

# Synthesis and characterisation of polyamide dendrimers with systematically varying surface functionality†

Helen Willcock, Andrew I. Cooper, Dave J. Adams and Steve P. Rannard\*

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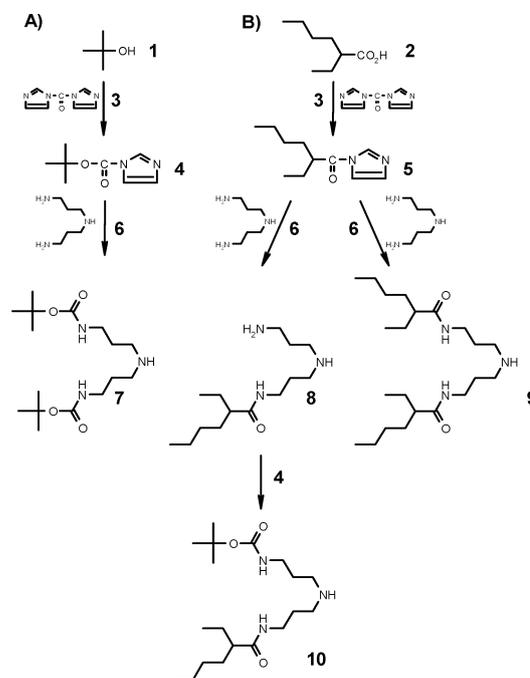
**Remarkable changes of properties result from systematically varying the surface functionality of polyamide dendrimers within a single generation.**

The combined control of polymer functionality and architecture is often difficult to achieve. Linear copolymers may be synthesised using addition polymerisation with exquisite control of chain length, composition and functional group segregation using a range of controlled synthesis techniques.<sup>1</sup> The introduction of branching leads only to a statistical control of average architecture and functionality on the individual molecule level.<sup>2</sup> Hyperbranched polymers synthesised by AB<sub>n</sub> step-growth methods also suffer from an averaged architecture,<sup>3</sup> whereas the number of functional groups present in each molecule is dependent on the architecture generated *i.e.* the number of linear, terminal and dendritic monomer residues.<sup>4</sup> Divergent growth of ideal dendrimers allows the control of branching architecture but ideal growth is only allowed if the surface is entirely functional, and usually of the same functional group.<sup>5</sup> Modification of reactive divergent dendrimers by post-synthesis reaction reverts to a statistical process and the placement of functional groups is not readily possible.<sup>6</sup> Recently, Matmour and Gnanou have shown the control of branched architectures using anionic polymerisation and generated narrow polydispersity materials of predetermined size and branching.<sup>7</sup> To date, the most flexible synthesis approach to the control of architecture combined with control of number and placement of functional groups is convergent dendrimer synthesis.<sup>8</sup> The majority of structure–property studies of dendrimers involve the formation of a series of materials that vary specifically by generation<sup>9</sup> and there are extremely few studies that utilise single generation materials with subtle variations in structure, chemistry or functionality. Some years ago, the formation of dendrimers with single functional groups or site-isolated functionality was demonstrated;<sup>10</sup> however, since those early papers, few studies of surface functionality control,<sup>11</sup> other than complete or statistical modification, have been reported. We describe here the first reported synthesis of a systematically varying, single generation series of polyamide dendrimers with controlled numbers and placement of surface

functional groups. We also describe early observations of the impact of surface group number and placement on dendrimer physical properties.

Our convergent strategy relies upon selective chemistries, previously developed within our group,<sup>12</sup> that utilise carbonyl imidazole derivatives. Three key dendrons (**7**, **9**, **10**) were required to generate the systematically varying polyamide dendrimer series, Scheme 1. Firstly, *tert*-butanol, **1**, was reacted in excess with 1,1'-carbonyl diimidazole (CDI), **3**, to form the monosubstituted imidazole carboxylic ester, **4**, as previously described.<sup>12</sup> In order to reduce the number of purification steps, dipropylentriamine (DPTA), **6** was added directly to the reaction mixture and the selectively substituted product, **7**, was recovered in 86% yield, Scheme 1A. Confirmation of selective reaction was provided by electrospray mass spectrometry (ESMS) ( $MH^+ = 332$  Da) and nuclear magnetic resonance spectroscopy (NMR) (selected resonances: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta = 2.65$  ppm (t, 4H, NH(CH<sub>2</sub>)<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta = 39.3$  ppm (NH(CH<sub>2</sub>)<sub>2</sub>), 156.6 (NHCO<sub>2</sub>tBu)).

A second symmetric dendron, **9**, was synthesised using 2-ethylhexanoic acid, **2**, Scheme 1B. **2** was reacted at ambient temperature with CDI to form the acid imidazolide **5** which



**Scheme 1** Selective synthesis of symmetric and asymmetric polyamide dendrons.

Department of Chemistry and Centre for Materials Discovery,  
University of Liverpool, Crown Street, Liverpool, UK L69 7ZD.  
E-mail: srannard@liv.ac.uk; Fax: +44 (0)151 794 3501;  
Tel: +44 (0)151 794 3501

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was not purified or isolated prior to addition of DPTA and warming to 60 °C. Polyamide dendron **9** was generated selectively (96% yield), confirmed by chemical ion mass spectrometry (CIMS) ( $MH^+ = 384$  Da) and NMR (selected resonances ( $CDCl_3$ ):  $^1H$  NMR  $\delta = 2.59$  ppm (t, 4H,  $NH(CH_2)_2$ );  $^{13}C$  NMR  $\delta = 38.4$  ppm ( $NH(CH_2)_2$ ), 179.2 (NHCOR)).

The asymmetric dendron **10** was synthesised using an initial 3-fold molar excess of DPTA. The monosubstituted triamine, **8**, was isolated in 95% yield (CIMS  $MH^+ = 258$  Da) and further reaction was achieved in a one-pot, multi-step synthesis, initially forming **4** using an excess of **1** to ensure full consumption of CDI. The synthesis of **4** was calculated to ensure a slight excess of **8**, which was directly added to the reaction mixture. Dendron **10** was isolated in an 84% yield after the reaction had stirred for 18 hours at 60 °C (ESMS,  $MH^+ = 358$  Da;  $^1H$  NMR  $\delta = 3.21$  ppm (q, 2H,  $CH_2NHCOR$ );  $^{13}C$  NMR  $\delta = 156.5$  ppm ( $NHCO_2^tBu$ ), 176.4 (NHCOR)).

To synthesise a series of dendrimers with systematically varying numbers of amide groups and urethane groups, derived from **2** and **1**, respectively, the dendrons **7**, **9** and **10** were coupled to a tetraamine core molecule (tris(aminoethyl)amine, **11**) in various combinations (Fig. 1).

Dendrons **7**, **9** and **10** were individually reacted with succinic anhydride to generate amic acid derivatives. Without purification, the acid functional dendrons were treated with CDI to produce the imidazolidine functional dendrons, followed by direct addition of **11** to form the uniformly coupled first generation dendrimers shown in Fig. 1A (top: six  $t$ BOC groups, **14**; middle: three  $t$ BOC and three ethyl hexyl (EH) groups, **16**; bottom: six EH groups, **18**). Dendrons **7** and **9** were also reacted to form the imidazolidine functional materials, and reacted to monofunctionalise **11**, Scheme 2 (recovered yields after purification: **12** (63%); **13** (65%)). Further reaction of **12** with imidazolidine functional **9**, and further reaction of **13** with the imidazolidine functional **7**, led to the formation of the non-uniformly substituted first generation dendrimers shown in Fig. 1B (top: four  $t$ BOC and two EH groups, **15**; bottom: two  $t$ BOC and four EH groups, **17**). The successful control of substitution was confirmed by ESMS and NMR analysis (see ESI $^\dagger$ ).

The introduction of the EH surface group into convergent dendrimers can also be achieved through the utilisation of bis(2-ethyl hexyl) amine (BEHA).<sup>12b</sup> A second analogous

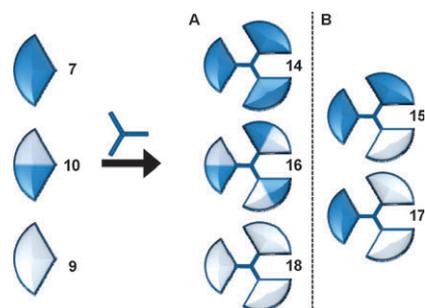
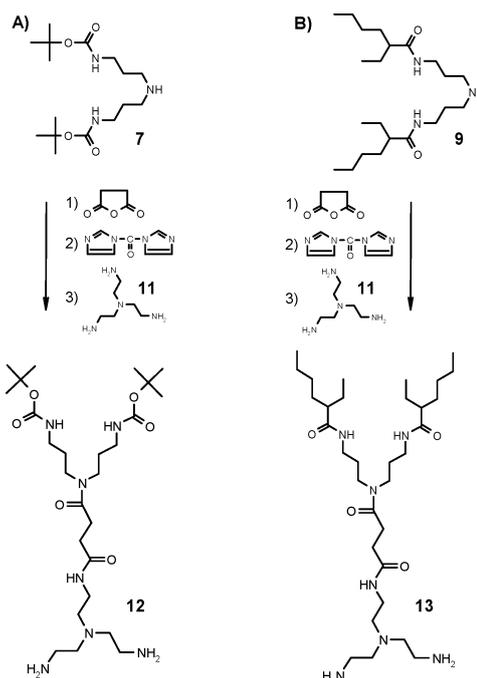


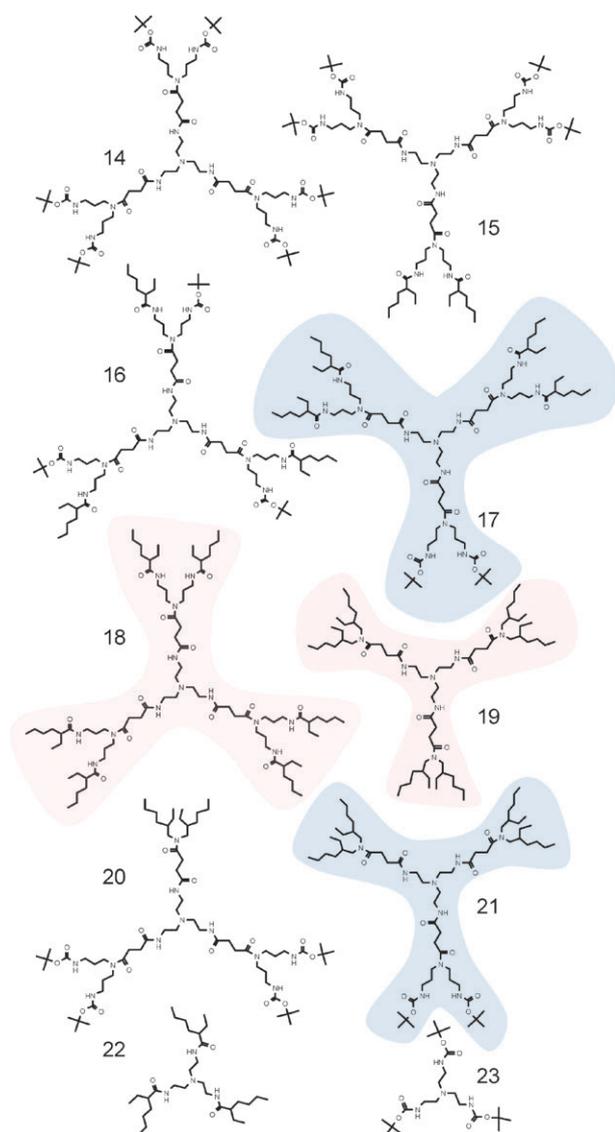
Fig. 1 Schematic representation of systematic coupling of dendrons to control surface functionality.



Scheme 2 Monosubstitution of tris(amino ethyl) amine by generation zero dendrons with varying surface functionality.

dendrimer series with systematically varying surface  $t$ BOC and EH groups was synthesised using similar approaches. Dendrimers **19**, **20** and **21** (see ESI $^\dagger$ ) are therefore analogous to **18**, **15** and **17** with respect to surface group composition and internal chemistry. The formation of an analogous structure to **16** (3  $t$ BOC and 3 EH groups) is, however, not possible using BEHA. Two lower generation dendrimers **22** and **23** were synthesised to complete the series. During the synthesis of these materials, the effect of the number, type and placement of the surface functional groups on solubility and organogelation behaviour became apparent. The dendrons **7** and **10** were synthesised without complication; however, dendron **9**, containing two EH groups and two secondary amides, gelled the toluene reaction solvent (also used to prepare **7** and **10**) during synthesis. The toluene gel persisted even at 60 °C. Reactions conducted in tetrahydrofuran (THF) also gelled at temperatures up to 60 °C. As shown in Fig. 1 and Scheme 2, dendron **9** was reacted with succinic anhydride and CDI to form the amic acid and subsequent imidazolidine derivatives. Both of these intermediates were able to gel THF and toluene at temperatures up to 60 °C.

The series of dendrimers (Fig. 2) showed variable organogelation (Table S1; Fig. S18, ESI $^\dagger$ ), directly related to the number and placement of EH groups and the type of amide present. **14**, **15** and **16** formed homogeneous solutions in THF,  $CH_2Cl_2$ , methanol (MeOH) and toluene; however, **17** gelled  $CH_2Cl_2$ . **18** gelled all solvents studied ( $CH_2Cl_2$ , THF (up to 60 °C), toluene (up to 60 °C) and MeOH). Although a full evaluation of the organogels has not been conducted, gelation was observed over a range of concentrations from 0.1 to 21 w/v%. The dendrimers **19**, **20**, **21**, **22** and **23** exhibited no organogelation behaviour under the conditions studied.



**Fig. 2** Polyamide dendrimers with controlled and systematically varying surface functional groups.

Organogelation has been widely reported for chiral, peptide and achiral dendrimers.<sup>13</sup> All structures within this study are achiral and the self-assembly is related directly to surface functionality. The inability of **19** and **21** to form organogels is interesting as these materials are analogous with **18** and **17**, respectively. **19** and **18** (highlighted) have six EH groups, identical polyamide core structures and similar molecular weights (**18** = 1543 Da; **19** = 1116 Da). The structures of **17** and **21** (highlighted) have greater similarity: four EH and two 'BOC surface groups, identical polyamide cores and similar molecular weights (**17** = 1491 Da; **21** = 1206 Da).

The dendrimers exhibiting organogelation possess secondary amides (**18** and **17**) whereas **19** and **21** comprise tertiary amides and are therefore less able to hydrogen bond through the periphery. The introduction of just two 'BOC groups into **18**, to form **17**, significantly disrupts the gelling

capability of the dendrimers whilst the introduction of a further 'BOC group, and the mixing of the functionalities on each component dendron (**16**), inhibits organogelation under these conditions. In conclusion, we report the first synthesis of two analogous single generation series of polyamide dendrimers with systematically varying surface functionality. Remarkably, the number, type and position of the surface groups control the ability of these achiral dendrimers to gel a range of common organic solvents. Further work will characterise the gel structures and gelation mechanisms.

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