SHORT PAPER

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Convergent synthesis of AB_2-AB_3 hybrid-type of amphiphilic oligoethyleneoxy-modified poly(benzyl ether) dendrons

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A new class of AB_2-AB_3 hybrid-type of amphiphilic oligoethyleneoxy-modified poly(benzyl ether) dendrons has been synthesised by a convergent route.

Keywords: dendrimer, amphiphilic, convergent route

Dendrimers or dendrons have been widely used to construct various functional systems because of their characteristic shape.[1-10] Recently hydrophilic dendritic functional systems have attracted more attention[11] in the fields of biology and medicine because of their high solubility in water, nonimmunogenecity, and improved biocompatibility or degradability into natural metabolites *in vivo*.[12] Usually these water-soluble dendrimers are limited to derivatives of aromatic polyethers, aliphatic polyethers, or aliphatic amines. They can be described as a new class of dendritic polymers – biodendrimers.[13]

There are two approaches available to the syntheses of water-soluble (or amphiphilic) dendrimers. The convergent approach was utilised to synthesise derivatives of aromatic polyethers – oligoethyleneoxy-modified poly(benzyl ether) dendrons[14,15] and the divergent approach was utilised to synthesise derivatives of aliphatic polyethers or aliphatic amines.[12,13] The former can provide well-defined macromolecules, whereas the latter produces imperfection and purification problems.[1,16] Recently amphiphilic oligoethyleneoxy-modified poly(benzyl ether) dendrons have been applied in the design of ion channel protein and enzyme mimics because of their appropriate rigidity and water-soluble property. However, all of these belong to AB_2-type dendrons.[14,15] A new class of AB_2–AB_3 hybrid-type of amphiphilic oligoethyleneoxy-modified poly(benzyl ether) dendrons, as upgraded amphiphilic dendrons, are reported in this paper. Such dendrons are expected to provide better water-solubility due to the increased number of the hydrophilic oligoethyleneoxy chains at the periphery as compared with the AB_2-type analogues.[16] Furthermore, this AB_2–AB_3 hybrid-type of dendrons has a large solid angle and can serve as new building blocks in the design of new functional system.

In the initial phase of this study, the AB_3-type of amphiphilic oligoethyleneoxy-modified poly(benzyl ether) dendrons were designed and synthesised according to the reported methods.[14,15,18] However be converted, the AB_3-type dendrons **6b** and **7b** could not to their corresponding bromide or chloride compounds **6c₁**, **7c₁** and **6c₂**, **7c₂** by using reagents of CBr_4/PPh_3[14,15] or $SOCl_2$,[18] respectively. Similarly, reaction of **6b** and **7b** with *p*-toluenesulfonyl chloride could not give the corresponding dendritic tosylate compounds.[19] The ^1H NMR results of the reaction mixtures revealed that the oligoethyleneoxy groups at the periphery of the dendrons were partially decomposed under the reaction conditions in the presence of $SOCl_2$ or *p*-toluenesulfonyl chloride. It was thus impossible to synthesise the AB_3-type of amphiphilic dendrons by the common methods.

Alternatively, a new class of AB_2–AB_3 hybrid-type of amphiphilic oligoethyleneoxy-modified poly(benzyl ether) dendrons were designed and the synthetic route is shown in Scheme 1. The AB_2 dendrons **3** and **4** were synthesised according to the literature methods.[14,15,18] Convergent coupling reaction of **3c₁** and **4c** with **5** in the presence of K_2CO_3 successfully gave the AB_2–AB_3 hybrid-type of dendritic esters **7a** and **8a** in moderate yield, respectively. **7a** and **8a** were further reduced by $LiAlH_4$ to provide the AB_2–AB_3 hybrid-type of dendrons with the hydroxy group at the focal point, respectively. **6b**, **7b** and **8b** were characterised by ^1H NMR and MALDI-TOF mass spectra. All compounds gave well-resolved ^1H NMR spectra consistent with their structures, and the results of MALDI-TOF mass spectra of these dendrons match the calculated values.

Experimental

Compound **1** was prepared by the similar methods.[20,21] Dendrons (**3**, **4)** were synthesised by appropriately modified procedures.[14,15,18]

Synthesis of **6a**: A mixture of **5** (2.21 g, 12 mmol), **1** (16.32 g, 72 mmol), anhydrous potassium bicarbonate (24.88 g, 0.18 mol) and potassium iodide (5.98 g, 36 mmol) was refluxed in acetone (70 ml) for 72 h under N_2. The mixture was filtered and the solvent was evaporated using a rotary evaporator. The residue was purified by chromatography on silica gel (eluent: ethyl acetate/methanol v/v = 19/1) and dried under vacuum to give a light yellow oil **6a** (6.14 g, 67.8%).δ_H($CDCl_3$, 300 MHz) 7.28 (s, 2 H), 4.18–4.26 (m, 6 H), 3.88 (s, 3 H), 3.61–3.89 (m, 36 H), 3.52–3.54 (m, 6 H), 3.34 (s, 6 H), 3.31 (s, 3 H).

Synthesis of **6b**: A mixture of **6a** (7.5 g, 9.94 mmol) and $LiAlH_4$ (470 mg, 12.4 mmol) in dry THF (20 ml) was stirred for 5 h at room temperature. H_2O (10 ml) was added and the mixture was filtered. The solvent was evaporated by rotary evaporator, and the residue was purified by chromatography on silica gel (eluent: ethyl acetate/methanol v/v = 9/1) and dried under vacuum to give a colorless oil **6b** (5.62 g, 77.8%).δ_H($CDCl_3$, 300 MHz) 6.43 (s, 2 H), 4.37 (s, 2 H), 3.95–3.98 (m, 6 H), 3.36–3.68 (m, 42 H), 3.20 (s, 3 H), 3.19 (s, 6 H): *m/z* (MALDI–TOF) calcd. 726.4 ($C_{34}H_{62}O_{16}$), found 749.2 ($M + Na^+$), 765.1 ($M + K^+$).

Dendron **7a**: Prepared according to the above method for **6a**, the resulting residue was purified by chromatography on silica gel (eluent: ethyl acetate/methanol v/v = 9/1) and dried under vacuum to give a light yellow oil **7a** (yield 75%).δ_H($CDCl_3$, 300 MHz) 7.35 (s, 2 H), 6.60 (s, 6 H), 6.46 (s, 2 H), 6.41 (s, 1 H), 5.06 (s, 6 H), 3.52–4.11 (m, 96 H), 3.88 (s, 3 H), 3.36 (s, 18 H).

Dendron **7b**: Prepared according to the above method for **6b**, the resulting residue was purified by chromatography on silica gel (eluent: ethyl acetate/methanol v/v = 9/1) and dried under vacuum to give a colourless oil **7b** (yield 61.4%). δ_H($CDCl_3$, 300 MHz) 6.28–6.54 (m, 11 H), 4.91 (s, 4 H), 4.87 (s, 2 H), 4.41 (d, J = 3.8 Hz, 2 H), 3.39–3.93 (m, 96 H), 3.23 (s, 18 H): *m/z* (MALDI–TOF) calcd. 1662.9 ($C_{82}H_{134}O_{34}$), found 1685.7 ($M + Na^+$), 1701.6 ($M + K^+$).

Dendron **8a**: Prepared according to the above method for **6a**, the resulting residue was purified by chromatography on silica gel (eluent: ethyl acetate/methanol v/v = 2/1) and dried under vacuum to give a light yellow oil **8a** (yield 67.7%).δ_H($CDCl_3$, 300 MHz) 7.36

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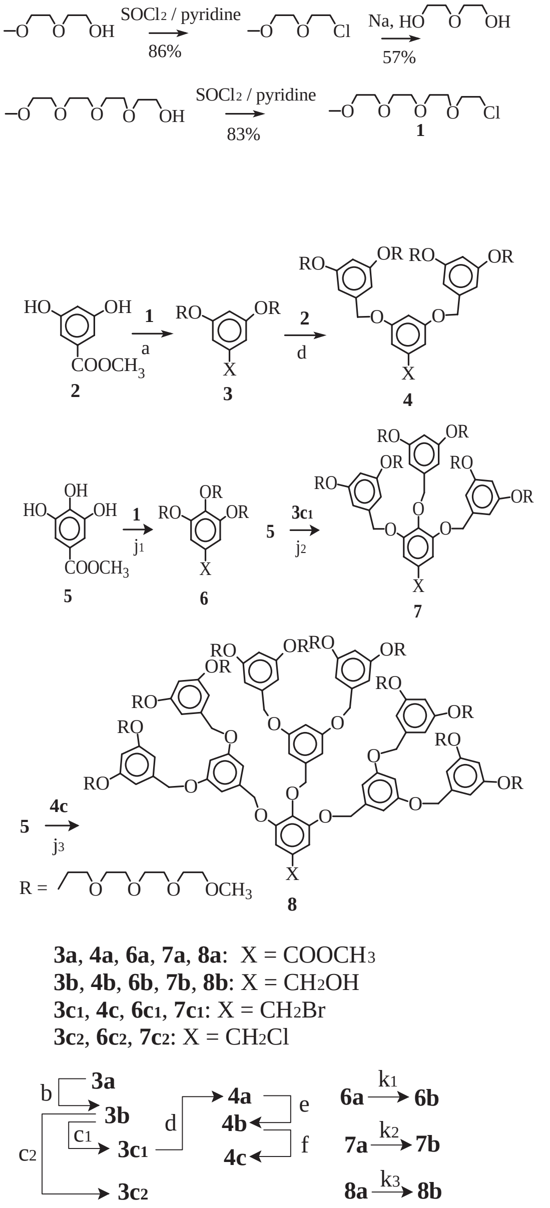
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 1 Synthesis of dendrons (**7a**, **7b**, **8a** and **8b**): (a) K_2CO_3, KI, acetone, nitrogen atmosphere, reflux, 72 h, 74%; (b) $LiAlH_4$, dry THF, RT, 8 h, 74%; (c_1) CBr_4/PPh_3, dry THF, RT, 4 h, 75%; (c_2) $SOCl_2$, pyridine/CH_2Cl_2, RT, 12 h, 70%; (d) same as (a), 78 %; (e) same as (b), 78%; (f) same as (c_1), 74%; (j_1) same as (a), 68%; (k_1) same as (b), 78%; (j_2) same as (a), 75%; (k_2) same as (b), 61%; (j_3) same as (a), 68%; (k_3) same as (b), 66%.

(s, 2 H), 6.40–6.67 (m, 27 H), 5.08 (s, 6 H), 4.82 (s, 8 H), 4.68 (s, 4 H), 3.50–4.06 (m, 192 H), 3.87 (s, 3 H), 3.35 (s, 36 H).

Dendron **8b**: Prepared according to the above method for **6b**, the resulting residue was purified by chromatography on silica gel (eluent: ethyl acetate/methanol v/v = 2/1) and dried under vacuum to give a colourless oil **8b** (yield 65.9%). δ_H($CDCl_3$, 300 MHz) 6.38–6.63 (m, 29 H), 5.04 (s, 6 H), 4.83 (s, 8 H), 4.72 (s, 4 H), 4.50 (s, 2 H), 4.00–4.06 (m, 24 H), 3.75–3.80 (m, 24 H), 3.60–3.67 (m, 120 H), 3.50–3.53 (m, 24 H), 3.34 (s, 36 H): *m/z* (MALDI–TOF) calcd. 3535.8 ($C_{178}H_{278}O_{70}$), found 3559.2 (M + Na^+), 3575.2 (M + K^+).

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References

1 C.J. Hawker and J.M.J. Fréchet, *J. Am. Chem. Soc.*, 1990, **112**, 7638.
2 J.M.J. Fréchet, *Science*, 1994, **263**, 1710.
3 T. Sato, D.-L. Jiang and T. Aida, *J. Am. Chem. Soc.*, 1999, **121**, 10658.
4 P.B. Rheiner and D. Seebach, *Chem. Eur. J.*, 1999, **5**, 3221.
5 D.-L. Jiang and T. Aida, *Nature*, 1997, **388**, 454.
6 M. Brewis, G.J. Clarkson, A.M. Holder and N.B. McKeown, *Chem. Commun.*, 1998, 969.
7 J.C.M. van Hest, D.A.P. Delnoye, M.W.P.L. Baars, M.H.P. van Genderen and E.W. Meijer, *Science*, 1995, **268**, 1592.
8 P.J. Dandliker, F. Diederich, M. Gross, C.B. Knobler, A. Louati and E.M. Sanford, *Angew. Chem. Int. Ed. Engl.*, 1994, **33**, 1739.
9 P.J. Dandliker, F. Diederich, J.-P. Gisselbrecht, A. Louati and M. Gross, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 2725.
10 J.W.J. Knapen, A.W.V. der Made, J.C. de Wiide, P.W.N.M. van Leeuwan, P. Wijkens, D.M. Grove and G. van Koten, *Nature*, 1994, **372**, 659.
11 M.W.P.L. Baars, R. Kleppinger, M.H.J. Koch, S.-L. Yeu and E.W. Meijer, *Angew. Chem. Int. Ed. Engl.*, 2000, **39**, 1285.
12 J.S. Choi, D.K. Joo, C.H. Kim, K. Kim and J.S. Park, *J. Am.Chem. Soc.*, 2000, **122**, 474.
13 M.A. Carnahan and M.W. Grinstaff, *J. Am. Chem. Soc.*, 2001, **123**, 2905.
14 Z. Bo, J.P. Rabe and A.D. Schlüter, *Angew. Chem. Int. Ed. Engl.*, 1999, **38**, 2370.
15 M.J. Hannon, P.C. Mayers and P.C. Taylor, *Angew. Chem. Int. Ed. Engl.*, 2001, **40**, 1081.
16 Q.H. Fan, R. Zhang, G. J. Deng and X. M. Chen, *J. Chem. Res.*, **2002**, 318-320.
17 J.-W. Weener, J.L.J. van Dongen and E.W. Meijer, *J. Am. Chem. Soc.*, 1999, **121**, 10346.
18 V. Percec, W.-D. Cho, P.E. Mosier, G. Ungar and D.J.P. Yeardley, *J. Am. Chem. Soc.*, 1998, **120**, 11061.
19 L. Brunsveld, H. Zhang, M. Glasbeek, J.A.J.M. Vekemans and E.W. Meijer, *J. Am. Chem. Soc.*, 2000, **122**, 6175.
20 M. Shirai, H. Ishida and M. Tanaka, *J. Polym. Sci., Part B: Polym. Phys.*, 1988, **26**, 2075.
21 R. Sinta and J. Smid, *Macromolecules*, 1980, **13**, 339.