedures as dendron growth. The synthesis of the G1 dendrimer, G1-[*t*-Bu-AEAP]TAEA, **5**, was attempted on a 10 g scale and produced the pure dendrimer (30%) after purification using column chromatography (TOF-MALDI $MH^+ = 1307$, GPC $M_w/M_n = 1.00$). The G2 dendrimer, G2-[*t*-Bu-AEAP$_2$]TAEA, **6**, was synthesized with a 32% yield (ES^+ $MNa^+ = 3055.1$, GPC $M_w/M_n = 1.00$) and the G3 dendrimer, G3-[*t*-Bu-AEAP$_3$]-TAEA, **7**, was produced as a colorless solid (20%) (TOF-MALDI $MH^+ = 6469$, GPC $M_w/M_n = 1.06$) (Figure 2).

This synthetic route has been successful in producing a number of dendrimers with different surface functionality. A series of aliphatic and aromatic, cyclic and acyclic, secondary and tertiary alcohols (*tert*-butyl alcohol (*t*-Bu), 4-heptanol (4-Hept), cyclohexanol (Cy), and benzhydrol (Ph_2CH)) have been used during the initial stages to form structures analogous to **2** (yields: *t*-Bu = 89%, $MH^+ = 361.0$; 4-Hept = 91%, $MH^+ = 446.0$; Cy = 86%, $MH^+ = 414.0$ Da; Ph_2CH = 75%, $MH^+ = 582.0$). These materials were subsequently reacted selectively with TAEA and AEAP **3** to form materials up to the third-generation polyurethane dendrimer (e.g., G3-[4-Hept-AEAP$_3$]TAEA = 7491 Da) and the fourth-

generation dendron (e.g., G4-[Cy-$AEAP_4$]OH = 4801.4 Da). Details of experimental conditions, yields, and the physical properties of this new series of dendrimers will be the subject of future reports.

In summary, we have described the first convergent synthesis of aliphatic polyurethane homodendrimers. The synthesis only uses urethane links and has a repeating structure that is consistent from the surface groups through to the core nitrogen atom. Dendrimer molecules up to the third generation and dendrons up to the fourth generation have been synthesized with masses over 7000 Da. Future work will focus on the properties of these and related polymers including the inherent chirality that is introduced into the structure at each generation through the methine carbon carrying the secondary alcohol functionality.

Supporting Information Available: Selected synthetic procedures and characterization (TOF-MALDI spectra, ^{1}H and ^{13}C NMR spectra, elemental analyses) for key reactions and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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