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Chemistry in the internal voids of dendrimers

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Contents

Abstract

P=N–P=S linkages placed in some layers within dendritic architectures allow the grafting of several types of functional groups at site and depth specific places in the internal layers of phosphorus containing dendrimers. These functional groups are either organic derivatives (allyl, propargyl, isothiocyanate, amine, aldehyde, azide, crown-ether) or metallic derivatives (gold chloride, anionic zwitterionic zirconocene). Furthermore, the dendrimeric architecture

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is flexible enough to allow the growing of new dendrimers inside the internal voids of the initial dendrimer.

Keywords: Dendrimer; Internal layers; Phosphorus; Gold; Zirconium

1. Introduction

Dendrimers are highly branched nanosized oligomers with precise architectures built by repetitive synthetic cycles [1]. Due to their particular structure, dendrimers have many functional groups located on the surface whose reactivity has been extensively studied [1,2]. In contrast, very few papers deal with the reactivity of functions located in the internal layers of dendrimers. Furthermore, most of these reactions are not layer specific, and only one group has reported site and depth specific reactions [3] before our work.

The inclusion of P=N–P=S linkages within the branches during the synthesis of phosphorus containing dendrimers leads to a versatile reactivity, due to the strong polarity of this linkage ($P^{(\delta+)}$=N–P=$S^{(\delta-)}$). The first part of this paper describes the synthesis of dendrimers built from different cores (difunctional and hexafunctional cores), including the P=N–P=S linkages at various levels. The reactivity of these linkages toward hard electrophiles will be described later as well as a desulfurization reaction leading to [P=N–P:] linkages. Then, the reactivity of these tricoordinated phosphorus atoms toward electrophiles and azides will be described, leading to the grafting of new functional groups whose reactivity is also explored.

2. Synthesis of dendrimers including P=N–P=S linkages

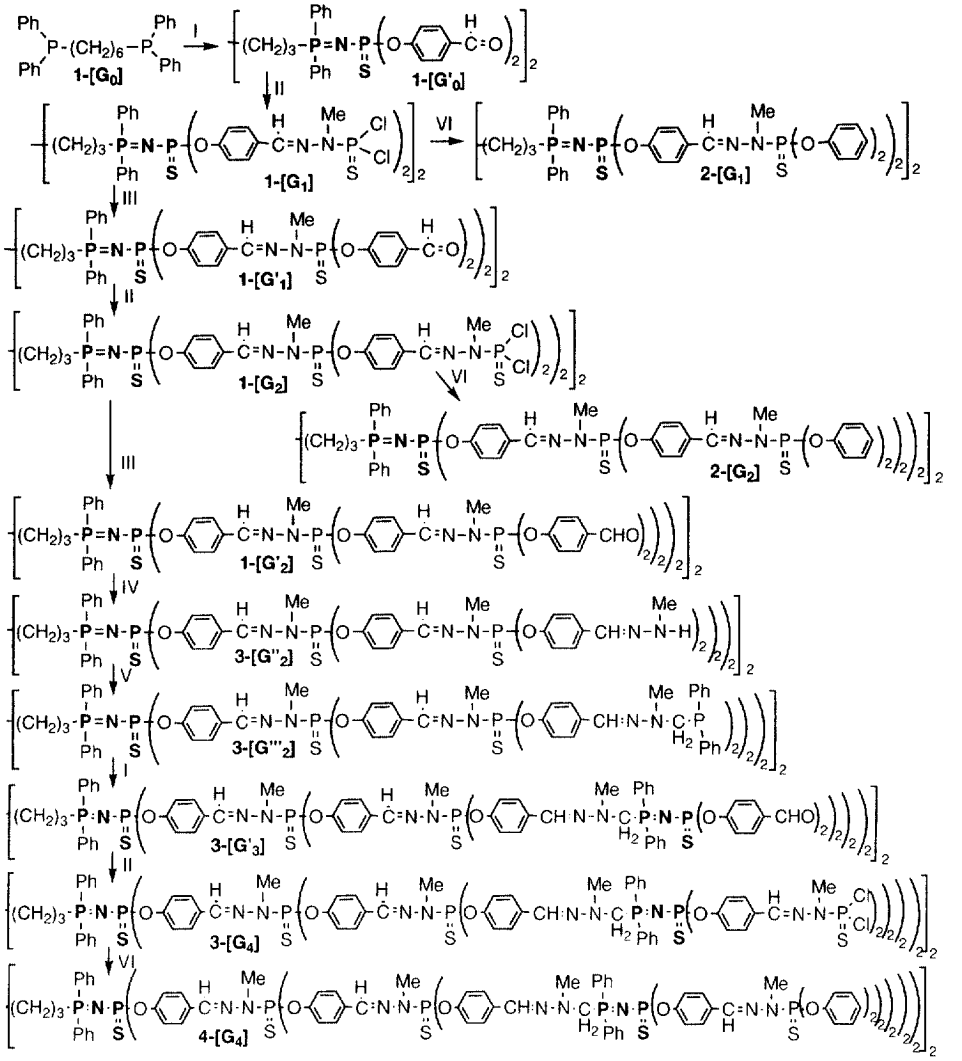
The P=N–P=S linkages are obtained in all cases by a Staudinger reaction between a tricoordinated phosphorus atom and $N_3P(S)[OC_6H_4CHO]_2$. These linkages are included at the level of the core starting from 1,6-bis(diphenylphosphino)hexane **1-[G_0]**. Reactions with $H_2NNMeP(S)Cl_2$ and $NaOC_6H_4CHO$ allow us to grow the branches and to multiply the number of terminal functions (Scheme 1) [4].

Other P=N–P=S linkages can be included when desired using a sequence of three reactions starting from the aldehyde end groups: condensation with methylhydrazine, then with Ph_2PCH_2OH, and finally reaction with $N_3P(S)[OC_6H_4CHO]_2$. For instance, the P=N–P=S linkages can be included in this way at the level of the third generation (**3-[G'_3]**, **3-[G_4]**, **4-[G_4]**, Scheme 1) or at the level of the fifth generation (**5-[G'_5]**, **5-[G'_6]**, Scheme 2) and the seventh generation (**6-[G'_7]**, Scheme 2). Up to 322 P=N–P=S groups are included in three layers for this later compound [5].

The same type of reaction is also applied from a hexafunctional core: the hexachlorocyclotriphosphazene **7-[G_0]**. For this series of dendrimers, the P=N–P=S linkages are included at the level of the first generation (six P=N–P=S groups) (Scheme 3) [6].

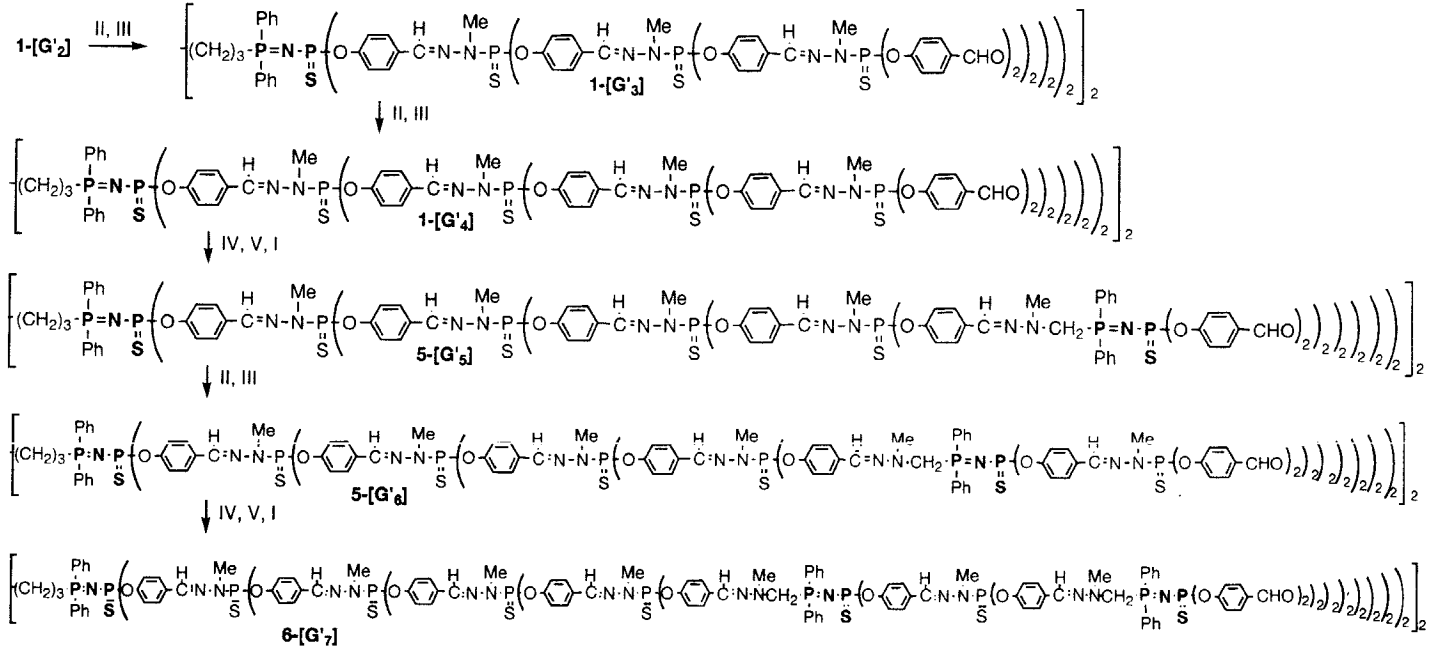
3. Alkylation of the P=N–P=S linkages

The polarity of the P=N–P=S linkages induces a facile and chemospecific reactivity toward strong electrophiles such as alkyl triflates. These reactions have been carried out first with methyl trifluoromethanesulfonate (Scheme 4). They are easily monitored by ^{31}P-NMR: for instance, the transformation **1-[G$_1$]** → **9-[G$_1$]** induces the disappearance of both doublets corresponding to the Ph_2P=N–P=S linkages of **1-[G$_1$]** (δ = 20.1 ppm (PPh_2); δ = 51.9 ppm (P=S); $^2J_{PP}$ = 35 Hz) on behalf

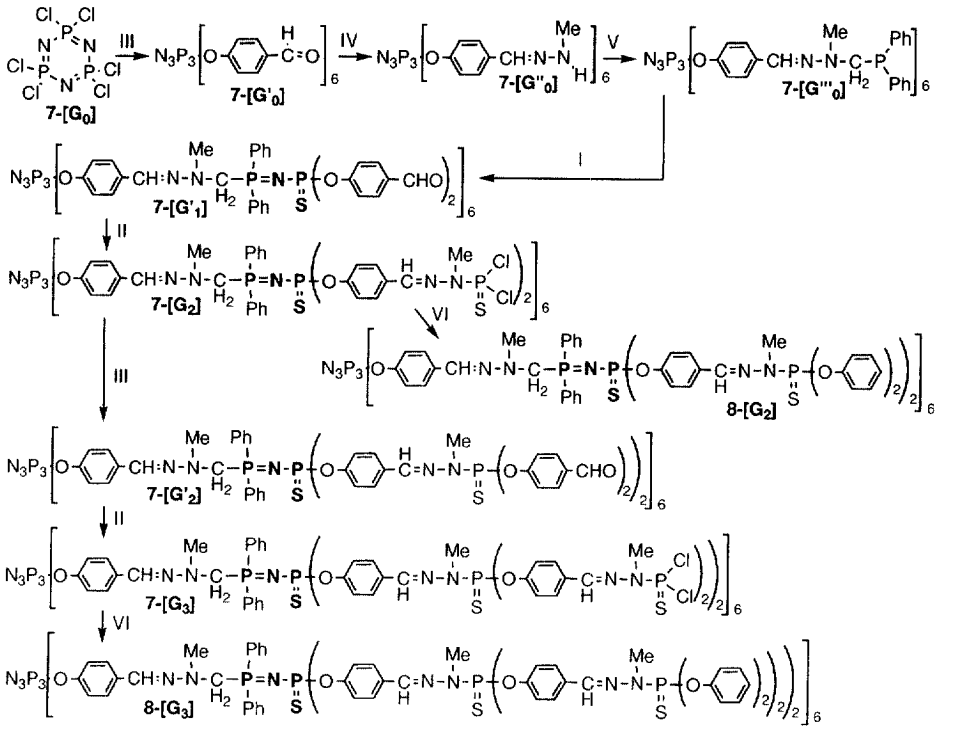


I) $N_3P(S)(OC_6H_4CHO)_2$ II) $Cl_2P(S)NMeNH_2$ III) $NaOC_6H_4CHO$ IV) H_2NNHMe V) Ph_2PCH_2OH VI) $NaOC_6H_5$

Scheme 1.


1-[G'2]
II, III
1-[G'3]
II, III
1-[G'4]
IV, V, I
5-[G'5]
II, III
5-[G'6]
IV, V, I
6-[G'7]
I) N3P(S)(OC6H4CHO)2 II) Cl2P(S)NMeNH2 III) NaOC6H4CHO IV) H2NNHMe V) Ph2PCH2OH

Scheme 2.

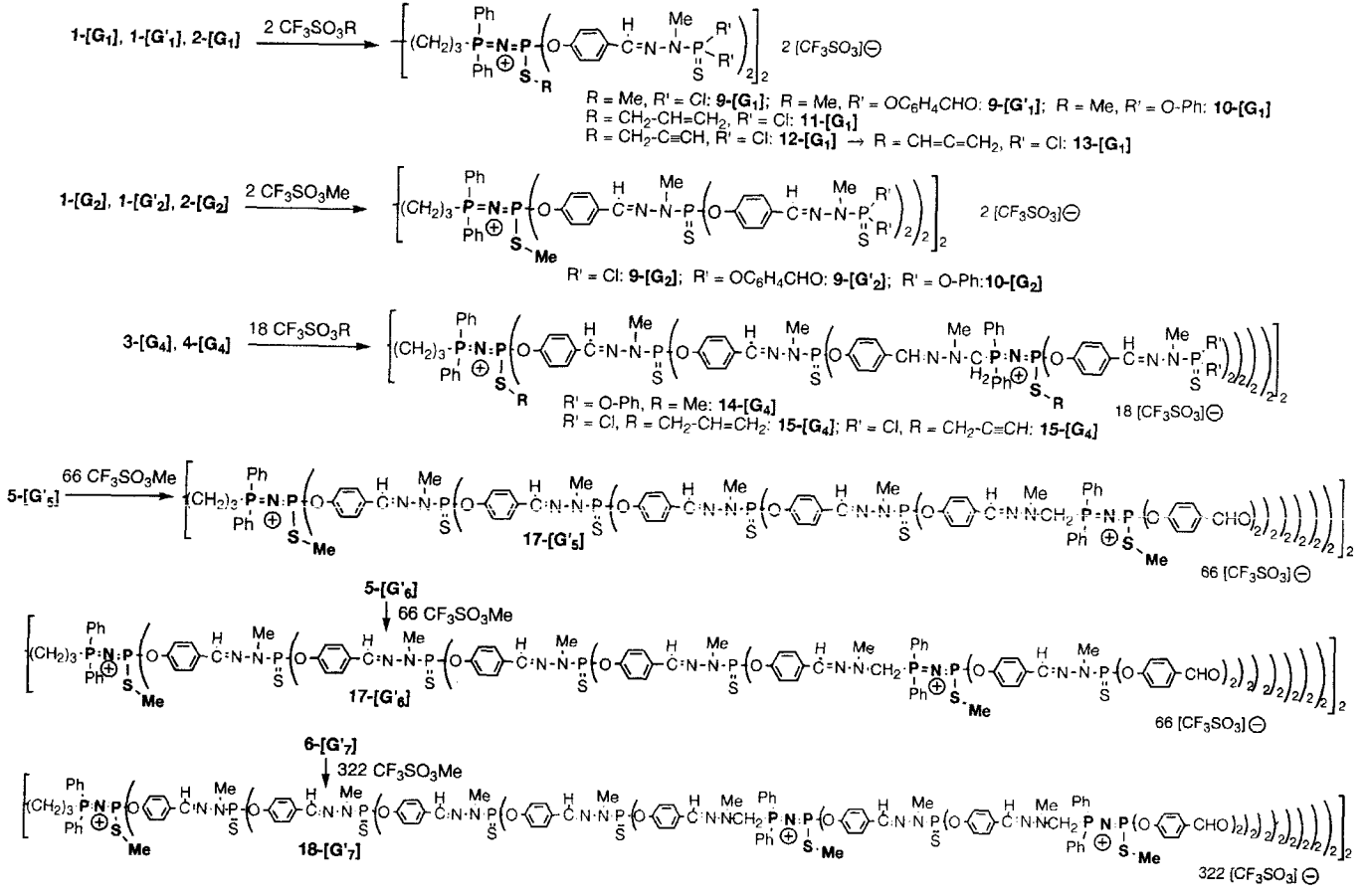


I) $N_3P(S)(OC_6H_4CHO)_2$ II) $Cl_2P(S)NMeNH_2$ III) $NaOC_6H_4CHO$ IV) H_2NNHMe V) Ph_2PCH_2OH VI) $NaOC_6H_5$

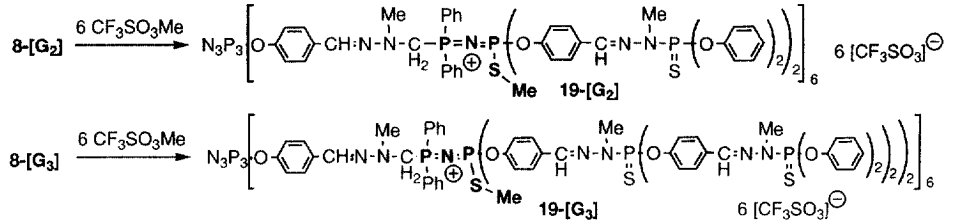
Scheme 3.

of two new doublets for **9-[G_1]** ($\delta = 33.0$ ppm (PPh_2); $\delta = 28.6$ ppm (P–S–Me); $^2J_{PP} = 17$ Hz). The other P=S groups which are not included in a P=N–P=S linkage remain unchanged ($\delta \cong 63$ ppm for **1-[G_1]** and **9-[G_1]**) [5]. This behavior is now unambiguously demonstrated by the determination of the structure of compound **9-[G_1]** by X-ray diffraction [4]. The specificity of the methylation reaction is also observed for higher generations either built from the diphosphine core [5] (Scheme 4) or from the cyclotriphosphazene core [6] (Scheme 5). Among them, one can notice the formation of dendrimers **17-[G'_6]** which includes 64 positive charges at the level of the fifth generation and two at the level of the core, as demonstrated by ^{31}P-NMR [5]. The alkylation of the core of this high generation illustrates the porosity of these dendrimers, and the possibility of introducing charges when and where desired.

In addition to charges, functional groups can be introduced within the dendrimer, using functionalized triflates such as allyl or propargyl triflates [7] (Scheme 4). The alkylation induces with both reagents a shielding of the signal corresponding to the P=S moieties of the Ph_2P=N–P=S linkages, and a deshielding of the signal of the PPh_2 moieties, as already observed with methyltriflate on ^{31}P-NMR spectra. The chemospecificity of these reactions is also proved by the X-ray structure


1-[G1], 1-[G'1], 2-[G1]
2 CF3SO3R
R = Me, R' = Cl: 9-[G1]; R = Me, R' = OC6H4CHO: 9-[G'1]; R = Me, R' = O-Ph: 10-[G1]
R = CH2-CH=CH2, R' = Cl: 11-[G1]
R = CH2-C≡CH, R' = Cl: 12-[G1] → R = CH=C=CH2, R' = Cl: 13-[G1]
1-[G2], 1-[G'2], 2-[G2]
2 CF3SO3Me
R' = Cl: 9-[G2]; R' = OC6H4CHO: 9-[G'2]; R' = O-Ph:10-[G2]
3-[G4], 4-[G4]
18 CF3SO3R
R' = O-Ph, R = Me: 14-[G4]
R' = Cl, R = CH2-CH=CH2: 15-[G4]; R' = Cl, R = CH2-C≡CH: 15-[G4]
18 [CF3SO3]⊖
5-[G'5]
66 CF3SO3Me
17-[G'5]
66 [CF3SO3]⊖
5-[G'6]
66 CF3SO3Me
17-[G'6]
66 [CF3SO3]⊖
6-[G'7]
322 CF3SO3Me
18-[G'7]
322 [CF3SO3]⊖

Scheme 4.

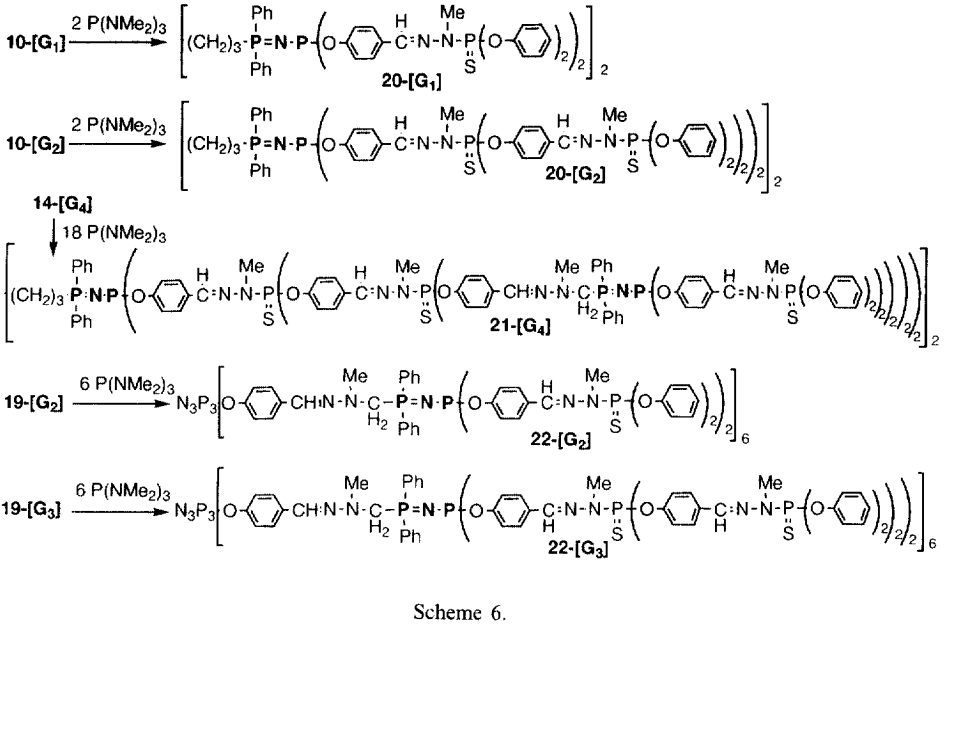


Scheme 5.

determination of compound **11-[G_1]**: no reaction occurred on the P=S groups not included in a P=N–P=S linkage [7]. Furthermore, the slow transformation **12-[G_1]** → **13-[G_1]** (CH_2–C≡CH → CH=C=CH_2) is also demonstrated by the X-ray structure determination of compound **13-[G_1]** [4]. Extension of these functionalization reactions to the fourth generation gives dendrimers **15-[G_4]** and **16-[G_4]** which possess charges and functions at the level of the core and of the third generation [4].

4. Desulfurization of the P=N–P=S linkages

The alkylation of the sulfur atom of the P=N–P=S linkages induces a weakening of the phosphorus–sulfur bond, which can lead to its cleavage in the presence of tris(dimethylamino)phosphine. This reaction has been applied to various methylated dendrimers, built either from the diphosphine core [5] or from the cyclot-



Scheme 6.

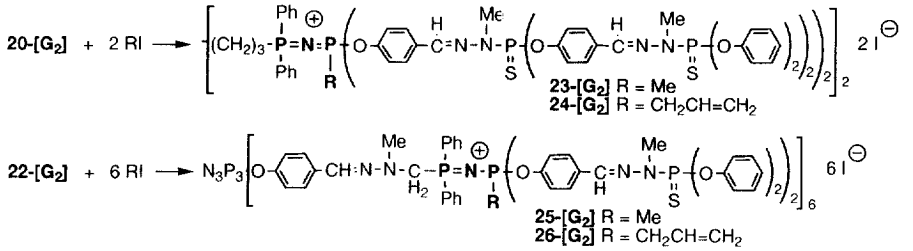
riphosphazene core [6] as shown in Scheme 6. It induces the formation of [P=N–P:] linkages including tricoordinated phosphorus atoms, characterized in ^{31}P-NMR spectra by the appearance of a highly deshielded doublet at $\delta \cong 144$ ppm ($^{2}J_{PP} \cong 40$ Hz). These aminophosphite groups are generally extremely sensitive toward oxidation, thus in most cases, compounds **20-[G$_n$]**, **21[G$_n$]**, and **22-[G$_n$]** are not isolated but reacted in situ.

5. Alkylation of the [P=N–P:] linkages

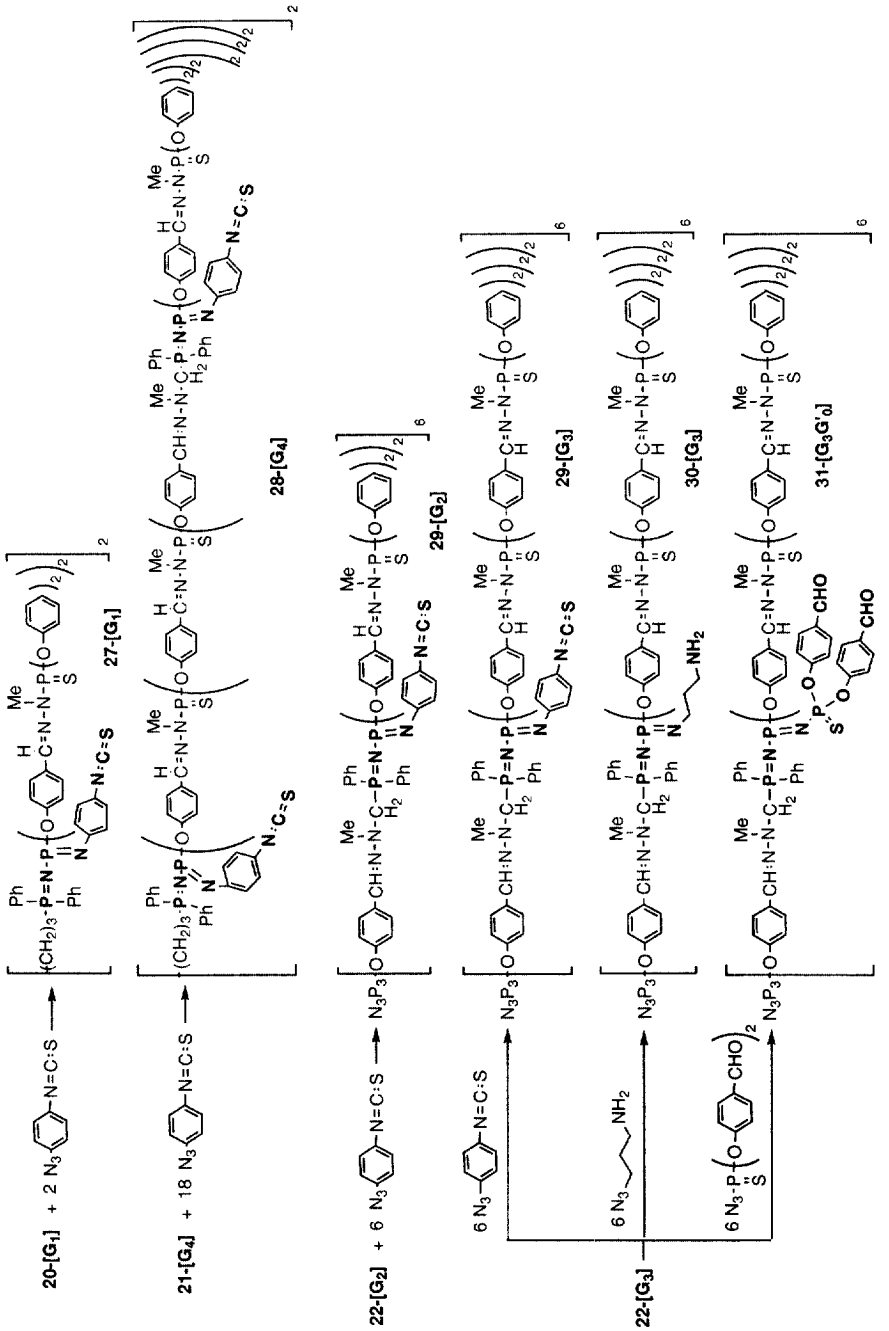
The quaternization of phosphines with alkyl halides is a well known reaction which can be applied to the aminophosphite groups of dendrimers **20-[G$_2$]** and **22-[G$_2$]**. No reaction occurs with alkyl bromides, whereas methyliodide and allyliodide react readily [4] (Scheme 7). The alkylation induces a large shielding of the signal corresponding to the phosphite, from $\delta \cong 144$ to 26 ppm in ^{31}P-NMR.

6. Staudinger reactions of the [P=N–P:] linkages with functionalized azides

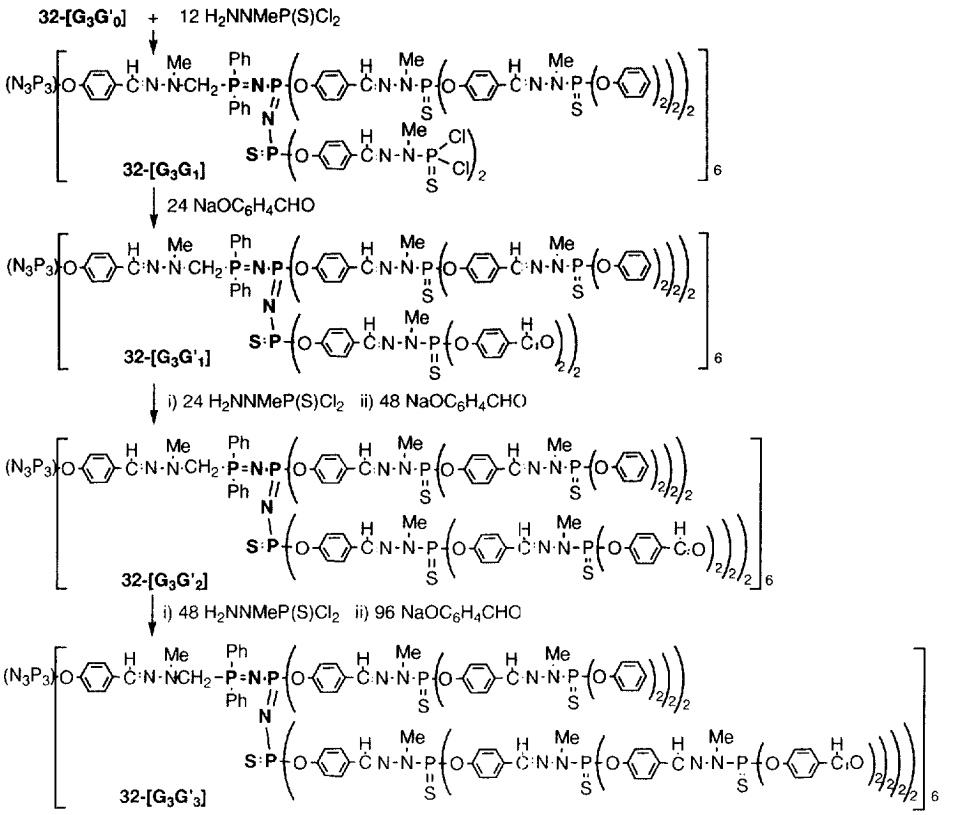
The Staudinger reaction, which is generally quantitative and proceeds with evolution of nitrogen as sole by-product, is the best way to introduce functions within dendrimers including tricoordinated phosphorus atoms. Up to 18 isothiocyanate groups have been grafted within a dendrimer, using 4-azidophenyl isothiocyanate and compound **21-[G$_4$]**, a fourth generation dendrimer built from the diphosphine core (Scheme 8) [4]. Analogous reactions applied to the third generation of the dendrimer built from the cyclotriphosphazene core **22-[G$_3$]** allows the grafting of six isothiocyanate groups [4]. Dendrimer **22-[G$_3$]** also reacts with other functionalized azides, such as 1-amino-3-azidopropane and $N_3P(S)[OC_6H_4CHO]_2$, leading to the grafting of six primary amine groups (**30-[G$_3$]**) or 12 aldehyde groups (**31-[G$_3$G$'_0$]**), respectively (Scheme 8) [6]. The later reaction induces, on the ^{31}P-NMR spectra, the appearance of two doublets ($\delta = 13.4$ ppm (PPh_2), $^{2}J_{PP} = 21$ Hz; $\delta = 44.7$ ppm (P=S), $^{2}J_{PP} = 62$ Hz) and one doublet of doublets ($\delta = -12.4$ ppm (N=P–N)). The presence of aldehyde groups in the internal layers of compound **31-[G$_3$G$'_0$]** is very interesting: indeed these functions constitute the starting point of a versatile reactivity.



Scheme 7.



Scheme 8.



Scheme 9.

7. Synthesis of dendrimers within dendrimers

The possibility of alkylating the internal layers and particularly the core illustrates the high porosity of these phosphorus containing dendrimers, even for high generations. However, one question remains: are the branches flexible enough to accommodate very bulky substituents and even to allow the growing of new dendritic frameworks within dendrimers? We have positively answered this question using the dendrimer possessing 12 internal aldehyde groups **31-[$G_3G'_0$]** [6].

Two different strategies were used to build supplementary branches within this dendrimer, both using reactions already described for the synthesis of phosphorus containing dendrimers. The simplest necessitates two steps to build one generation: first, condensation of the aldehyde internal groups with $H_2NNMeP(S)Cl_2$, then reaction with hydroxybenzaldehyde sodium salt. This sequence of reactions leads to the formation of dendrimer **32-[$G_3G'_1$]**, then **32-[$G_3G'_2$]**, and finally to dendrimer **32-[$G_3G'_3$]**, whose internal dendritic branches are longer than those of the initial dendrimer (Scheme 9, Fig. 1) [6].

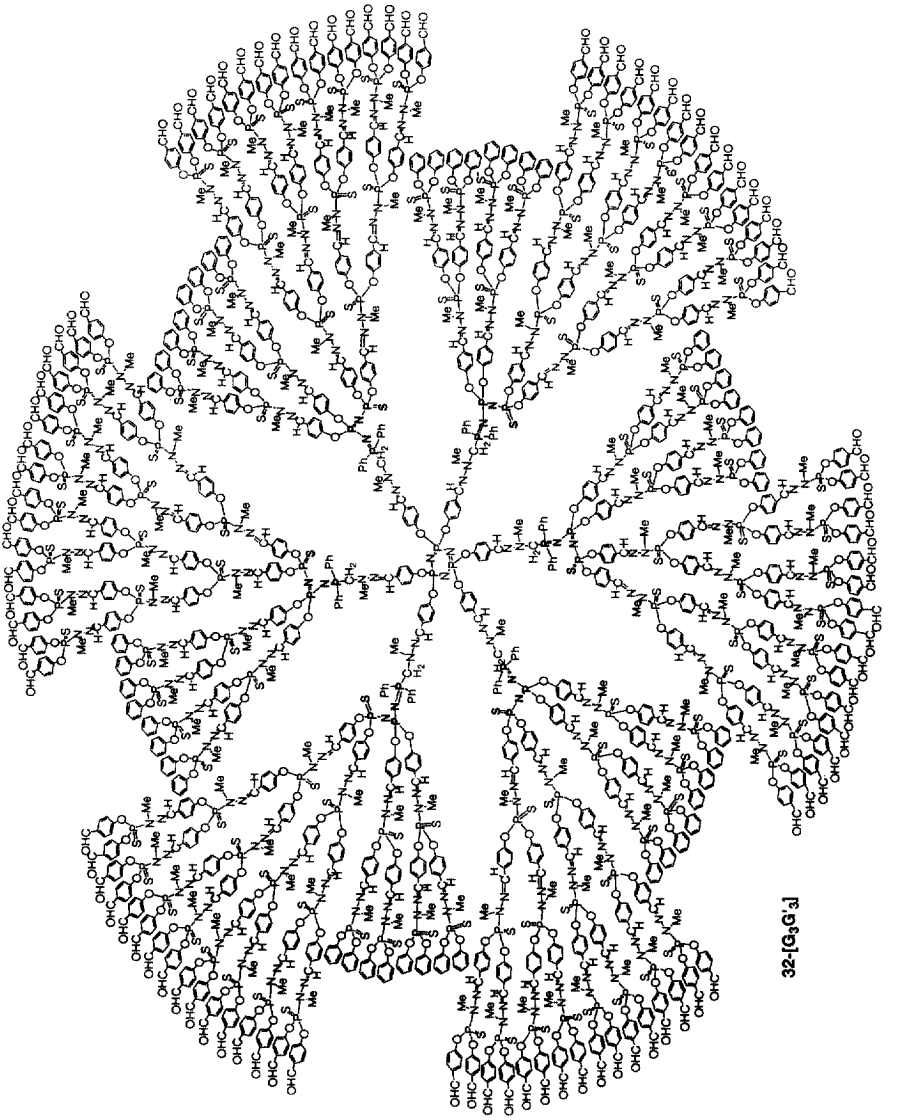
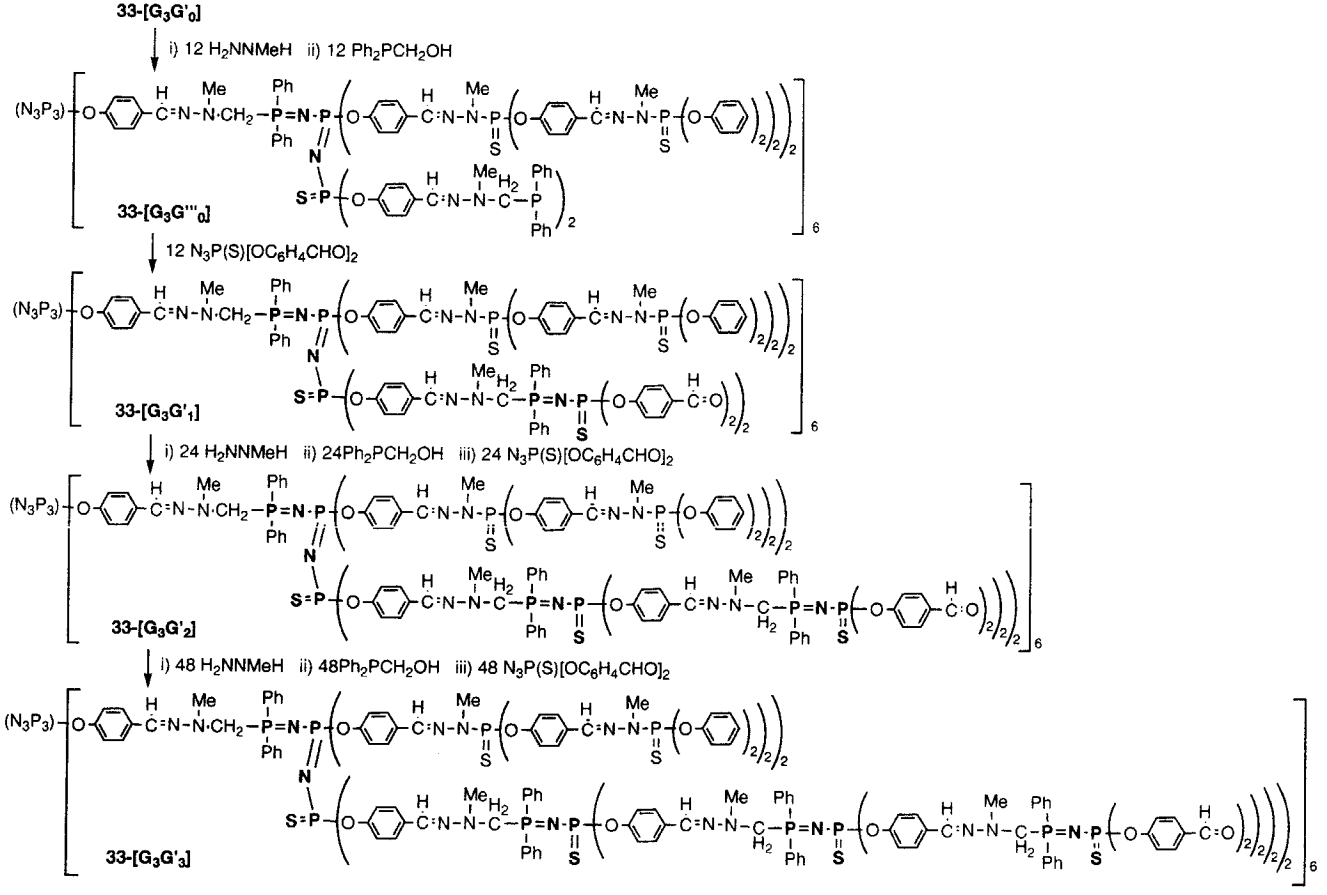


Fig. 1.


33-[G3G'0]
i) 12 H2NNMeH ii) 12 Ph2PCH2OH
33-[G3G'''0]
12 N3P(S)[OC6H4CHO]2
33-[G3G'1]
i) 24 H2NNMeH ii) 24Ph2PCH2OH iii) 24 N3P(S)[OC6H4CHO]2
33-[G3G'2]
i) 48 H2NNMeH ii) 48Ph2PCH2OH iii) 48 N3P(S)[OC6H4CHO]2
33-[G3G'3]

Scheme 10.

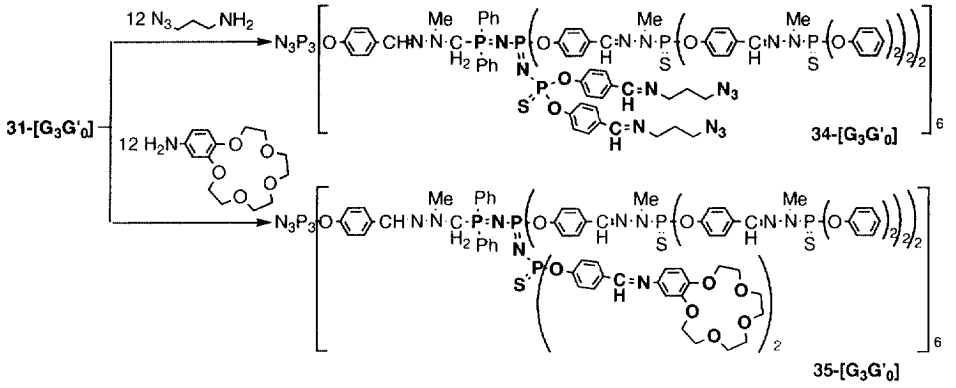
The second strategy necessitates three steps to build one new generation within the dendritic structure. The first step is a condensation with methylhydrazine, the second step is a condensation with Ph_2PCH_2OH, and the third step is a Staudinger reaction with $N_3P(S)[C_6H_4CHO]_2$ (Scheme 10) [6]. In all cases these reactions are easily monitored by ^{31}P-NMR. This synthetic procedure is longer than the previous, but it induces the formation of P=N–P=S linkages at each generation, which should confer a particular reactivity to dendrimers **33-[$G_3G'_n$]**. The largest compound synthesized in this series is **33-[$G_3G'_3$]** in which six third generation dendrons, each of them including 14 P=N–P=S groups, are grafted within a third generation dendrimer.

8. Other examples of reactivity of the aldehyde internal groups

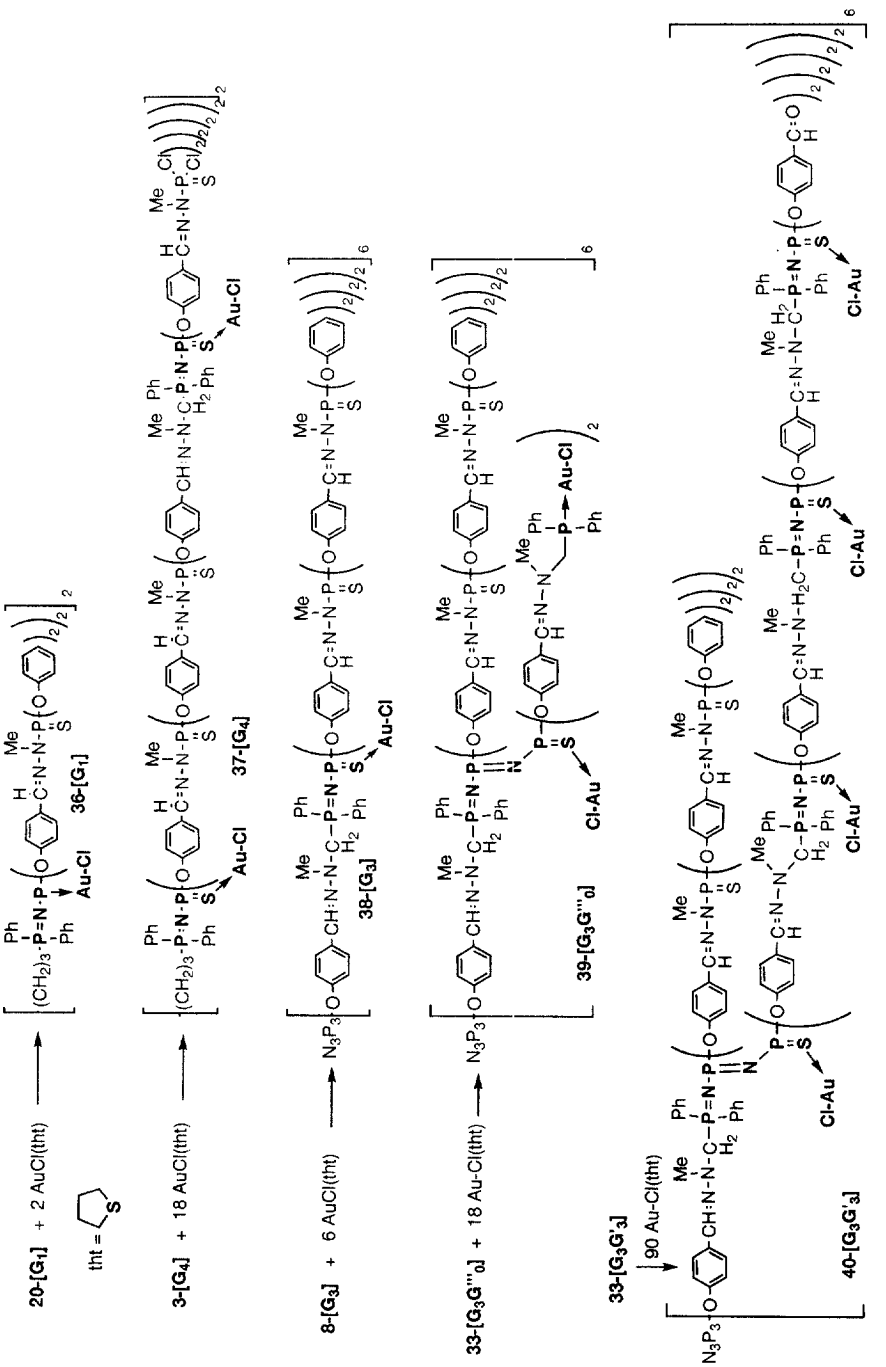
In addition to the synthesis of dendrimers within dendrimers, the aldehyde internal groups should allow the grafting of various functional groups using Schiff type condensation reactions. Scheme 11 illustrates two examples concerning the reactivity of compound **31-[$G_3G'_0$]**. A total of 12 equivalents of 1-amino-3-azidopropane or 4′-aminobenzo-15-crown-5 can be incorporated within the dendrimer [4]. The condensation is monitored by ^1H-NMR, which indicates a rapid reaction at room temperature in the former case, but a long reaction (1 week in refluxing THF) in the later case, presumably due to a combination of steric and (mainly) electronic effects. These condensations lead to the presence of azides (**34-[$G_3G'_0$]**) or crown ethers cavities (**35-[$G_3G'_0$]**) within the dendritic structure.

9. Complexation properties of the internal layers of dendrimers

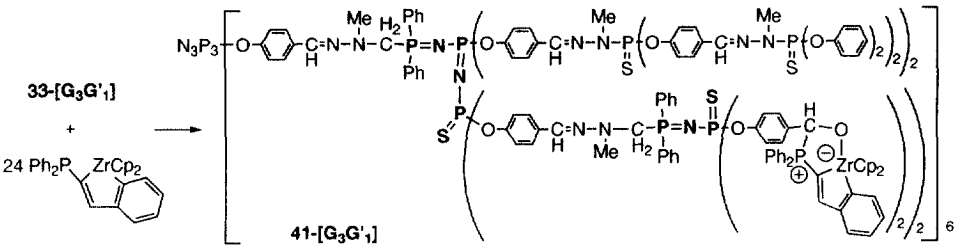
Most of the dendritic structures described in this paper possess functions such as phosphines, phosphites, P=N–P=S linkages or even aldehydes, which can poten-



Scheme 11.



Scheme 12.



Scheme 13.

tially interact with transition metals. For instance, gold can be directly bounded to tricoordinated phosphorus atoms, as indicated by the formation of compound **36-[G_1]** (Scheme 12). The sulfur atom of the P=N–P=S linkages can also act as a donor ligand, leading to compounds **37-[G_4]** from **3-[G_4]** and **38-[G_3]** from **8-[G_3]**. Both tricoordinated phosphorus atoms and P=N–P=S linkages can complex gold when they are present together in one compound such as **33-[$G_3G''_0$]**, leading to the formation of dendrimer **39-[$G_3G''_0$]** which possesses six P=N–P=S → AuCl and 12 Ph_2P → AuCl groups. The complexation reaction can be extended to the multidendritic compound **33-[$G_3G'_3$]**. In this case, all the P=N–P=S groups are complexed by gold including the P=N–P=N–P=S linkages, leading to compound **40-[$G_3G'_3$]** which possesses complexed and uncomplexed branches in its structure (Scheme 12) [8].

Finally, the aldehyde groups can also be used to react with an early transition metal derivative, the 2-phosphino-1-zirconaindene. This compound is able to react with various unsaturated species [9], for instance aldehydes, leading to the formation of stable 18 electron anionic zirconocenes. Application of this reaction to the multidendritic system **33-[$G_3G'_1$]** induces the formation of the multizwitterionic species **41-[$G_3G'_1$]**, obtained by formal [3 + 2] cycloaddition reactions (Scheme 13). It must be noted that no reaction occurs on the other unsaturated bonds of the molecule, such as hydrazones or P=N–P=S linkages [10].

10. Conclusion

The presence of P=N–P=S linkages in the internal layers of various phosphorus containing dendrimers allows the development of a versatile reactivity. Indeed, the formal negative charge borne by the sulfur atom of this linkage induces a chemospecific reactivity of this atom toward electrophiles such as methyl, allyl or propargyl triflates, and toward gold chloride. Furthermore, the alkylation induces a weakening of the phosphorus–sulfur bond which is easily cleaved to give tricoordinated aminophosphite groups. The reactivity of these groups toward electrophiles, and above all, toward functionalized azides opens new perspectives for the synthesis of dendritic structures with very original architectures. For instance, bulky groups and even other dendritic branches can be grafted or built within dendrimers, illustrating the high porosity of these dendrimers and the

flexibility of their framework. Furthermore, the alternance of branches incorporating or not the P=N–P=S linkage confers, to these multidendritic systems, interesting complexation properties leading for instance to the formation of compounds incorporating 90 gold atoms or 24 zwitterionic anionic zirconocenes within the cascade structure.

Acknowledgements

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