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Synthesis of a novel class of chiral polyaromatic amide dendrimers bearing an amino acid derived C_3-symmetric core

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Abstract—Chiral polyaromatic amide dendrimers incorporating a C_3-core have been prepared as potential catalysts for asymmetric reactions.

1. Introduction

Dendrimers represent a novel class of polymers[1] that possess regular highly branched and well-defined structures. The primary interest of early dendrimer research; the preparation and characterization of new hyperbranched polymers that possess minimal structural defects, has now led to detailed investigations of the chemical and physical properties of this class of macromolecules. The modulation of these properties via minimal structural modifications has resulted in numerous applications of these functionalized dendrimers including drug delivery systems,[2] artificial antennae,[3] sensors,[4] unimolecular micelles[5] and catalysts.[6] Indeed, one of the most promising developments of dendrimer research is the preparation of novel and efficient catalytically active hyperbranched macromolecules.[7] Dendrimers combine the main advantages of both homogeneous and heterogeneous catalysts, i.e. excellent solubility in common organic solvents (an advantage of homogeneous catalysts) and ease of removal from the reaction media by membrane and ultrafiltration techniques as a direct result of their large size in comparison to the products (an advantage of heterogeneous catalysts).[8]

As part of a programme directed towards the preparation of dendritic catalysts for use in metal catalyzed asymmetric transformations, we hereby report the synthesis of a novel class of polyaromatic amide dendrimers that incorporate a chiral C_3-symmetric core unit that is analogous to the tris(2-ethylamino)amine (TREN) ligand.[9] The first, second and third generation polyaromatic amide dendrons have been synthesized via a convergent approach[10] using 1,3-diamino-2-hydroxypropane and 4-carboxybenzaldehyde as the building blocks. The multifunctional C_3-symmetric core system has been prepared via reductive alkylation of ammonia with the so-called Garner aldehyde.

2. Results and discussion

A convergent approach[11] was chosen in order to avoid formation of structural defects during dendrimer construction. Commercially available 1,3-diamino-2-hydroxypropane was selected as the AB_2 type monomer, and 4-carboxybenzaldehyde has been used as the rigid 'linker' between the branched points. After initial protection of the amino groups (with Boc moieties) of the branching unit to form the peripheral surface of the resultant dendrimers, coupling with 4-carboxybenzaldehyde using dicyclohexylcarbodiimide (DCC) as the coupling agent afforded the first generation dendron featuring an aldehyde focal point. Subsequent oxidation of the aldehyde functionality with $KMnO_4$ yielded the corresponding first generation dendron with a carboxylic acid at the focal point **1** (Fig. 1). Selective coupling with the amino functionalities of a further equivalent of 1,3-diamino-2-hydroxypropane led to the formation of the second generation dendron that featured a hydroxyl group at the focal point. Repetition of the esterification, oxidation and amide formation steps led to the second and third generation dendrons **2** and **3**, respectively (Fig. 1). Optimum conditions for selective amide bond formation involved use of either diphenylphosphorylazide (DPPA) or 1-benzotriazolyloxy-tris-(dimethylamino)-phosphonium hexa-

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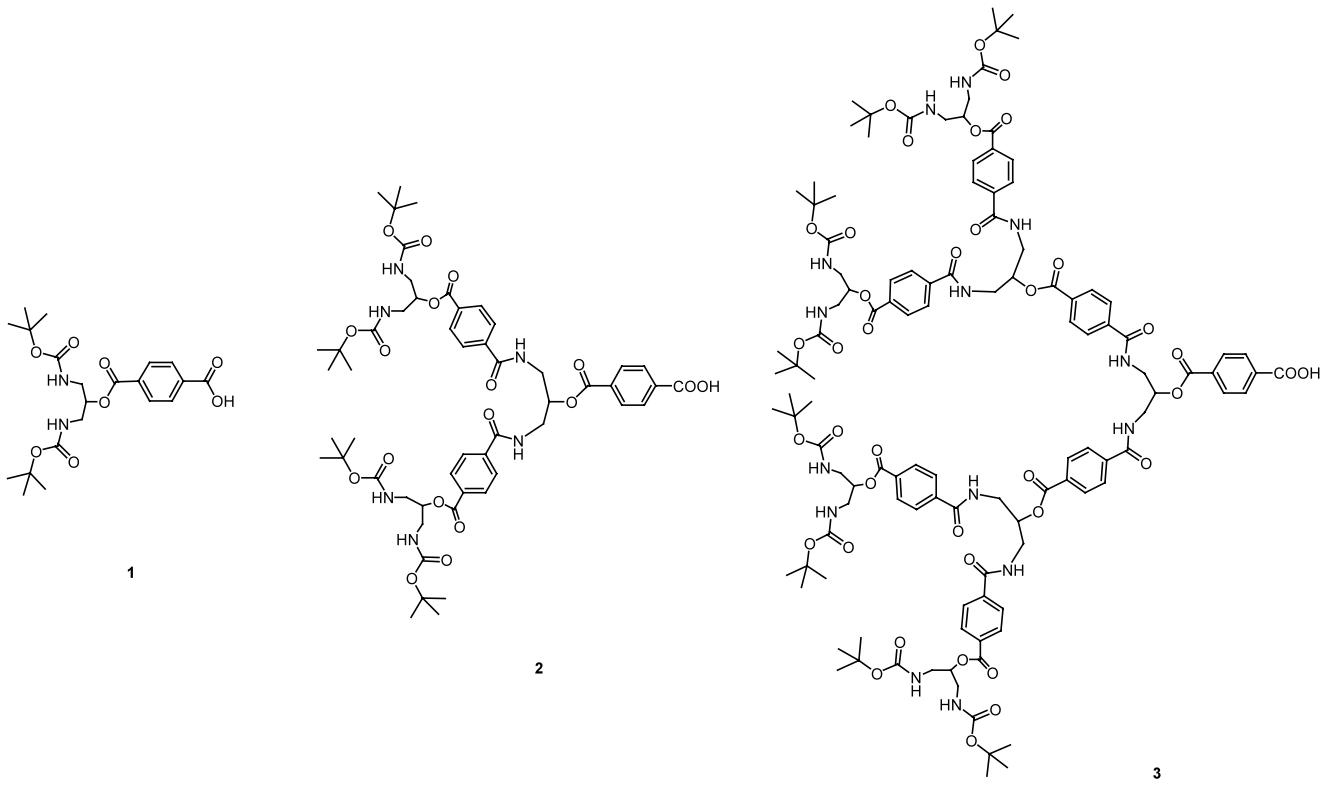


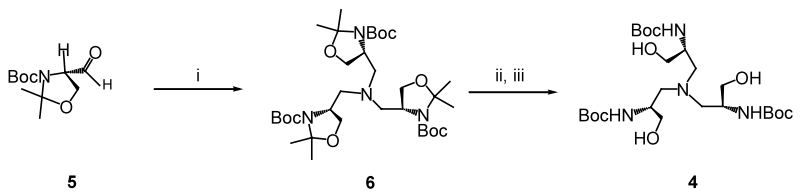
Figure 1. The first, second and third generation polyaromatic amide dendrons featuring carboxylic acid focal points.

fluorophosphane (BOP). The second and third generation dendrons were thus constructed in yields of 83 and 65%, respectively.[11]

In a parallel study to the work of Raymond et al.,[12] we have prepared the chiral C_3-symmetric core unit **4** in an efficient manner (Scheme 1) from the so-called L-Garner aldehyde **5**. L-Garner aldehyde **5** was synthesized from L-serine using an efficient four step route described by Taylor and co-workers.[13] Reductive alkylation of ammonium acetate with the Garner aldehyde in the presence of $NaBH(OAc)_3$ led to the formation of the trialkylated system **6** in 90% yield. This intermediate was then exposed to HCl (6N) to effect complete deprotection of the oxazolidine and Boc groups to afford the corresponding triamino-triol. Selective Boc protection[14] of the three amino functionalities then afforded the desired optically pure C_3-symmetric core system **4** (>90% overall yield from the trialkylated system **6**). The enantiomeric chiral core system has also been prepared from the D-Garner aldehyde derivative (in turn obtained from D-serine) in an equally efficient manner.

The final coupling step between the dendrons **1**, **2** and **3** with the chiral core system **4** was performed using DCC as the coupling agent to afford the corresponding dendrimers (see **7** in Fig. 2).[15,16] All of the dendritic systems have been characterized via ^1H NMR, ^{13}C NMR and IR spectroscopy, optical rotation, MALDI-TOF mass spectrometry and GPC analyses.[15]

The binding efficacy of these chiral dendritic ligands for a range of transition metals is being assessed at present and the use of these complexes in metal catalyzed asymmetric transformations will be reported in due course.



Scheme 1. Synthesis of the chiral C_3-symmetric core unit derived from L-serine. (i) $NaBH(OAc)_3$, CH_3OH, 4 h, rt, 90%; (ii) HCl (6N), >99%; (iii) $(Boc)_2O$, THF/water, >90%.

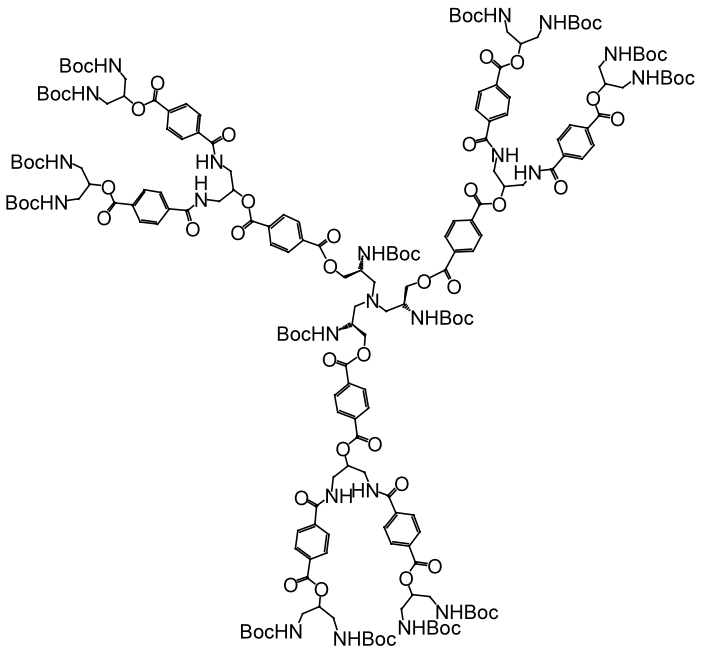


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Figure 2. The second generation chiral polyaromatic amide dendrimer **7** (*RRR*-enantiomer shown above—both enantiomers have been synthesized).

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14. To a solution of the fully deprotected core (0.15 g, 0.43 mmol) and triethylamine (0.546 mL, 3.92 mmol) in THF/water (10 mL, 9:1), di-*tert*-butyl-dicarbonate (0.72 g, 3.25 mmol) dissolved in THF (4 mL) was added dropwise. After 4 h of stirring at room temperature the solvent was evaporated to afford the crude product as a yellowish oil that was purified by column chromatography ($CHCl_3$:EtOH, 90:10) (0.21 g, 92%).
Mp 119–121°C, $[\alpha]_D^{20}$ −44.6 (*c* 1.0, $CHCl_3$). TLC $R_f = 0.7$ ($CHCl_3$:EtOH, 85:15). ^{1}H NMR (250 MHz, d_6-DMSO) δ, ppm 1.44 (27H, s, (CH_3)C-); 2.26 (3H, m, -CH_2NH-); 2.65 (3H, m, -CH_2NH-); 3.45–3.48 (3H, bm, -NHC$H$$CH_2$-, 3H, m, -$CH_2$OH); 4.49 (3H, m, -$CH_2$OH); 6.39 (3H, d, $J = 6.6$, -NH-); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ, ppm 28.6 (CH_3)$_3$C; 50.9, -NHC$H$$CH_2$-; 56.4, -$CH_2$N-; 61.9, -$CH_2$OH; 79.6, ($CH_3$)$_3$$C$-; 155.5,

-OCONH-. Accurate mass MS (CI) m/z 537.3517 (M+1). Elemental analysis, required 53.71% C, 9.01% H, 10.43% N, found 53.29% C, 9.14% H, 10.32% N, IR ν_{max} 3388, 3340, 2977, 1716, 1677, 1536, 1367 cm^{-1}.

15. A solution of **2** (0.36 g, 0.34 mmol), the chiral core **4** (0.03 g, 0.056 mmol) and a catalytic amount of dimethylaminopyridine (DMAP) in dry CH_2Cl_2 (5 mL) was cooled to 0°C under nitrogen. DCC (0.07 g, 0.34 mmol) in dry CH_2Cl_2 (3 mL) was then added dropwise to the stirred solution. The mixture was stirred for 12 h and then filtered to isolate the white solid containing dicyclohexylurea and the product **7**. Purification by size exclusion chromatography (THF) afforded the pure product in 55% yield (0.11 g).
$[\alpha]_D^{20}$ −10.1 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-DMSO) δ, ppm 1.30 (135H, s, $(CH_3)_3C$); 2.45 (3H, bm, -$(CH_2)_2$N-); 2.80 (3H, bm, -$(CH_2)_2$N-); 3.20 (24H, bm, -CONHCH_2-); 3.75 (12H, bm, -CONHCH_2-); 3.92 (3H, bm, -CH_2CHNH-); 4.19 (3H, bm, -CHCH_2O-); 4.40 (3H, bm, -CHCH_2O-); 4.90 (6H, bm, -C$H(CH_2)_2$); 5.40 (3H, bm, -C$H(CH_2)_2$); 6.95 (12H, bm, -OCONH-); 7.10 (3H, bm, -OCONH-); 7.90 (12H, bm, H-ArCONH-); 7.99 (24H, bm, H-ArOCO-); 8.80 (6H, bm, -NHCO-). ^{13}C NMR (100.1 MHz, d_6-DMSO) δ, ppm 27.9, 28.1 (CH_3)$_3$C-; 40.6 -(CH_2)$_2$CH; 47.8 -CH_2CHNH; 56.0 -(CH_2)$_3$N-; 65.2 -$CHCH_2$OCO-; 73.0, 73.2 -$CH(CH_2)_2$-; 77.8, 79.2 $(CH_3)_3C$; 127.1, 129.5, 130.1, H-Ar; 132.4, 133.4, 133.6, 138.1 -OC-Ar; 155.3 -NHOCO-; 155.7 -NHOCO-; 164.8 -OCO-; 166.0 -OCO-. MALDI-TOF MS: calculated for $C_{183}H_{252}O_{60}N_{22}$ (M+Na)+3740.9, found: 3756.3 $(M+K)^+$. IR ν_{max} 3355, 2976, 1711, 1530, 1503, 1268, 1168, 1107, 871 cm^{-1}.
16. The first and second generation dendrimers were isolated in 75 and 55% yield, respectively. In contrast to the smaller dendrimers, isolation of the third generation dendrimer proved difficult (despite extensive chromatographic separation attempts) and therefore an approximate yield (30%) is reported. Problematic purifications involving structurally related polyamide dendrimers have also been documented in the literature by several other research groups (see Appelhans, D.; Komber, H.; Vogt, D.; Häussler, L.; Voit, B. I. *Macromolecules* **2000**, *33*, 9494–9503; Ishida, Y.; Jikei, M.; Kakimoto, M.-A. *Macromolecules* **2000**, *33*, 3202.)