6698 *J. Am. Chem. Soc.* **2001,** *123,* 6698−6699

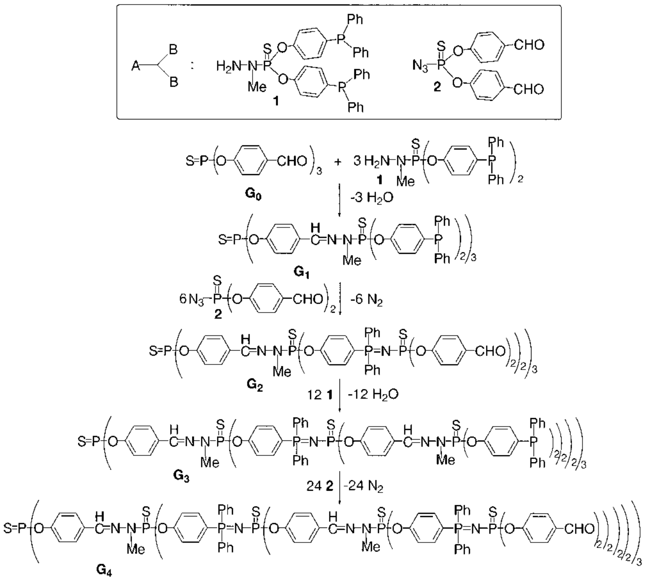
First Divergent Strategy Using Two AB_2 Unprotected Monomers for the Rapid Synthesis of Dendrimers

Laurent Brauge, Germinal Magro,
Anne-Marie Caminade,* and Jean-Pierre Majoral*

Laboratoire de Chimie de Coordination
CNRS, 205 route de Narbonne
31077 Toulouse Cedex 4, France

Received August 7, 2000

Scheme 1



Dendrimers and dendritic molecules[1] offer a fascinating palette of very unique properties, with applications in numerous fields ranging from chemistry, catalysis, or material sciences to biology. However, their synthesis is tedious, due to the large number of steps needed to grow these macromolecules. Several ways have been proposed to accelerate the synthesis by diminishing the number of steps. The first one, often called "double-stage",[2] implies the grafting of dendrons to the surface of small dendrimers called "hypercores". However, the total number of reactions used to obtain the dendron and the hypercore is the same as for the simple step-by-step synthesis of the final dendrimer. A second type of method used to improve the synthesis of dendrimers is called "double exponential growth".[3] In this case, the growing of the dendron occurs bidirectionally (periphery and focal point). This type of strategy could be interesting for the rapid synthesis of high-generation dendrimers, but it has been experienced only for middle-sized dendrons, leading, for instance, to a fourth generation dendron in seven steps (instead of eight by a classical way). A third way to accelerate the synthesis of dendrimers consists of using hypermonomers;[4] this means compounds of type AB_4 or AB_8 instead of the AB_2 or AB_3 monomers classically used in dendrimer chemistry. This strategy increases rapidly the number of end groups, but it does not improve the number of steps needed to obtain one generation (generally 2). Finally, a fourth method called "orthogonal coupling strategy"[5] consists of using two types of AB_2 units, which contain two pairs of complementary coupling functionalities. This type of "orthogonal system" implies a set of completely independent class of protecting groups.[6] Thus, in all cases at least one of these functions needs to be activated using another reagent, which of course generates byproducts, implying purification at each step. However, this strategy designed for the convergent synthesis of dendrons is powerful since it gives a new generation at each step. To the best of our knowledge, this type of strategy has never been applied to a divergent synthesis of dendrimers, or to two pairs of complementary functions able to react spontaneously without any activating agent. This last point appears highly desirable, since it could theoretically allow the growing of dendrimers without purification, provided each reaction is chosen to be quantitative. In the course of our researches concerning the synthesis of phosphorus-containing dendrimers, we have demonstrated that the condensation reaction between phosphorhydrazides and aldehydes[7] on one side, and the Staudinger reaction between phosphines and azides[8] on the other side, possess both properties. Indeed, these reactions are quantitative; there is no need for an activating agent, and the byproducts are only water for the condensation and nitrogen for the Staudinger reaction. Having in hand these reactions, the goal was to design two types of AB_2 monomers, one with aldehyde and azide functions, the other one with hydrazine and phosphine functions. The later one is obtained in two steps from $P(S)Cl_3$. Two equivalents of $NaOC_6H_4PPh_2$[9] are first reacted at low temperature to yield $ClP(S)(OC_6H_4PPh_2)_2$. A

---

(1) For reviews, see for example: (a) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138. (b) Tomalia, D. A.; Durst, H. D. In *Topics in Current Chemistry*; Weber, E., Ed.; Supramolecular Chemistry I, Vol. 165; Springer-Verlag: Berlin, 1993; pp 193−313. (c) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. In *Dendritic Molecules*; VCH: Weinheim Germany, 1996. (d) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681. (e) Archut, A.; Vögtle, F. *Chem. Soc. Rev.* **1998**, *27*, 233. (f) Chow, H. F.; Mong, T. K. K.; Nongrum, M. F.; Wan, C. W. *Tetrahedron* **1998**, *54*, 8543. (g) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 884. (h) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665. (i) Majoral J. P.; Caminade A. M. *Chem. Rev.* **1999**, *99*, 845.

(2) (a) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4252. (b) Miller, T. M.; Neenan, T. X.; Zayas, R.; Bair, H. E. *J. Am. Chem. Soc.* **1992**, *114*, 1018. (c) Xu, Z. F.; Kahr, M.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4537. (d) Ihre, H.; Hult, A.; Fréchet, J. M. J.; Gitsov, I. *Macromolecules* **1998**, *31*, 4061. (e) Forier, B.; Dehaen, W. *Tetrahedron* **1999**, *55*, 9829. (f) Maraval, V.; Laurent, R.; Donnadieu, B.; Mauzac, M.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 2499.

(3) (a) Kawaguchi, T.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 2159. (b) Chang, H. T.; Chen, C. T.; Kondo, T.; Siuzdak, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 182. (c) Klopsch, R.; Franke, P.; Schlüter, A. D. *Chem. Eur. J.* **1996**, *2*, 1330. (d) Ashton, P. R.; Anderson, D. W.; Brown, C. L.; Shipway, A. N.; Stoddart, J. F.; Tolley, M. S. *Chem. Eur. J.* **1998**, *4*, 781.

(4) (a) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 82. (b) Twyman, L. J.; Beezer, A. E.; Mitchell, J. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 407. (c) L'abbé, G.; Forier, B.; Dehaen, W. *Chem. Commun.* **1996**, 2143. (d) Ohta, M.; Fréchet, J. M. J. *J. Macromol. Sci. Pure Appl. Chem.* **1997**, *A34*, 2025. (e) Bo, Z. S.; Zhang, X.; Zhang, C. M.; Wang, Z. Q.; Yang, M. L.; Shen, J. C.; Ji, Y. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2931. (f) Morgenroth, F.; Berresheim, A. J.; Wagner, M.; Müllen, K. *Chem. Commun.* **1998**, 1139. (g) Wiesler, U. M.; Müllen, K. *Chem. Commun.* **1999**, 2293. (h) Gilat, S. L.; Adronov, A.; Fréchet, J. M. J. *J. Org. Chem.* **1999**, *64*, 7474. (i) Scott, D. A.; Krülle, T. M.; Finn, M.; Fleet, G. W. J. *Tetrahedron Lett.* **2000**, 3959.

(5) (a) Spindler, R.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 913. (b) Xu, Z.; Moore, J. S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1354. (c) Zeng, F. W.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1996**, *118*, 5326. (d) Deb, S. K.; Maddux, T. M.; Yu, L. P. *J. Am. Chem. Soc.* **1997**, *119*, 9079. (e) Deb, S. K.; Maddux, T. M.; Yu, L. P. *Polym. Mater. Sci. Eng.* **1997**, *77*, 163. (f) Klopsch, R.; Koch, S.; Schlüter, A. D. *Eur. J. Org. Chem.* **1998**, *1275*, 5. (g) Ingerl, A.; Neubert, I.; Klopsch, R.; Schlüter, A. D. *Eur. J. Org. Chem.* **1998**, *2551*, 1. (h) Freeman, A. W.; Fréchet, J. M. J. *Org. Lett.* **1999**, *1*, 685. (i) Ishida, Y.; Jikei, M.; Kakimoto, M. *Macromolecules* **2000**, *33*, 3202.

(6) Barany, G.; Merrifield, R. B. *J. Am. Chem. Soc.* **1977**, *99*, 7363.

(7) (a) Launay, N.; Caminade, A. M.; Lahana, R.; Majoral, J. P. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1589. (b) Launay, N.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 3282. (c) Slany, M.; Bardají, M.; Casanove, M. J.; Caminade, A. M.; Majoral, J. P.; Chaudret, B. *J. Am. Chem. Soc.* **1995**, *117*, 9764. (d) Lartigue, M. L.; Donnadieu, B.; Galliot, C.; Caminade, A. M.; Majoral, J. P.; Fayet, J. P. *Macromolecules* **1997**, *30*, 7335.

(8) (a) Galliot, C.; Prévôté, D.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 5470. (b) Maraval, V.; Laurent, R.; Donnadieu, B.; Mauzac, M.; Caminade, A. M.; Majoral, J. P. *J. Am Chem. Soc.* **2000**, *122*, 2499. (c) Sebastian, R. M.; Magro, G.; Caminade, A. M.; Majoral, J. P. *Tetrahedron* **2000**, *56*, 6269.

(9) Merino, S.; Brauge, L.; Caminade, A. M.; Majoral, J. P.; Taton, D.; Gnanou, Y. *Chem. Eur. J.* **2001**. Accepted for publication.

10.1021/ja0029228 CCC: $20.00

second reaction with methyl hydrazine affords $H_2NNMeP(S)(OC_6H_4PPh_2)_2$ **1**, an AB_2 type compound with A = NH_2 and B = PPh_2. The second type of molecule should have A = N_3 and B = CHO. Compound **2** ($N_3P(S)(OC_6H_4CHO)_2$)[10] perfectly fits these requirements. However, the reaction between compounds **1** and **2** would lead to an hyperbranched polymer; to avoid this situation, and to grow a dendrimer in a divergent way, one has to react, first, one of the AB_2 monomers with a core, to deactivate its A function. We choose to use $(S)P(OC_6H_4CHO)_3$[7] $\mathbf{G_0}$ as a core. Thus, the first step is the condensation reaction between $\mathbf{G_0}$ and 3 equiv of the AB_2 monomer **1** (Scheme 1). The first generation $\mathbf{G_1}$, having six diphenylphosphino end groups is easily obtained. The next step is the Staudinger reaction between $\mathbf{G_1}$ and 6 equiv of the azide **2**, which affords the second generation $\mathbf{G_2}$ (12 aldehyde end groups). The dendrimer is then grown using again monomer **1**, then monomer **2** (Scheme 1). Thus, the formation of the fourth generation $\mathbf{G_4}$ having 48 aldehyde end groups, necessitates only four steps from the core $\mathbf{G_0}$. ^1H and ^{13}C NMR give good evidence for the completion of reactions, but ^{31}P NMR appears to be the most powerful technique for this purpose. Indeed, the condensation reaction induces the shielding of the signal of the P=S group of the phosphorhydrazide **1** from $\delta = 67.0$ to 61.6 (for $\mathbf{G_1}$) or 61.9 (for $\mathbf{G_3}$) ppm, whereas the Staudinger reaction induces the appearance of a set of two doublets at $\delta = 14.3$ (P=N) and $\delta = 50.2$ ppm (P=S). Furthermore, the narrow polydispersity of all compounds has been checked by size exclusion chromatography, which gives very narrow peaks for $\mathbf{G_2}$ and $\mathbf{G_4}$ (see Supporting Information). The enlargement observed for $\mathbf{G_3}$ is presumably due to oxidation of the phosphine end groups during the analysis or interactions of the phosphine with the column.[9]

The compounds obtained are layered dendrimers made of O-C_6H_4-Z-P(S) linkages, the difference between two layers being the nature of Z, CH=N−N(Me) or Ph_2P=N groups. The presence of P=N−P=S groups is particularly interesting since we have already demonstrated their specific reactivity with electrophiles, which opened large avenues for the obtaining of dendritic structures having very original architectures.[11] Furthermore, compounds **1** and **2** could be used also in a convergent strategy, provided the B functions of one of them could be deactivated in a first step. Deactivation of phosphino groups in **1** can be performed by oxidation, sulfuration, or complexation, while deactivation of aldehyde groups in **2** can be done, that is, by a Schiff reaction involving Girard P or T reagents.[12]

In fact, the type of synthesis we propose here is not *stricto sensus* an orthogonal system since no deprotection of both AB_2 monomers is required, but this particularity offers a marked advantage over previously reported systems. Indeed, it is clear that with a strict control of the stoichiometry, this sequence of reactions does not require any isolation, since the only byproducts are H_2O and N_2. Thus, we have tried to carry out a one-pot experiment to obtain directly the fourth generation starting from the core. Two aspects of the synthesis require a particular care: (i) this type of synthesis necessitates a strict control of the stoichiometry, (ii) we observed that the condensation step is slower during the one-pot process; thus, it is advisable to concentrate the solution before adding **1**. The spectroscopic characteristics of $\mathbf{G_4}$ obtained by the one-pot process are very similar to those described for $\mathbf{G_4}$ obtained step-by-step. However, a slight broadening of the peaks is detectable in ^{31}P NMR (Figure 1), as well as for SEC traces. A very small peak at a higher retention time indicates that a slight excess of one reagent was used at one step, leading to the formation of a small dendrimer. The slight broadening of the base of the main peak corresponds to uncompleted reactions of $\mathbf{G_4}$.

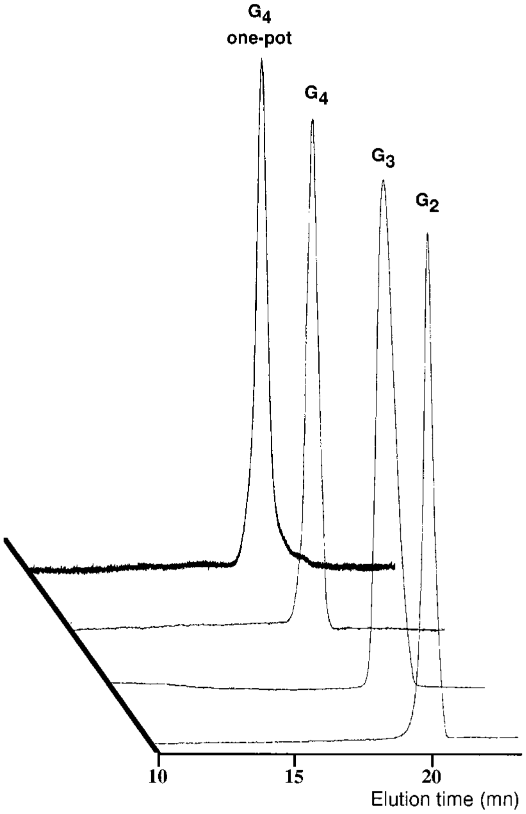


Figure 1. ^{31}P NMR spectra of dendrimers **G4** step-by-step and **G4** one-pot.

To the best of our knowledge, this is the first example of the one-pot synthesis of a fourth generation dendrimer obtained rather cleanly. The easy obtaining of such a compound opens the way to a broad range of reactivity.

Supporting Information Available: Experimental details of syntheses; ^{31}P, ^1H, ^{13}C NMR, IR, elemental analyses data, ^{31}P NMR spectra for $\mathbf{G_1}$, $\mathbf{G_2}$, $\mathbf{G_3}$, $\mathbf{G_4}$, and $\mathbf{G_4}$ one-pot; numbering scheme used for NMR; expanded formulas of $\mathbf{G_4}$; SEC traces for dendimers $\mathbf{G_2}$, $\mathbf{G_3}$, $\mathbf{G_4}$, and $\mathbf{G_4}$ one-pot (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0029228

---

(10) Mitjaville, J.; Caminade, A. M.; Daran, J. C.; Donnadieu, B.; Majoral, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 1712.

(11) (a) Larré, C.; Caminade, A. M.; Majoral, J. P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 596. (b) Galliot, C.; Larré, C.; Caminade, A. M.; Majoral, J. P. *Science* **1997**, *277*, 1981. (c) Larré, C.; Donnadieu, B.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **1998**, *120*, 4029. (d) Larré, C.; Bressolles, D.; Turrin, C.; Donnadieu, B.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **1998**, *120*, 13070.

(12) Marmillon, C.; Gauffre, F.; Gulik-Krzywicki, T.; Loup, C.; Caminade, A. M.; Majoral, J. P.; Vors, J. P.; Rump, E. *Angew. Chem., Int. Ed. Engl.* **2001**. Accepted for publication.