Divergent Dendrimer Synthesis

Dendrimer Design: How to Circumvent the Dilemma of a Reduction of Steps or an Increase of Function Multiplicity?

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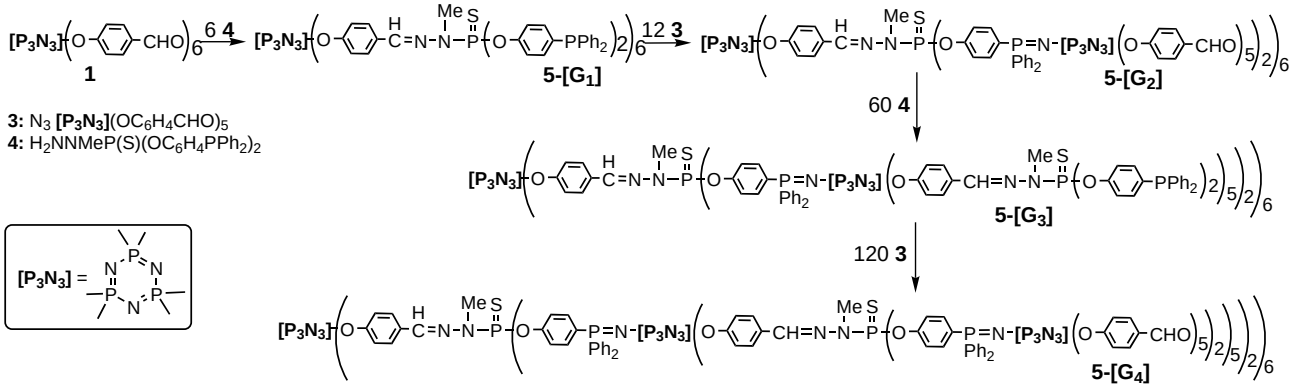
The development of dendrimer chemistry is due, without any doubt, to the extraordinary pallet of very unique properties of these monodisperse polymers which have applications in numerous fields which include biology, material sciences, catalysis, surface modification, electronics, electrooptics, chemical or biological sensors, and coatings.[1] It is clear that further growth depends crucially on the availability of new or more efficient synthetic methods which offer precise atom-by-atom control but remain as close as possible to the conditions required for a green and cheap chemistry.[2–7]

One of the most important and promising class of dendrimers, phosphorus dendrimers,[8] has also to fulfill this last point even though convenient syntheses have already been proposed. Up to the end of the 1990s the most convenient method of preparation of phosphorus-containing dendrimers was the reiteration of a sequence of two reactions dealing with an AX_2 system (mono(methylhydrazino)dichlorothiophosphane) and a YD one (sodium salt of the hydroxybenzaldehyde).[9,10] Then in 2001 the first divergent strategy using AB_2 ($H_2NN(CH_3)P(S)(OC_6H_4PPh_2)_2$, $B = PPh_2$) and CD_2 ($N_3P(S)(OC_6H_4CHO)_2$) unprotected monomers for the rapid synthesis of phosphorus-containing dendrimers was proposed.[7] Four steps were necessary to prepare a dendrimer of generation 4 (G_4) decorated on the surface with 48 aldehyde groups. This approach was attractive but does not allow a significant increase in the number of terminal groups for a given generation. This last point appears to be highly desirable since it is well demonstrated that the properties, and therefore the applications of dendrimers strongly depend on the nature and the density of functional groups grafted onto the surface.[1,11] These problems can be addressed in large part by designing highly functionalized cores of the form D_6 and new monomers AB_5 and CD_5.

To apply such a concept, we prepared monomers offering more possibilities for the design of targeted phosphorus dendrimers. Monomers **2** (AB_5 type) and **3** (CD_5 type, for preparation of **2** and **3** see the Supporting Information) were prepared from hexachlorocyclotriphosphazene, a commercially available reagent. Remarkably, they can react spontaneously without any activating agent by two reactions known to be quantitative (the condensation reaction between phosphorhydrazides and aldehydes, and the reaction between phosphanes and azides) and give only environmentally friendly byproducts: water and dinitrogen.

We choose the hexaaldehyde **1** as a core, and to react in an alternate fashion an AB_2 monomer, namely the hydrazinodiphosphane **4** and the CD_5 monomer **3** (Scheme 1). Such a strategy allows a generation per reaction to be created, and



Scheme 1. Divergent synthesis of the dendrimer **5-[G_4]** through the alternate use of the AB_2 monomer **4** and the CD_5 monomer **3**.

also allows the number of end groups of the dendrimer at each generation to be multiplied by two when **4** is involved or by five when **3** is used. This divergent synthesis of dendrimers was conducted up to generation 4 and was monitored by NMR spectroscopy (^1H, ^{13}C, ^{31}P) as well as by IR spectroscopy and by MALDI-TOF mass spectrometry in some cases. As far as the condensation of aldehyde groups with hydrazino groups is concerned, the reaction can be monitored by ^1H NMR (disappearance of the signal of the aldehyde protons), and by ^{13}C NMR (disappearance of the signal of the carbonyl group, and appearance of the signal of the hydrazino carbon atom CH=N–N) spectroscopy. In the case of the Staudinger reaction between phosphanyl end groups

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Supporting information (experimental details) for this article is available on the WWW under http://www.angewandte.org or from the author.

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and azido groups the disappearance of the N_3 groups is monitored by IR spectroscopy and the formation of P=N–P units through the incorporation of the P_3N_3 unit by ^{31}P NMR spectroscopy. MALDI TOF experiments (PerSeptive Biosystems Voyager Elite TOFMS-Framingham, USA; dithranol matrix with addition of LiI) conducted on some of these dendrimers confirm their structure. The molecular peak was observed for the dendrimer of generation 2 **5-[G_2]** ([*M*Li]$^+$ 13791.8) and for the dendrimer of generation 3 **5′-[G_3]** prepared after sulfuration of the terminal phosphanyl groups of **5-[G_3]** ([*M*li]$^+$ 56315.3). Some fragmentation patterns were also detected which result from two types of bond breaking: cleavage of the exocyclic nitrogen–phosphorus bond in N-[P_3N_3] linkages and cleavage of nitrogen–nitrogen bond in HC=N–N–P moieties. None of these fragmentation patterns comes from incomplete coupling (Figure 1). The molecular peak for the dendrimer **5-[G_4]**

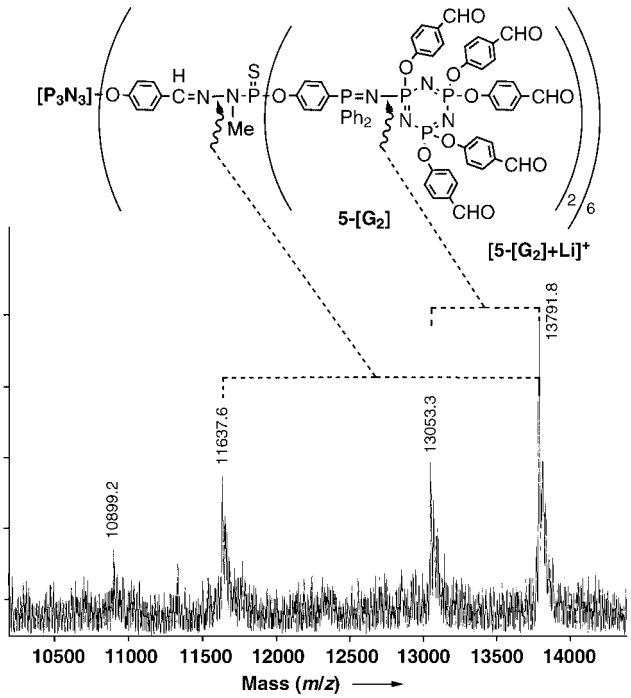

Figure 1. MALDI TOF analysis for **5-[G_2]** showing the molecular peak [*M*Li]$^+$ and the two types of fragmentation.

was not observed because of numerous fragmentation patterns (N–N and =N–P bond cleavages as in the G_2 and G_3 dendrimers).Thus the new dendrimers **5-[G_1], 5-[G_2], 5-[G_3]**, and **5-[G_4]**, were obtained cleanly and in good yields. (92–95%, Figure 2)

This process allows the preparation of a dendrimer of generation 4 bearing 600 aldehyde end groups in just 4 steps! This can be compared to the classical way (use of AX_2 and YD monomers) which gives rise, using 4 steps, to a dendrimer of generation 2 bearing only 24 terminal groups and also to our previous accelerated method using AB_2 and CD_2 monomers which affords after 4 steps generation 4 dendrimer having only 96 end groups! (Figure 3)

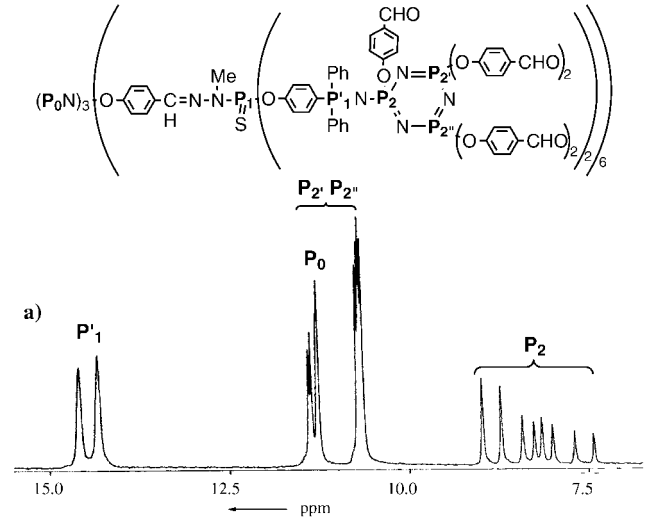

Figure 2. a) ^{31}P NMR spectrum of **5-[G_2]** in THF (the singlet at $\delta = 64.4$ ppm corresponding to the P_1=S unit is not shown). b) Theoretical ^{31}P NMR spectrum of **5-[G_2]** without the singlet at $\delta = 64.4$ ppm.

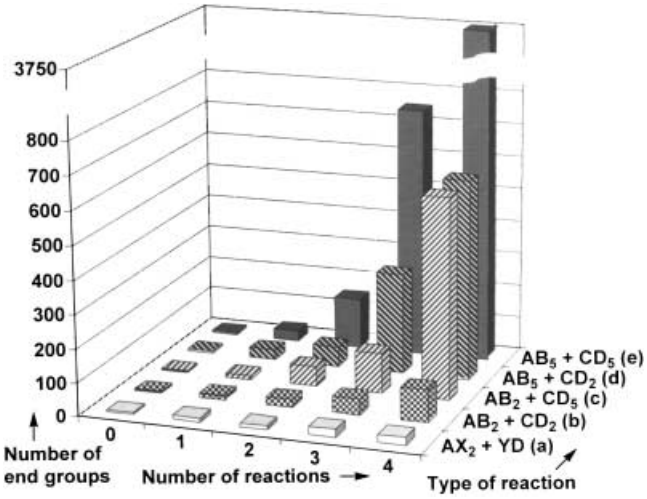

Figure 3. Comparison of the variation of the number of end groups at each generation a) use of AX_2 and YD monomers, b) use of AB_2 and CD_2 monomers, c) use of AB_2 and CD_5 monomers, d) use of AB_5 and CD_2 monomers, e) use of AB_5 and CD_5 monomers.

To have an idea of the scope and limitations of this method, we tried to perform similar reactions starting from the hexaaldehyde **1** which was treated with the AB_5 monomer **2** and not with the AB_2 monomer **4** as reported above. As a result the number of functions, here phosphanyl groups, is multiplied by five, which gives a dendrimer of generation 1, **6-[G_1]**, decorated with 30 phosphanyl groups (Scheme 2).

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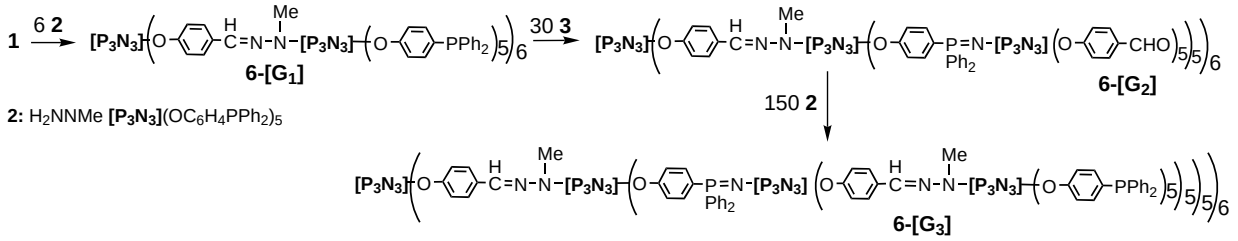

Scheme 2. Divergent synthesis of the dendrimer **6-[G$_3$]** by the alternate use of the AB$_5$ monomer **2** and the CD$_5$ monomer **3**.

These functional groups remain accessible to further transformation since the addition of the CD$_5$ monomer **3** allows the formation of the dendrimer of generation 2, **6-[G$_2$]**, bearing 150 aldehyde groups on the outer shell to go to completion. Lastly treatment of this dendrimer with the monomer **2** leads to the dendrimer of generation 3, **6-[G$_3$]** (Scheme 2). Indeed this methodology permits the preparation of a dendrimer of generation 3 bearing 750 phosphanyl end groups in only 3 steps (Figure 3)! The reaction leading to generation 4 was not attempted because of the expected steric hindrance of the third generation outer shell.

Therefore this method can be considered as the most convenient reported to date, offering several advantages 1) a strict minimum of steps is needed to build a generation: one step per generation, 2) a maximum number of functional groups is anchored to the surface of a dendrimer of a given generation, 3) purification of the resulting dendrimers is easy (simple washings), 4) reactions are easily monitored (^{1}H and ^{31}P NMR spectroscopy) 5) a minimum of solvent is used and the byproducts, water and dinitrogen are compatible with a green chemistry, 6) the degree of freedom for the construction of dendrimers is very high: depending of the sequence of monomer additions, dendrimers with different backbones but with the same number of identical functional groups on the surface can be obtained. This is illustrated in Scheme 1 and Scheme 3 and in Figure 4 where it is shown that by changing the order of addition of the reagents to **1** (AB$_2$, CD$_5$, AB$_2$, CD$_5$, Scheme 1 and, AB$_5$, CD$_2$, AB$_5$, CD$_2$, Scheme 3) it is possible to obtain different dendrimers of generation 2 (**5-[G$_2$], 7-[G$_2$]**,[12] (Figure 4) or generation 4 (**5-[G$_4$], 7-[G$_4$]**) bearing the same number of aldehyde end groups, 60 or 600, respectively, 7). This concept could be applied to other multifunctionalized cores (A$_6$, C$_6$, and the corresponding octafunctionalized monomers built from P$_4$N$_4$Cl$_8$), and to other unsymmetrical systems bearing, like AB$_5$ or CD$_5$, two different functions or to other easily accessible multifunctionalized starting reagents (A$_2$B$_4$…).

Experimental Section

General procedure for the reaction of phosphane-terminated dendrimers **5-[G$_1$], 5-[G$_3$], 6-[G$_1$], 7-[G$_3$]**, with CD$_2$ or CD$_5$ monomers: A 2% excess of the CD$_2$ or CD$_5$ monomer dissolved in THF (5 mL) was added to a solution of the dendrimer (0.200 g) in distilled and degassed THF (5 mL). The resulting solution was stirred at room temperature (in the case of CD$_2$) or at 45 °C (in the case of CD$_5$) for 2 days, then the solvent was removed under vacuum. The residue was washed three times with a mixture THF/pentane (1/5) for the reaction performed with CD$_2$, or with a mixture ethylacetate/diethyl ether/pentane (1/1/2) for the reaction performed with CD$_5$, to remove the small excess of monomer. Products **5-[G$_2$], 5-[G$_4$], 6-[G$_2$], 7-[G$_2$]**, and **7-[G$_4$]** were obtained as white powders.

General procedure for the reaction of aldehyde terminated dendrimers **5-[G$_2$], 6-[G$_2$]**, and **7-[G$_2$]** with AB$_2$ or AB$_5$ monomers. A 2% excess of the AB$_2$ or AB$_5$ monomer dissolved in THF (5 mL) was added to a solution of the dendrimer (0.200 g) in distilled and degassed THF (5 mL). The resulting solution was stirred in a sealed flask for 2 days (for AB$_2$) or 4 days (for AB$_5$) at 100 °C. After cooling at room temperature, the solvent was removed under vacuum and the residue was washed three times with diethyl ether (for AB$_2$) or with a mixture THF/pentane (1/5) (for AB$_5$) to give **5-[G$_3$], 6-[G$_3$]**, and **7-[G$_3$]** as white powders.

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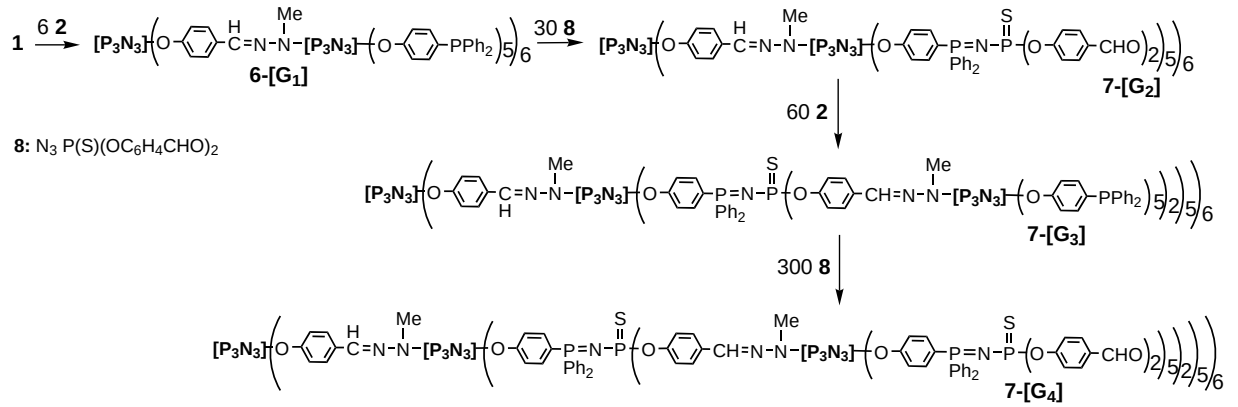

Scheme 3. Divergent synthesis of the dendrimer of generation 4, **7-[G$_4$]**, by the alternate use of the AB$_5$ monomer **2** and the CD$_2$ monomer **8**.

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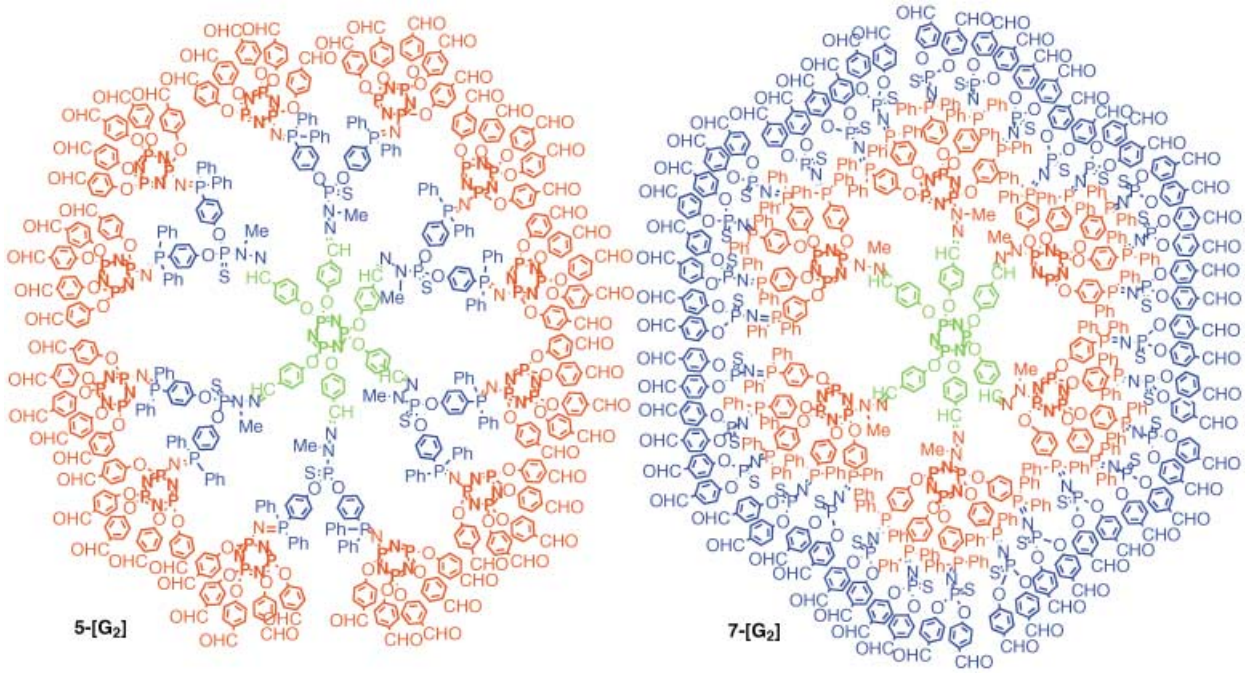

Figure 4. Representation of dendrimers **5-[G$_2$]**, and **7-[G$_2$]** bearing 60 aldehyde end groups.

Keywords: dendrimers · divergent synthesis · green chemistry · phosphorus · synthetic methods

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[12] **7-[G_2]** was characterized by ^{31}P, ^{1}H, ^{13}C NMR spectroscopy as well as by mass spectrometry (MALDI TOF; [*M*Li^+] 13739.7) and elemental analysis.

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