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Synthesis of aromatic hyperbranched PAMAM polymers

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Abstract—Our preliminary results towards the synthesis of hyperbranched polyamidoamine (PAMAM) polymers as 'dendrimer equivalents' is described. An aromatic AB_2 bis-amino acid monomer was polymerised at 165 °C (under vacuum) and the crude mixture purified by dialysis. Analysis by GPC and MALDI-TOF mass spectroscopy showed that the purified hyperbranched polymers possessed an M_n of 2000 and a PD of 3.2.

We are interested in the synthesis of unsymmetrical/functionalised polyamidoamine (PAMAM) dendrimers[1] for a variety of applications, including catalysis,[2] gene delivery,[3] biomimetics[4] and drug delivery.[5] For some of these applications it is often desirable to utilise a small or medium sized dendrimer. For example, we recently demonstrated that when compared to much larger dendrimers, small and medium sized PAMAM dendrimers were superior at enhancing the rate of a simple aminolysis reaction (due to steric crowding at the dendrimer surface).[6] Dendrimer synthesis is a time consuming stepwise process requiring two (or more) iterative synthetic (and purification) steps to produce the final dendrimers.[7] In contrast, hyperbranched polymers (HBP) can be prepared in a convenient and cheap one-pot synthesis. In general the physical properties of these HBP are similar to the synthetically more challenging dendrimers. Furthermore, the mass of the final product can be controlled by using 'initiator' cores or by applying carefully optimised polymerisation conditions, and pseudo-generation HBP can be prepared. Once again, *giant* structures are not always required and small/medium sized HBP are successfully being applied as binders and ink additives[8,9] (to improve light stability, adhesion, density and water fastness), and as additives in paints and powder coatings.[10] We became interested in synthesising and studying amine terminated hyperbranched PAMAM polymers as 'dendrimer equivalents' for application to a number of potential areas (catalysis, drug and gene delivery and as polymer additives). Hyperbranched PAMAM polymers have previously been reported by Feast et al.,[11] unfortunately in our hands we were unable to synthesise *and* purify these compounds on a large scale (i.e., a multi-gram scale). We therefore turned our attention to developing our own simple and convenient procedure for synthesising hyperbranched PAMAM polymers.

Our preliminary studies involved the condensation polymerisation of an aromatic monomer with two amine groups and a single acid (an AB_2 monomer). Monomer **1** was selected as it could easily be synthesised from 4-aminomethyl benzoic acid **2** using standard PAMAM synthesis.[7,12] Diester **3** was produced in quantitative yield after Michael addition of two equivalents of methyl acrylate to **2**. Diester **3** was then reacted with a large excess of ethylenediamine to give monomer **1** in quantitative yield (Scheme 1). This two step procedure is extremely efficient and requires no purification (the by-products, excess reagents and solvents are volatile and can all be removed under vacuum). Polymerisation of **1** was carried out in bulk (Scheme 2). The viscous oil was heated at 165 °C under vacuum for 30 h.[13] After several hours of reaction, the liquid sample began to solidify and turn darker in colour (some condensed material had collected around the top of the reaction vessel and the vacuum tap). At the end of the polymerisation, the crude product was obtained as a honey coloured glassy solid, in 76% recovery (by mass). Accounting for the loss of water we would expect a maximum mass recovery of ~95%, therefore some degradation of the product must be occurring. PAMAM dendrimers are known to be sensitive to heat and undergo *retro* Michael additions at

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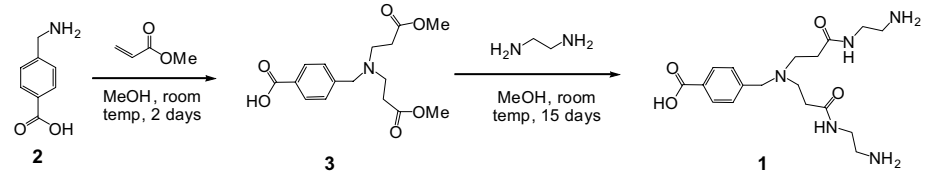
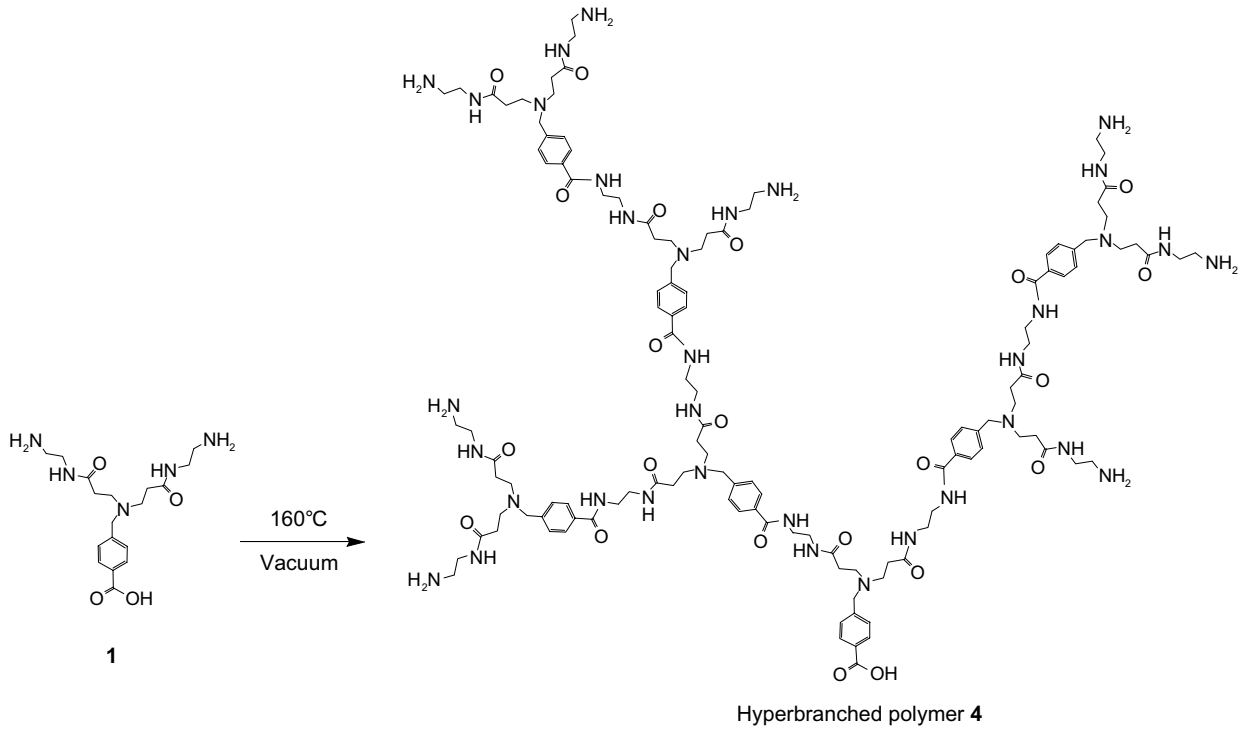


Scheme 1. Preparation of the AB_2 monomer.



Scheme 2. Polymerisation of monomer **1**.

high temperature. It has also been reported that PAMAM dendrimers become fractured when exposed to high temperatures for prolonged periods of time (i.e., during the commercial preparation of the gene vector Superfect[14]). In other words, a certain amount of our product probably consists of fractured as well as 'perfect' polymers.

Purification of the crude product was carried out using dialysis.[15] GPC analysis[16] of the solution outside the dialysis bag revealed that it consisted predominantly of monomer, with a small tail corresponding to low molecular weight oligomers (dimers and trimers). The sample inside the dialysis bag was concentrated and GPC analysis of the polymer gave an M_n of 1200 and a polydispersity of 3.1 (relative to linear polyethylene glycol). It is well known that GPC calibrated with linear standards, significantly underestimates M_n for branched systems.[17] In an effort to be more certain about the polymers molecular weights, MALDI-TOF mass spectroscopy of the dialysed polymer was attempted. Satisfyingly, the spectrum showed a Gaussian distribution of peaks centred around 2000 g mol^{-1}. The H^1 NMR (D_2O) spectrum of the product consisted of a series of very broad peaks in the aromatic and aliphatic regions. The ratio of aromatic to aliphatic protons was found to be equivalent to the monomer, as determined by integration. Overall the chromatographic and spectral data suggested that a polymer whose average structure consisted of 6–7 monomer units had been synthesised (Scheme 2 shows a representative structure **4**[18]).

In conclusion, we have demonstrated that a bis-amino acid AB_2 monomer can be polymerised in the bulk to give a hyperbranched polymer. The molecular weight of this polymer is in the range of the perfectly branched second generation dendrimer analogue (M_n 2546). We are currently investigating the properties of this hyperbranched polymer.

Acknowledgements

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12. Monomer **1** was prepared using the following PAMAM synthesis. Methyl acrylate (1.71 g, 19.87 mmol) was added to a solution of 4-aminomethyl benzoic acid (1.0 g, 6.62 mmol) in methanol (20 mL) and the resulting mixture stirred for 12 h. The solution was then filtered and the filtrate concentrated on a rotary evaporator to give the ester terminated intermediate **3** as a pale yellow oil in quantitative yield. δ_H ppm (250 MHz, $CDCl_3$); 2.54 (4H, t, CH_2CO, $J = 7$ Hz), 2.87 (4H, t, NCH_2, $J = 7$ Hz), 3.70 (2H, s, $ArCH_2$), 3.72 (6H, s, OCH_3), 7.36 (2H, d, Ar, $J = 5.7$ Hz), 8.04 (2H, d, Ar, $J = 5.7$ Hz), 9.02 (1H, br, CO_2H). δ_C ppm (63 MHz, $CDCl_3$); 32.49, 49.22, 51.54, 58.12, 128.36, 129.78, 131.79, 143.20, 171.08, 172.82. m/z (ES^+) 324 (100%, MH^+).
13. Compound **3** (1.0 g, 3.10 mmol) was then reacted with an excess of ethylenediamine (3.66 g, 61.00 mmol) in methanol (20 mL) to give monomer **1** as a yellow oil in quantitative yield. δ_H ppm (250 MHz, D_2O); 2.41 (4H, t, CH_2CO, $J = 6.5$ Hz), 2.75 (8H, m, $CH_2NH_2 + N(CH_2)_2$), 2.81 (4H, s, NH_2), 3.26 (4H, t, $NHCH_2$, $J = 6.4$ Hz), 3.74 (2H, s, $ArCH_2$), 7.31 (2H, d, Ar, $J = 8.24$ Hz), 7.83 (2H, d, Ar, $J = 8.24$ Hz). δ_C ppm (63 MHz, D_2O); 32.82, 39.56, 39.76, 49.12, 56.97, 129.05, 129.42, 135.44, 141.07, 175.16, 175.54. m/z (MALDI-TOF) 380 (M^+). GPC (pH 4.5 aqueous) M_n 348, polydispersity 1.16. Monomer **1** (1.2 g, 3.16 mmol) was placed in a microvial in a metal block and placed under vacuum (<0.1 mmHg) and heated at 165 °C for 30 h then left to cool to room temperature. The crude product was obtained as a honey coloured glassy solid (0.91 g, 76% recovery by mass). δ_H ppm (250 MHz, D_2O); 1.7–4.3 [m (br), aliphatic], 7.35–7.45 [d (br), Ar], 7.85–7.95 [d (br), Ar].
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15. A solution of the crude product (~0.5 g) in deionised water (100 mL) was placed inside a dialysis bag (Visking tubing, pore size 2.4 nm), which was left in deionised water (1 L) with stirring for 48 h (the external solution was changed and replaced with fresh water after 24 h). The solution inside the bag was concentrated under reduced pressure to give a yellow oil (~0.1 g) and the external solution was reduced to produce a yellow oily solid (~0.35 g). Purified polymer (inside dialysis bag): δ_H ppm (250 MHz, D_2O); 1.7–4.3 [m (br), aliphatic], 7.36–7.42 [d (br), Ar], 7.88–7.90 [d (br), Ar]. GPC M_n 1153, PD 3.21. m/z (MALDI-TOF) a series of peaks (Gaussian shaped) from 600 to 3700 with the highest intensity peak at 1974 g mol^{-1}.
16. Aqueous GPC analysis was carried at 40 °C, at pH 4.5 (0.2 M sodium nitrate/0.01 M sodium dihydrogen orthophosphate buffer), using a TSK-oligomer column, an HP1047a RI detector and a flow rate of 1 mL min^{-1}. Monomer and polymer samples were injected as ~0.1% solutions (by mass). The column was calibrated using narrowly dispersed polyethylene glycol standards (200–10,000 MW).
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18. It should be noted that structure **4** represents the 'idealised' product, and that due to the extreme conditions used to synthesise the polymer, the actual polymeric mixture probably consists of degraded/fractured polymers derived from higher molecular weight products.