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A Highly Selective, One-Pot Multiple-Addition Convergent Synthesis of Polycarbonate Dendrimers

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The formation of dendrimers[1] via convergent or divergent routes[2] often uses reiterative growth strategies that require protection/deprotection chemistry[3] or methods that involve generating essential reactive functionality. These steps and their subsequent purification procedures are additional to the actual molecular architecture construction process.[1]

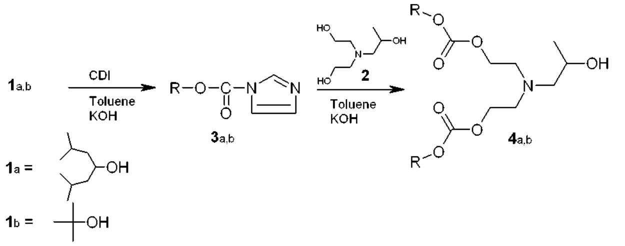
In our recent reports of the highly selective reactivity of imidazole carboxylic esters,[4,5] intermediates that were derived from the reaction of 1,1′-carbonyl diimidazole (CDI) and secondary or tertiary alcohols were shown to react selectively with primary alcohol groups. Carbonate formation occurs in the presence of unprotected secondary and tertiary hydroxyl functionality. We have no evidence for the formation of dialkyl carbonates from combinations of secondary or tertiary alcohols even when they are used as the reaction solvent.

This selectivity seemed ideal for the synthesis of dendrimers using convergent growth. Although Bolton and Wooley[6] have described the formation of polycarbonate hyperbranched materials, we believe that this is the first description of ideal polycarbonate dendrimer synthesis. The AB$_2$ branching units required for convergent polycarbonate dendrimer synthesis must contain mixtures of primary and secondary or tertiary hydroxyls. The branching unit is actually an AA$'_2$ group as the hydroxyl functionalities differ only in the substituents of the α-carbon atom. By reacting imidazole carboxylic esters of secondary or tertiary alcohols with these building blocks, carbonate formation exclusively at the primary hydroxyls can be expected. The unreacted secondary or tertiary hydroxyl group may then be converted to the imidazole carboxylic ester via reaction with CDI, without the risk of symmetric carbonate formation, and reacted with the triol branching unit to form higher-generation dendrimer wedges.

For the purposes of this study, two surface molecules were chosen, 2,6-dimethyl-4-heptanol (DMH) **1a** and *tert*-butyl alcohol (*t*-Bu) **1b** although any secondary or tertiary alcohol may be used. Synthetic details throughout this report will describe dendrimers with a DMH surface, but the reactions are identical when using **1b** and analytical details showing results when using **1b** are also given.

To accomplish a convergent polycarbonate dendrimer synthesis, the AB$_2$ branching group should contain two primary hydroxyls and one secondary or tertiary group. Initially, glycerol was considered as a candidate building block but, as we have recently reported,[4] the use of 1,2-diols results in cyclic carbonate formation through initial selective reaction of the imidazole carboxylic ester with the primary hydroxyl and subsequent intramolecular cyclization with the secondary hydroxyl and elimination of the parent alcohol. Another commercially available AB$_2$ triol is 1-[*N*,*N*-bis-(2-hydroxyethyl)amino]-2-propanol (HEAP) **2**. The hydroxyl groups of HEAP are five atoms apart, and intramolecular cyclic amino-carbonate formation is unlikely.

Scheme 1



The initial stage of polycarbonate dendrimer synthesis requires the synthesis of an imidazole carboxylic ester. The synthesis of the imidazole carboxylic ester of DMH, G0-[DMH]-Im **3a**, has been reported[4] and involves the facile reaction of equimolar amounts of CDI and DMH in anhydrous toluene at 60 °C, in the presence of a catalytic amount of KOH, Scheme 1. G0-[DMH]-Im was purified via a conventional aqueous wash, to remove the imidazole byproduct, and isolated in 97% yield. Confirmation of the synthesis was obtained using electrospray mass spectrometry ($MH^+ = 239.55$) and ^{1}H and ^{13}C NMR spectroscopy. (G0-[*t*-Bu]-Im **3b**, $MH^+ = 169.36$).

When 2 mol equiv of **3a** were reacted with **2**, using the same conditions and purification described above, the first generation wedge, G1-[DMH−HEAP]-OH **4a**, was produced in 93% yield ($MH^+ = 504.68$, $MNa^+ = 526.62$), Scheme 1. Selectivity of the carbonate formation was confirmed by the unchanged methyl ($\delta = 1.10$; 20.00 ppm) methylene ($\delta =$ inequiv 2.34 and 2.65; 63.30 ppm) and methine ($\delta = 3.73$; 64.00 ppm) resonances in the ^{1}H and ^{13}C NMR spectra. (G1-[*t*-Bu-HEAP]-OH **4b**, $MH^+ = 364.63$, $MNa^+ = 386.58$).

Activation of **4a** with CDI was an identical reaction to the formation of **3a**. Isolation of the imidazole carboxylic ester **5** via an aqueous wash gave the activated wedge G1-[DMH]-Im **5** in 92% yield ($MH^+ = 598.69$, $MNa^+ = 620.51$). Subsequent reaction of 2 mol equiv of **5** with **2** yields the second-generation wedge G2-[DMH−HEAP$_2$]-OH **6** in 99.6% yield ($MH^+ = 1222.23$, $MNa^+ = 1245.27$), Scheme 2. (G2-[*t*-Bu-HEAP$_2$]-OH, $MH^+ = 942.84$).

There are many advantages of using CDI in the synthesis of dendrimers. First, the carbonate formation is completely selective, and no impurities from reaction at the secondary hydroxyl of **2** have been detected. Second, the imidazole carboxylic ester functionality is much more stable to hydrolysis than a chloroformate, which allows the simple purification through an aqueous wash. Third, both CDI and the imidazole byproduct are soluble in warm toluene but insoluble when cold. This allows much of the purification of the products to be conducted through a filtration of imidazole after cooling, prior to removal of toluene in vaccuo. Finally, residual imidazole is not detrimental to further generation growth, and therefore we have not needed to purify the materials using column chromatography at any stage.

It is the final advantage that led us to attempt a one-pot multiple-addition synthesis of polycarbonate dendrimers. In principle, there is no need to isolate and purify the imidazole carboxylic esters as selective asymmetric carbonate formation can be achieved in a single pot reaction by sequential addition of secondary alcohol, CDI and primary alcohol.[4] The one-pot multiple-addition synthesis of **6** was conducted on a 100 g scale in a 1 L flask starting from **1a** followed by two CDI/**2** sequential

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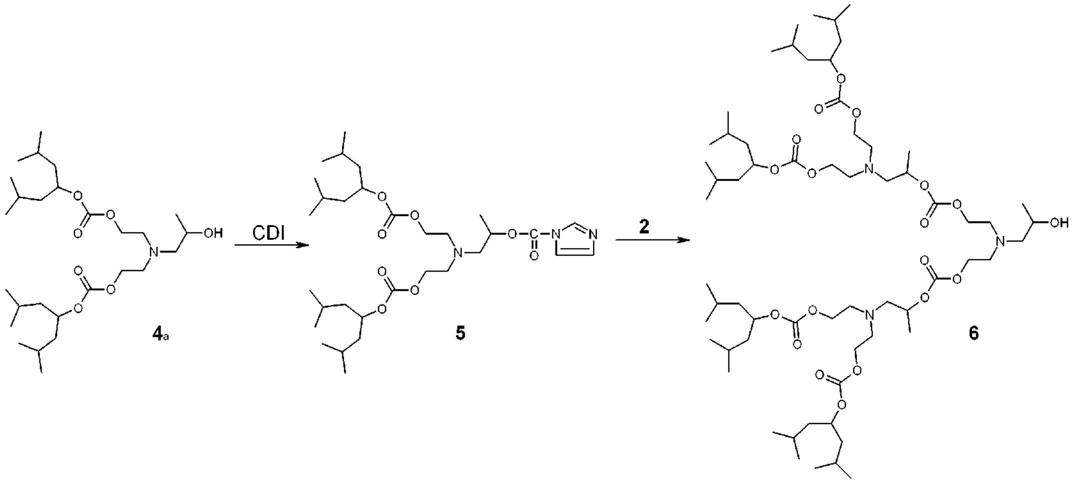
Scheme 2



additions, Scheme 2. Each stage of the reaction was monitored by TLC to ensure full conversion of alcohol to imidazole carboxylic ester and full reaction of the imidazole carboxylic ester to carbonate. The reaction was stopped at this stage as the solution had become quite viscous due to the concentration of imidazole byproduct and the dendron **6**. The facile purification of the product via a series of aqueous washes yielded **6** in 89% yield. The atmospheric pressure ionization mass spectrum of **6** produced from the one-pot reaction is shown in Figure 1.

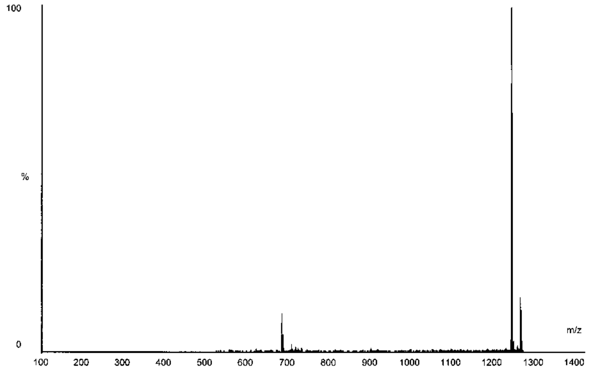


Figure 1. API-MS spectrum of **6** from a one-pot synthesis.

The API-MS spectrum of the one-pot reaction shows the $MH^+ = 1222.23$ and $MNa^+ = 1245.27$ signals for the controlled formation of **6**. This confirms that we have successfully achieved four sequential selective reactions in a single reaction vessel including the two selective imidazole carboxylic ester syntheses. The spectrum also shows a significant signal corresponding to a species with a mass of 674.5 daltons. Assuming this is a protonated molecular ion, it may correspond to carbonate formation by the reaction of **3a** with the secondary hydroxyl group of **4a** (MW = 673.98). This contradicts the small-molecule model reactions that we have reported as we have not observed carbonate formation between two secondary alcohols. An alternative explanation is an impurity in our sample of **2**. This impurity could possibly be [*N*,*N*-bis(2-hydroxyethyl)]-2-aminopropan-1-ol which would contain three primary hydroxyl groups and may be formed during the ring opening of propylene oxide by diethanolamine, the probable synthetic route to **2**. No species of mass greater than that of **6** were detected.

Finally, we have investigated the asymmetric coupling of different polycarbonate wedges. Asymmetric coupling of dendritic wedges was first introduced by Hawker and Fréchet.[7] During this example, the G2 wedge **6** was activated with CDI to form the imidazole carboxylic ester G2-[DMH−HEAP$_2$]-Im and reacted in situ with a 10-fold excess of 1,5-pentanediol (PND) to form G2-[DMH−HEAP$_2$−PND]-OH in 87% yield ($MH^+ = 1352.83$, $MNa+ = 1374.85$). Coupling with G2-[*t*-Bu-HEAP$_2$]-Im produced **7** in 85% yield ($MH^+ = 2319.56$) (Figure 2).

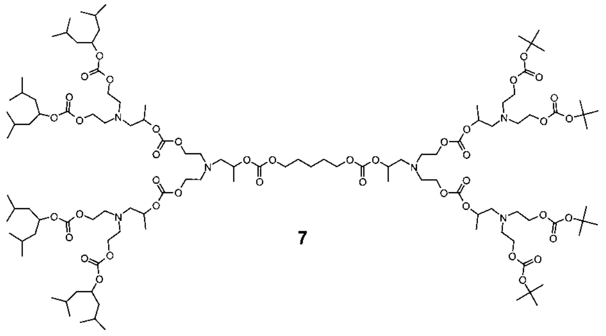


Figure 2. Asymmetric polycarbonate dendrimer

In summary, we have demonstrated the use of a new selective carbonate synthesis in the formation of the first ideal polycarbonate dendrimers.[8] The synthesis proceeds very well and has allowed two generations of convergent growth to be achieved on a 100 g scale in a single reaction vessel without purification between synthetic steps. The synthesis of higher generations will be the focus of further work.

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[8] General procedure for the formation of polycarboante dendrimers is exemplified by the one-pot synthesis of **4a**. Dry toluene (100 mL) was added to a 250 mL round-bottom flask fitted with a dry N_2 inlet and magnetic stirrer. 1,1′-carbonyl diimidazole, CDI, (0.16 mol), **1a** (0.14 mol) and KOH (12 mmol) were added to the flask. The mixture was heated at 60 °C with stirring until the complete formation of **3a** was determined by TLC. **2** (70 mmol) was added dropwise to the solution and left to stir until complete carbonate formation was determined by TLC. The mixture was left to cool to rt, filtered and concentrated in vacuo. The residue was dissolved in CH_2Cl_2, washed with water (3 × 50 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo to give **4a** as a clear liquid (93%). Selected analytical data for **4a**, ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 0.92$ ppm (m, CH_3), 1.10 ppm (d, $CH{-}CH_3$), 3.73 (m, $HOCH{-}CH_3$) 4.20 (t, $O(C{=}O)OCH_2$), 4.88 (m, $O(C{=}O)OCH$), ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 64.00$ ($HOCH{-}CH_3$), 67.95 ($O(C{=}O)OCH_2$), 75.97 ($O(C{=}O)OCHR_2$), 155.55 (C=O). *m*/*z* (Es^+) 504.68 (MH^+, 100%). For higher generations, CDI and **2** are added alternately and monitored by TLC.