FEATURE ARTICLE

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The specific contribution of phosphorus in dendrimer chemistry

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Besides properties commonly found for all types of dendrimers, phosphorus-containing dendrimers possess some specific properties seldom or never found for other types of dendrimers. Emphasis will be put on these specificities.

Introduction

Dendrimers[1] constitute an exponentially growing area of research since more than fifteen years. The large interest arisen by dendrimers is illustrated by the fact that around 1000 papers related to this topic were published in 2001. After the synthetic aspects, which were the first goals and still constitute a living field of research, interest in dendrimers is now more directed towards applications. Heteroatom-containing dendrimers,[2] and particularly phosphorus-containing dendrimers benefit from the global interest in dendrimers, but they have also their own specificities and properties. In this paper, we will describe first the most important methods of synthesis of phosphorus-containing dendrimers, then some aspects of their reactivity at various levels (surface, internal layers, core), with emphasis on some aspects more specific to these dendrimers. The end of this paper will focus on some properties and applications, also in this case with emphasis on the specificities brought by phosphorus.

Jean-Pierre Majoral received his Ph. D. from the Université Paul Sabatier of Toulouse in 1972. In 1972–1973 he worked as a Post-doc with Prof. A. Katritzky (University of East Anglia, Norwich, UK). He became Directeur de Recherche at the Centre National de la Recherche Scientifique in Toulouse in 1978. His research interest is mainly focused on the use of main group elements, especially phosphorus in different areas of chemistry. Presently, he is involved in the preparation and the properties of macromolecules such as dendrimers and hyperbranched polymers. Emphasis is also laid on the studies of interactions between heavier main group elements and group 4 elements (titanium, zirconium, hafnium) with applications in organic and organometallic chemistry. He is a member of the Polish Academy of Sciences and of the Academia Europaea.

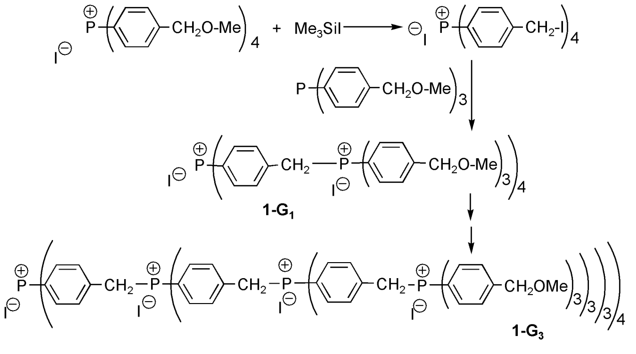
Anne-Marie Caminade received two Ph. D.s in Toulouse (1984 and 1988). She worked as a Post-doc at the Institut Français du Pétrole (1984) and in Prof. M. Veith's group (1988–1989, Saarbrücken, Germany). She is working since 1985 at the CNRS with Jean-Pierre Majoral, where she is "Directeur de Recherche" since 1997. Her research interest is on main group elements. She developed several aspects of the chemistry of phosphorus, including low coordinated compounds, coordination of transition metals, reactivity of metallic hydrides, synthesis of macrocycles. Her current research interest is on the synthesis, reactivity and study of properties of dendrimers.

Valérie Maraval received her Ph. D. in 2000 from the Université Paul Sabatier of Toulouse in the group of J. P. Majoral. After working as a Post-doc with B. Meunier (2001), she is now Ingénieur de Valorisation at the CNRS in J. P. Majoral's group.

Syntheses, characterization and reactivity of phosphorus-containing dendritic macromolecules

Methods of synthesis

Several groups in the world have described the synthesis of phosphorus-containing dendrimers, using in all cases divergent synthetic processes.† The first method was described by Rengan and Engel in 1991, using the repetition of two steps, which gives a phosphonium salt at each branching point.[3] The first step is the cleavage of an ether linkage by Me_3SiI, affording an alkyl iodide. This alkyl iodide is used in the second step for the alkylation of a phosphine possessing three ether groups, to give the first generation of the dendrimer **1-G$_1$**. This process allows multiplying by three the number of end groups at each generation, and it was applied up to the third generation **1-G$_3$** (Scheme 1). Various other cores such as phosphine oxide were also used.[4]



Scheme 1 Synthesis of dendrimers having a phosphonium salt at each branching point.

In 1994, DuBois and coworkers described the first synthesis of small dendrimers having a phosphine at each branching point.[5] This method necessitates two steps to obtain one generation, and to multiply by two the number of end groups. The first step is the radical addition of primary phosphines on the vinyl group of phosphonates. The second step is the reduction of the phosphonates to give primary phosphines. This method was applied only up to the second generation **2-G$_2$** (Scheme 2).

Larger dendrimers having a phosphine at each branching point were recently obtained by Kakkar and coworkers.[6] The key point of this two-steps method is the controlled acid–base hydrolysis of diaminosilanes with phosphines having terminal OH groups. Characterization of these compounds indicates dendrimer rather than hyperbranched polymer growth, despite the necessity to react only one alcohol group of

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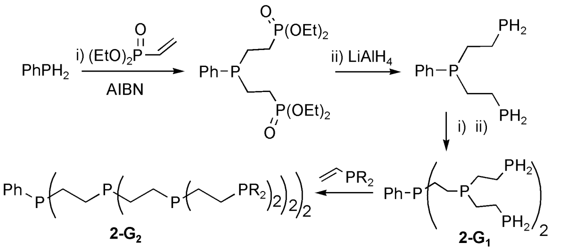
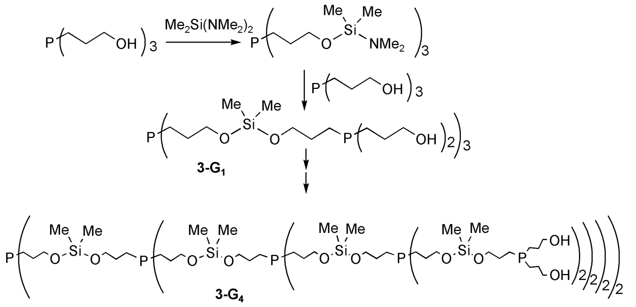


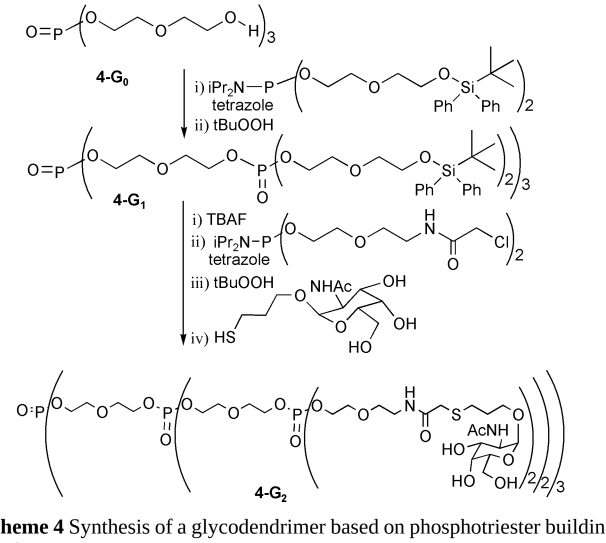
Scheme 2 Synthesis of small dendrimers having a phosphine at each branching point.

$P(CH_2CH_2CH_2OH)_3$ at each generation. This method was applied up to generation 4, **3-G$_4$** (Scheme 3).



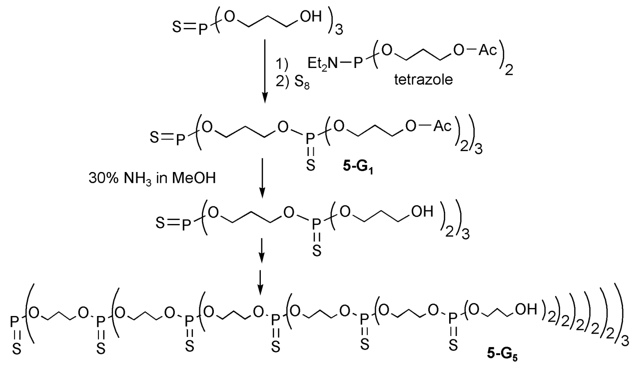
Scheme 3 Synthesis of dendrimers having a phosphine at each branching point up to generation 4.

Two methods of synthesis giving other polyether linkages and phosphotriester branching points were also reported. Both are based on phosphoramidite building blocks. The first method was described by Roy.[7] Coupling of diisopropylphosphoramidite with the alcohol groups of **4-G$_0$** in the presence of tetrazole, followed by oxidation gave the first generation **4-G$_1$** (Scheme 4). After deprotection of the end groups by tetrabutylammonium fluoride, an analogous sequence of reactions using another phosphoramidite, followed by the grafting of thiolated *N*-acetylgalactosaminide affords the glycodendrimer **4-G$_2$**.



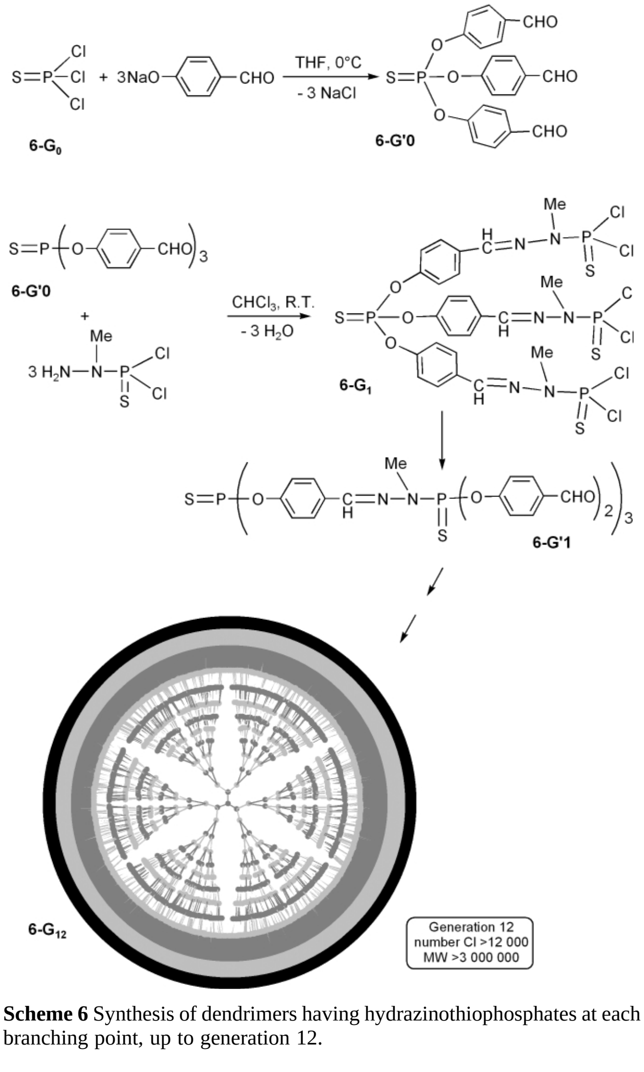
Scheme 4 Synthesis of a glycodendrimer based on phosphotriester building blocks.

Salamonczyk *et al*. described recently the use of an analogous method for the synthesis of dendrimers based on thiophosphate derivatives at each branching point.[8] The phosphitylation of a triol with $Et_2NP(OCH_2CH_2CH_2OAc)_2$ followed by oxidation with elemental sulfur gives a dendrimer having acetate end groups. Cleavage of the acetates by NH_3 in MeOH affords the first generation dendritic polyol **5-G$_1$** (Scheme 5). The repetition of this process was carried out up to generation 5, **5-G$_5$**. The same type of method was used for the synthesis of the first dendrimer having P=Se linkages instead of P=S linkages.[9]



Scheme 5 Dendrimers having a thiophosphate at each branching point.

Our group has developed several ways of synthesis of phosphorus-containing dendrimers. The first one dates back to 1994 and was the first method of synthesis of neutral phosphorus dendrimers.[10] It is a two-step process consisting first in the reaction of 4-hydroxybenzaldehyde in basic conditions with compounds having P–Cl functions, such as $S{=}PCl_3$. The second step is a condensation reaction between the aldehydes and $H_2NNMeP(S)Cl_2$. Both steps are quantitative, and the only by-products are sodium chloride and water. The



Scheme 6 Synthesis of dendrimers having hydrazinothiophosphates at each branching point, up to generation 12.

repetition of this two-steps process was carried out up to the twelfth generation **6-G$_{12}$**[11] (Scheme 6). Even if it is obvious that defects cannot be ruled out, this compound constitutes the highest generation ever synthesized in dendrimer chemistry. The presence of aldehyde or $P(S)Cl_2$ end groups allowed us to develop a versatile reactivity on the surface of these dendrimers (see later).

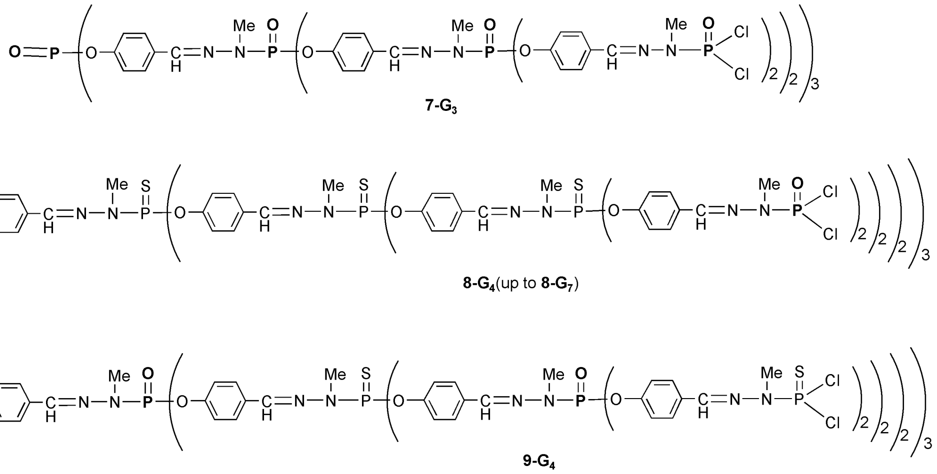
The same method of synthesis can be applied to H_2NNMe-$P(O)Cl_2$ instead of $H_2NNMeP(S)Cl_2$, in order to have phosphoryl groups either at each layer or at particular layers. Fig. 1 shows some examples, in which the phosphoryl layers are within all the structure (up to **7-G$_3$**),[12] or only on the surface (up to **8-G$_7$**),[13] or every two layers (up to **9-G$_4$**).[14] The later compound was the first ‘layer-block’ dendrimer built with a regular alternation of two types of repeating units up to the fourth generation.

This method of synthesis, using generally $H_2NNMeP(S)Cl_2$ can be also applied to various cores having P–Cl linkages such as $N_3P_3Cl_6$,[15] and also to cores possessing aldehyde groups. For instance, we obtained in this way dendritic wedges (dendrons[16]) possessing a vinyl group at the core and various functions as end groups.[17] The divergent synthesis of these dendrons was generally carried out only up to generation 3, in order to detect easily all the reactions which were done later at the level of the core (Scheme 7).

This method creates a P=N–P=S linkage[18] at the level of the core by a Staudinger reaction between a phosphine and an azide linked to a P(S) group. The P=N–P=S linkage is particularly interesting for further functionalizations (see the Section ‘Reactivity of the internal layer’), and we tried to obtain this type of linkage at specific layers within the structure of a dendrimer. The way we generally used necessitates three successive steps: (i) condensation of methylhydrazine on aldehyde groups, (ii) condensation of the N–H end groups with Ph_2PCH_2OH, leading to phosphine end groups, and finally (iii) the Staudinger reaction with $N_3P(S)[OC_6H_4CHO]_2$ (Scheme 8). The synthesis of the dendrimer can be continued starting from the aldehydes, and using the method described Scheme 6.[19]

All the various methods described in Schemes 1–8, as well as most of the methods of synthesis of organic dendrimers, necessitate at least two steps to multiply the number of end groups. All these methods are time consuming and there is a need to find more rapid methods. We recently proposed an improvement, which allows doubling the number of end groups at each step instead of every two steps.[20] This new method uses in alternation **AB$_2$** and **CD$_2$** monomers, in which **A** (NNH_2) is able to react only with **D** (CHO), and **B** (PRR'_2) is able to react only with **C** (N_3). Generation 4 is obtained in only four steps instead of eight using traditional methods (Scheme 9). Furthermore, the only by-products of these quantitative reactions are water and nitrogen; thus generation 4 can be also obtained in one-pot with a good purity, by adding successively and repetitively strictly stoichiometric amounts of each reagent.[20]

In order to find an even more rapid method of synthesis, we also tried to obtain hyperbranched polymers in only one step. For this purpose, we needed a monomer having one **A** function

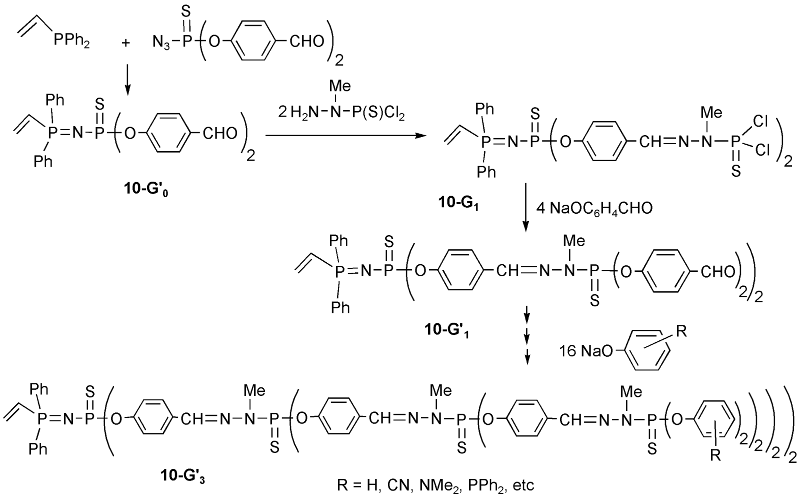


7-G$_3$

8-G$_4$(up to **8-G$_7$**)

9-G$_4$

Fig. 1 Dendrimers having phosphoryl groups instead of thiophosphoryl groups at some branching points.

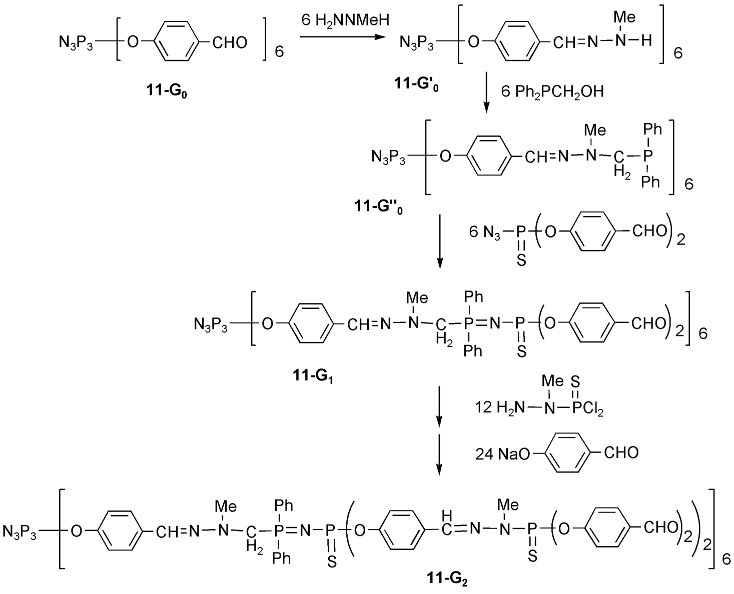


Scheme 7 Divergent synthesis of dendrons.

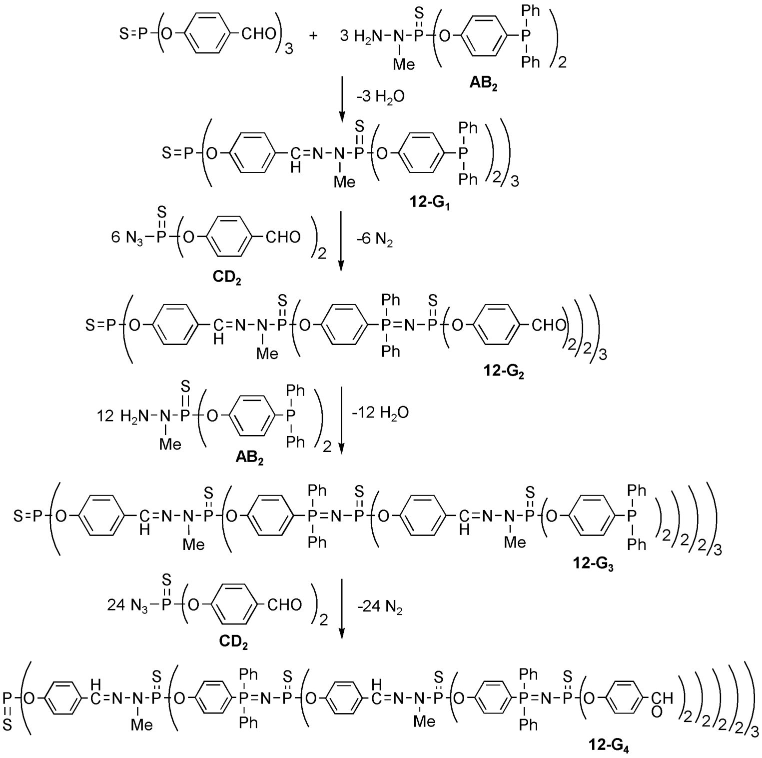
and two **B**-protected functions, with **A** able to react with deprotected **B**. The monomer **13** was treated with DABCO to deprotect the phosphines, which reacted readily with the azide, leading to the hyperbranched polymer **14**. A dendrimer having the same chemical composition was also synthesized step by step, in order to be able to compare the properties of both compounds. It was shown that the polymer **14** has a high polydispersity index, which precludes using it in place of dendrimers **15-G*n***[21] (Scheme 10).

Characterization by ^{31}P NMR

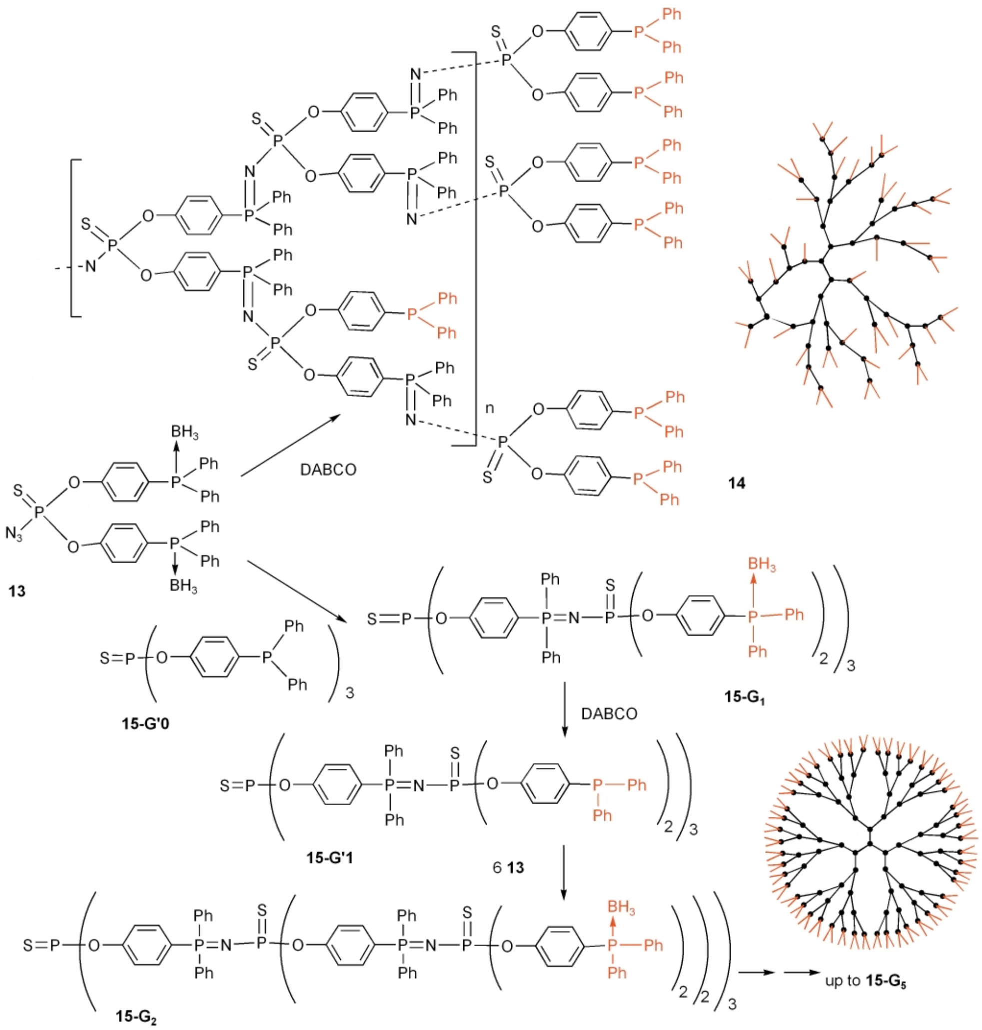
One of the main advantages of synthesizing phosphorus-containing dendrimers is the use of ^{31}P NMR, which is an extraordinary tool to characterize each step of the synthesis. For instance, the signals corresponding to each layer are clearly distinguishable for dendrimers **6-G*n*** and **6-G′*n*** ($n \leqslant 4$). Furthermore, the reaction **6-G*n*** → **6-G′*n*** ($n \leqslant 11$) induces a deshielding of the signal of the phosphorus that undergo the reaction, and the condensation reaction **6-G′*n*** → **6-G*n* + 1** ($n \leqslant 11$) induces both a shielding of the phosphorus bearing the benzaldehyde groups and the appearance of a new signal corresponding to the $n + 1$ layer. As an example, Fig. 2 displays the ^{31}P NMR spectra of dendrimers **6-G₃**, **6-G′₃** and **6-G₄**,[10] showing in particular the modifications of the chemical shift value corresponding to the phosphorus of the third generation (P_3, dashed lines). Remarkably the signal of the core (P_0) is distinguishable up to the sixth generation. In this case, the ratio P_0/P_6 is 1/96; this value gives the precision of the technique (at least 1%), thus, even one uncompleted substitution on the



Scheme 8 Synthesis of a dendrimer having P=N–P=S linkages.



Scheme 9 Rapid synthesis of dendrimers using AB₂ and CD₂ monomers.



Scheme 10 Synthesis of a hyperbranched polymer and a dendrimer having the same chemical composition.

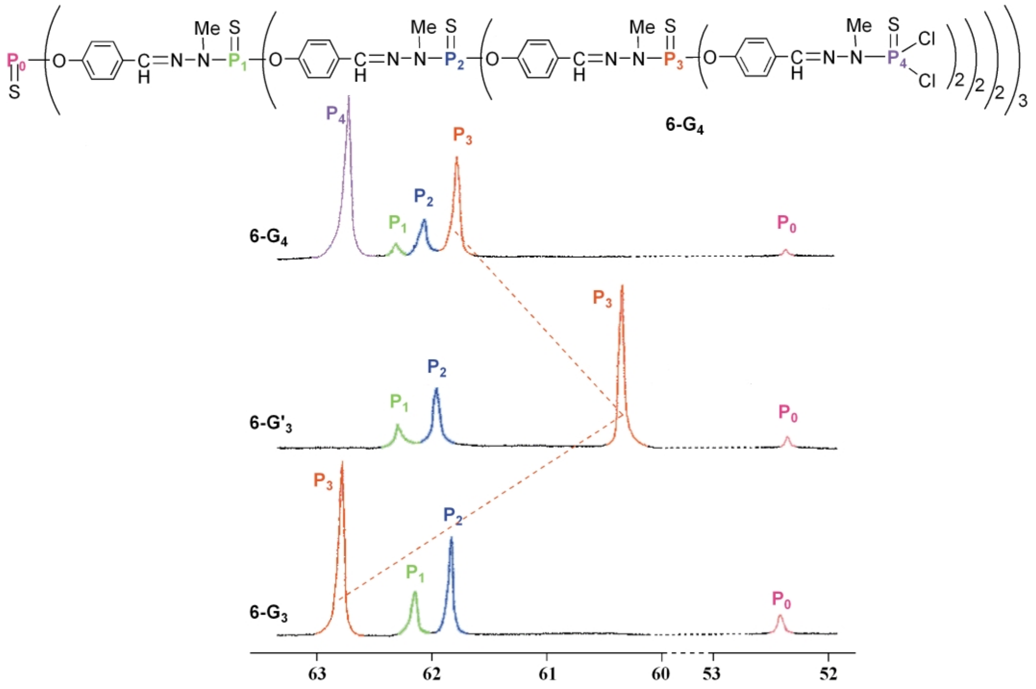


Fig. 2 ^{31}P NMR spectrum of dendrimers **6-G$_3$**, **6-G′$_3$** and **6-G$_4$**.

surface should be detectable up to this step.[22] For higher generations, an overlap of the signals corresponding to the internal layers is observed, but at least four signals corresponding to the most external layers are distinguishable even up to generation 12.[11]

The rapid synthesis of dendrimers shown in Scheme 9 was also monitored by ^{31}P NMR. Seven types of phosphorus signals are expected for **12-G$_4$**, four of them pertaining to P=N–P linkages should be doublets. Fig. 3 shows that all the expected signals are really observed.[20]

Some examples of reactivity of the end groups

We have carried out a huge number of reactions on the P(X)Cl$_2$ (X = S, O) and aldehyde end groups of dendrimers **6-G$_n$**, **6-G′$_n$**, and **9-G$_n$**.[23] Some of them are particularly worth to be mentioned, because they give several types of compounds seldom obtainable from other types of dendrimers. For instance, we have described, for the first time, dendrimers having three or even four different types of end groups simultaneously. We called this very special and so far unique type of functionalization ‘multiplurifunctionalization’. These compounds were generally obtained thanks to the ability of the P(X)Cl$_2$ (X = S, O) end groups to undergo a single substitution reaction, using primary or secondary amines. One example of a succession of reactions giving three, then four types of end groups is shown on Scheme 11.[13] Only one end group of dendrimers is shown to represent all the dendrimer; the global chemical structure of dendrimer **19-G$_3$** is shown in Fig. 4.

Another example of ‘multitrifunctionalization’ is also observed starting from the ‘multidifunctionalized’ dendrimer

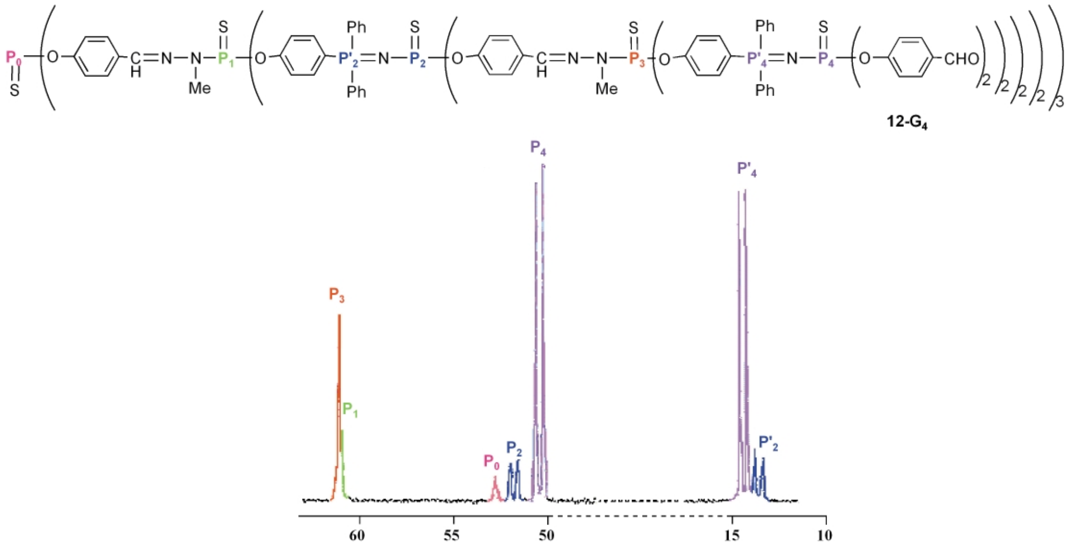


Fig. 3 ^{31}P NMR spectrum of the fourth generation of dendrimer **12**.

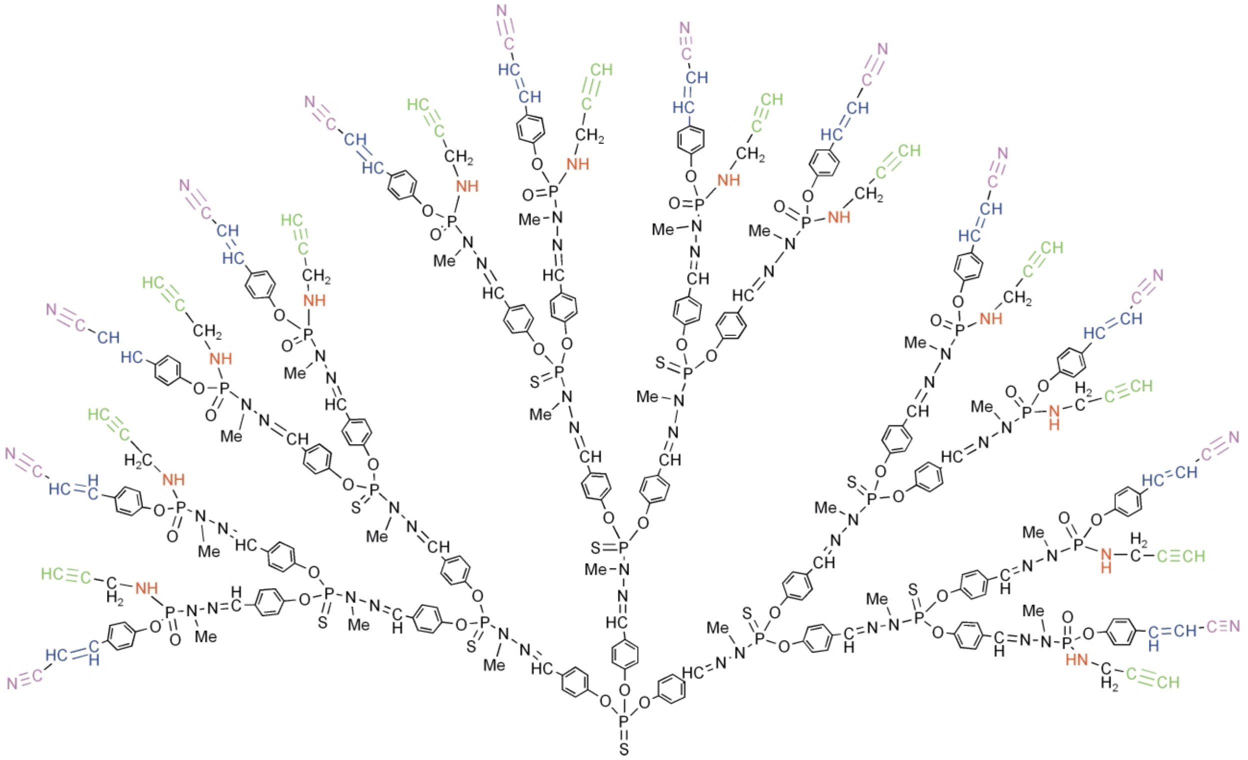
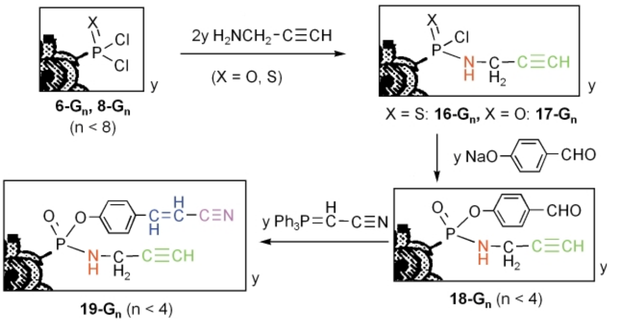
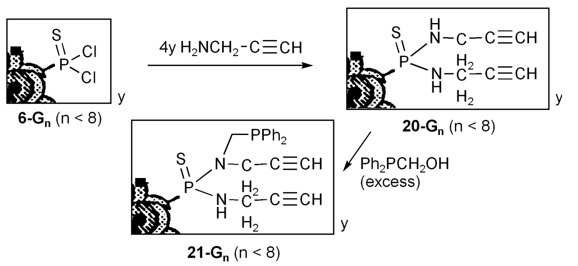


Fig. 4 Structure of dendrimer **19-G$_3$**, with four types of end groups.



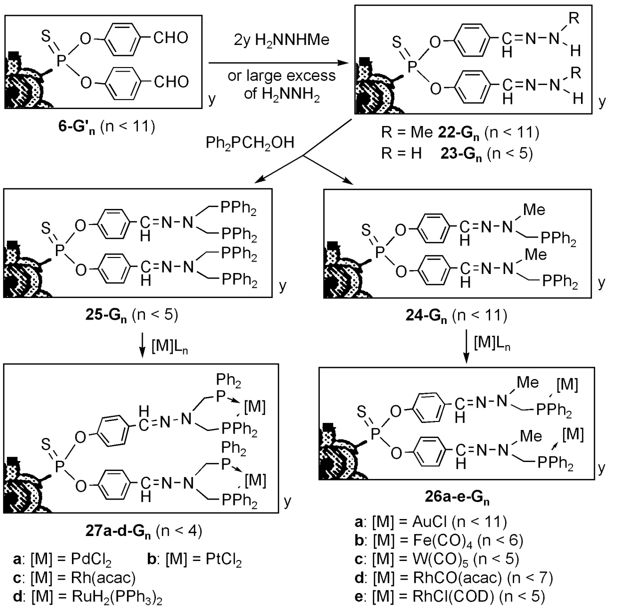
Scheme 11 Synthesis of 'multitri- and multitetra-functionalized' dendrimers.

20-G$_n$.[24] Indeed, Ph_2PCH_2OH reacts only with one NH group of each $P(S)(NHallyl)_2$ end group (Scheme 12).[25]



Scheme 12 Synthesis of 'multidi- and multitri-functionalized' dendrimers.

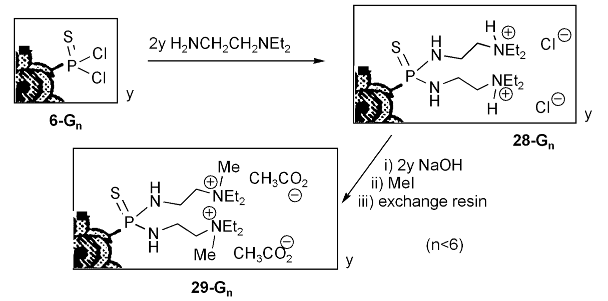
We used also Ph_2PCH_2OH to graft monophosphines or 1,3-diphosphines[26] on other types of dendrimers having NH or NH_2 end groups issued from the condensation of methylhydrazine or hydrazine with the aldehyde end groups[24] (Scheme 13).



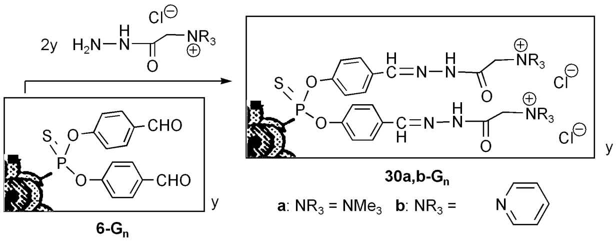
Scheme 13 Synthesis of dendrimers having phosphines or diphosphines as end groups, and some of their complexes.

Compound **24-G$_{10}$** is the largest dendritic polyphosphine synthesized up to now.[27] These compounds are able to complex various metallic derivatives. The monophosphine end groups were used for the complexation of Au–Cl (up to G$_{10}$),[27] $Fe(CO)_4$ (up to G$_5$), $W(CO)_5$ (up to G$_4$), RhCO(acac) (up to G$_6$) and RhCl(COD) (up to G$_4$).[28] Compounds **26a-G$_n$** were the first dendrimers ever synthesized possessing metallic phosphine complexes as end groups.[27] The diphosphine end groups were used in particular for the complexation of $PdCl_2$, $PtCl_2$, Rh(acac),[29] and $RuH_2(PPh_3)_2$,[30] up to generation 3 in all cases (Scheme 13).

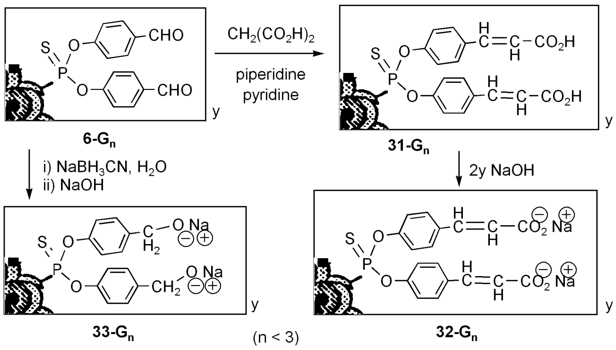
All the dendrimers described previously in this paper (except **4-G$_2$**) are soluble in a variety of organic solvents, but not in water. It appeared interesting to have water-soluble dendrimers, particularly for biological purposes. Thus, we tried several ways to modify the solubility of the phosphorus-containing dendrimers by modifying their end groups, starting generally from the $P(S)Cl_2$ (Scheme 14) or aldehydes (Schemes 15 and 16) end groups. The reaction of 2 equivalents of $H_2NCH_2CH_2NEt_2$ with each $P(S)Cl_2$ end group gives directly the water-soluble dendrimers **28-G$_n$**. The solubility of these dendrimers is pH dependent, whereas the solubility of dendrimers **29-G$_n$** is not (Scheme 14).[31]



Scheme 14 Synthesis of water-soluble dendrimers from $P(S)Cl_2$ end groups.



Scheme 15 Synthesis of water-soluble dendrimers from aldehydes



Scheme 16 Synthesis of polyanionic water-soluble dendrimers.

Other ammonium groups can be used to obtain water-soluble dendrimers, from aldehyde end groups. For instance, the condensation of various hydrazide derivatives of trimethylammonium or pyridinium,[32] affords water-soluble compounds (Scheme 15).

Besides ammonium groups, anionic groups such as carboxylates or alcoholates afford dendrimers soluble in water. A modified Doebner reaction of the aldehyde end groups with $CH_2(CO_2H)_2$ gives carboxylic acid end groups, whose reaction with NaOH affords the water-soluble dendrimers **32-G$_n$**. Reduction of the aldehyde groups, followed by reaction with NaOH gives another type of water-soluble dendrimers, **33-G$_n$**

(Scheme 16).[33] Finally, another way to obtain water-soluble dendrimers consists in condensation reactions between hydrazide end groups of dendrimers and various benzaldehydes functionalized by a carboxylic acid, a boronic acid or a carbohydrate.[34]

In contrast to most water-soluble dendrimers, which possess both hydrophilic interior and hydrophilic surface, all these phosphorus-containing dendrimers have a hydrophobic interior.

Reactivity of the internal layers

Most types of dendrimers can be functionalized on the surface after the repetitive synthesis, but very few can be chemically modified within the structure after the synthesis. Only one example concerning the reactivity of the internal layers was described by Newkome before our work; it consisted in the complexation of $Co_2(CO)_6$ by alkynes.[35] The P=N–P=S linkages included at precise places within the skeleton of some of our dendrimers (see for instance compound **11-G*n***) appeared very useful for post-synthetic modifications of dendrimers, due to the existence of a mesomeric form (P^+–N=P–S^-) which should favour the attack of electrophiles on sulfur.

In first attempts, we have shown the possibility to have charges exactly were desired, at some layers within the dendritic structure, using the chemiospecific alkylation of the sulfur included in P=N–P=S linkages by methyltrifluoromethane sulfonate[36] or various functionalized triflates;[37] the other P=S groups (not included in P=N–P=S linkages) do not react (Scheme 17). The reaction is easily monitored by ^{31}P NMR: the alkylation induces an important shielding of the signal corresponding to the thiophosphoryl groups from 52 ppm for **34-G$_1$** to 28 ppm for **35-G$_1$**, and a deshielding of the signal corresponding to the diphenylphosphino groups from 21 ppm for **34-G$_1$** to 33 ppm for **35-G$_1$**.[36]

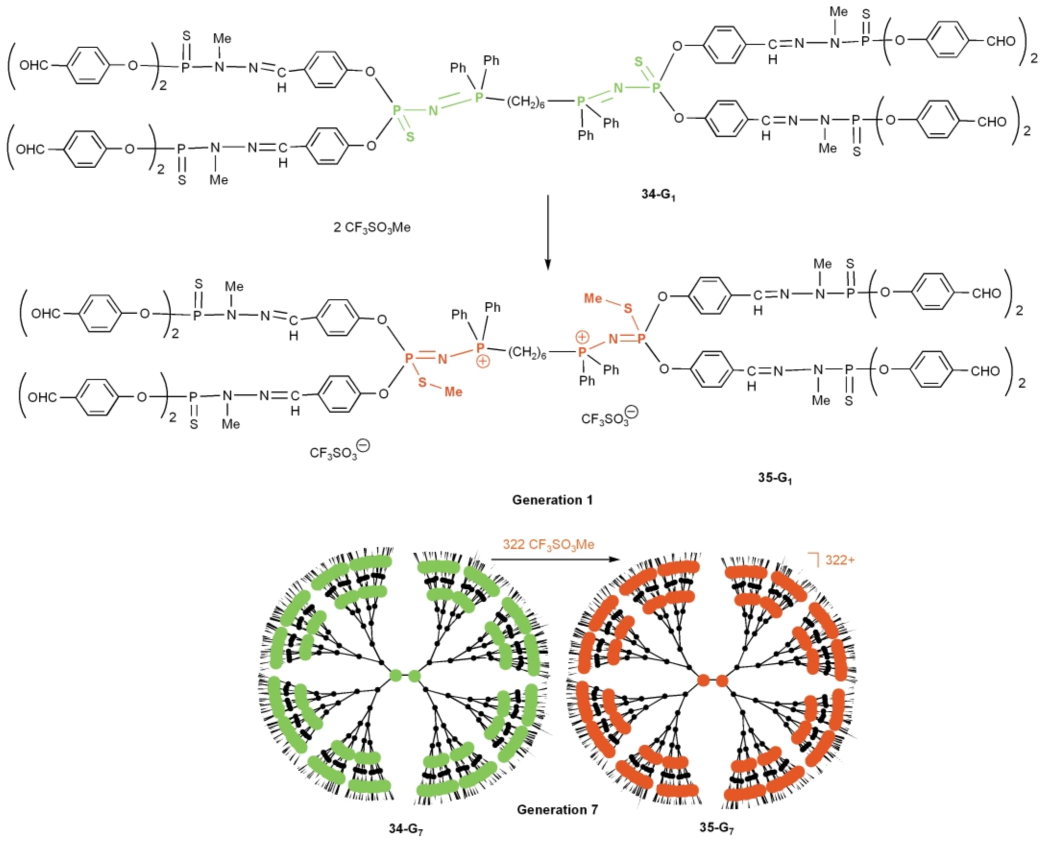
If the P=N–P=S linkages are located at several layers within the dendrimer, such as for compound **34-G$_7$**, which possesses these linkages at the level of the core, the fifth and the seventh layers, the alkylation occurs at all these particular layers (Scheme 17).[36] This reaction shows the high porosity of these dendrimers, since methyl triflate is able to penetrate right up to the core.

This alkylation reaction induces a weakening of the phosphorus–sulfur bond, which can be easily cleaved using nucleophilic phosphines such as $P(NMe_2)_3$.[38] This reaction gives tricoordinated phosphorus atoms inside the dendrimer, which can be used for several purposes, such as alkylation reactions, complexation reactions, and mainly Staudinger reactions.[39] These reactions are particularly interesting since they allow to use various functionalized azides, in order to bring new functions inside the dendrimer, such as isothiocyanates, primary amines, aldehydes,[39] or fluorescent labels.[40] The sequence of reactions (alkylation, desulfurization, Staudinger reaction with various azides) is illustrated on Scheme 18, starting from dendrimer **11-G$_3$**, which possesses 6 P=N–P=S functions.

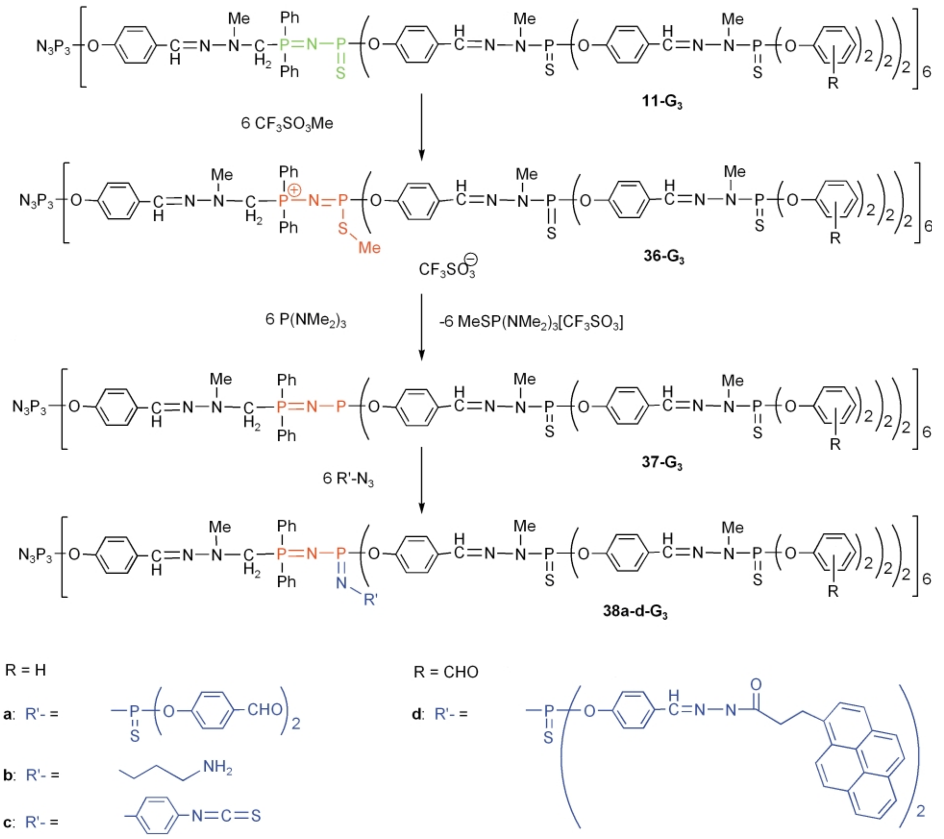
The presence of aldehydes inside the dendrimer is particularly important since it opens the way to a versatile and very original reactivity. Indeed, all the reactions that we have carried out previously on the surface can be accomplished also inside the dendrimer. As an example, Scheme 19 shows a condensation reaction with a NH_2 functionalized crown-ether, but we have also grafted phosphines and azides.[39]

These reactions demonstrate that there is enough space inside the dendrimer to accommodate large groups. Similar information was obtained from fluorescence data of dendrimer **38d-G$_3$**, which shows that the fluorescent labels move freely inside the dendrimer.[40] Thus we envisaged the very original possibility to grow new branches within a main dendrimer.

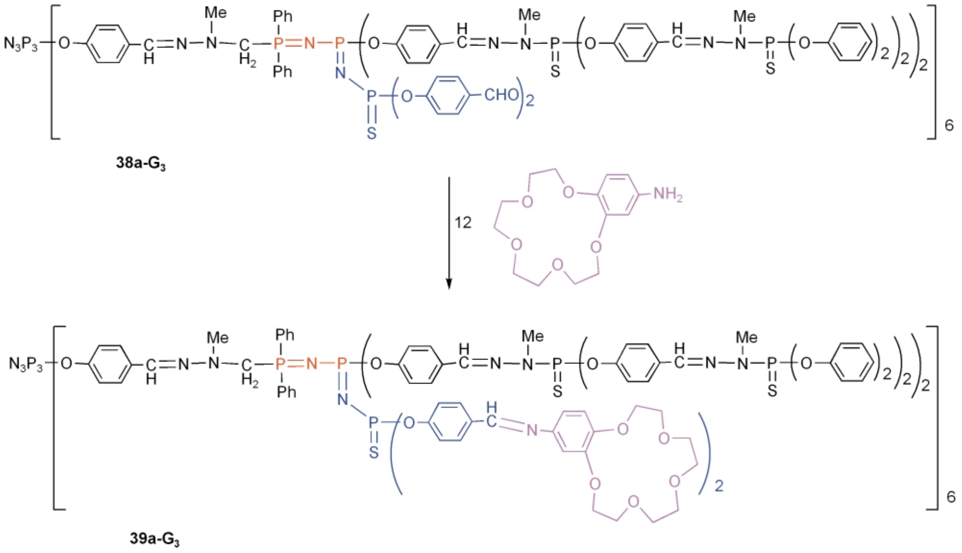
For this purpose, we tested two different ways of synthesis: the two-steps process already shown in Scheme 6, using $H_2NNMeP(S)Cl_2$ and hydroxybenzaldehyde, and the three-



Scheme 17 Synthesis of multicationic dendrimers having charges precisely where desired in the interior.



Scheme 18 Grafting of new functional groups inside dendrimers.



Scheme 19 Grafting of 12 crown-ethers inside a dendrimer.

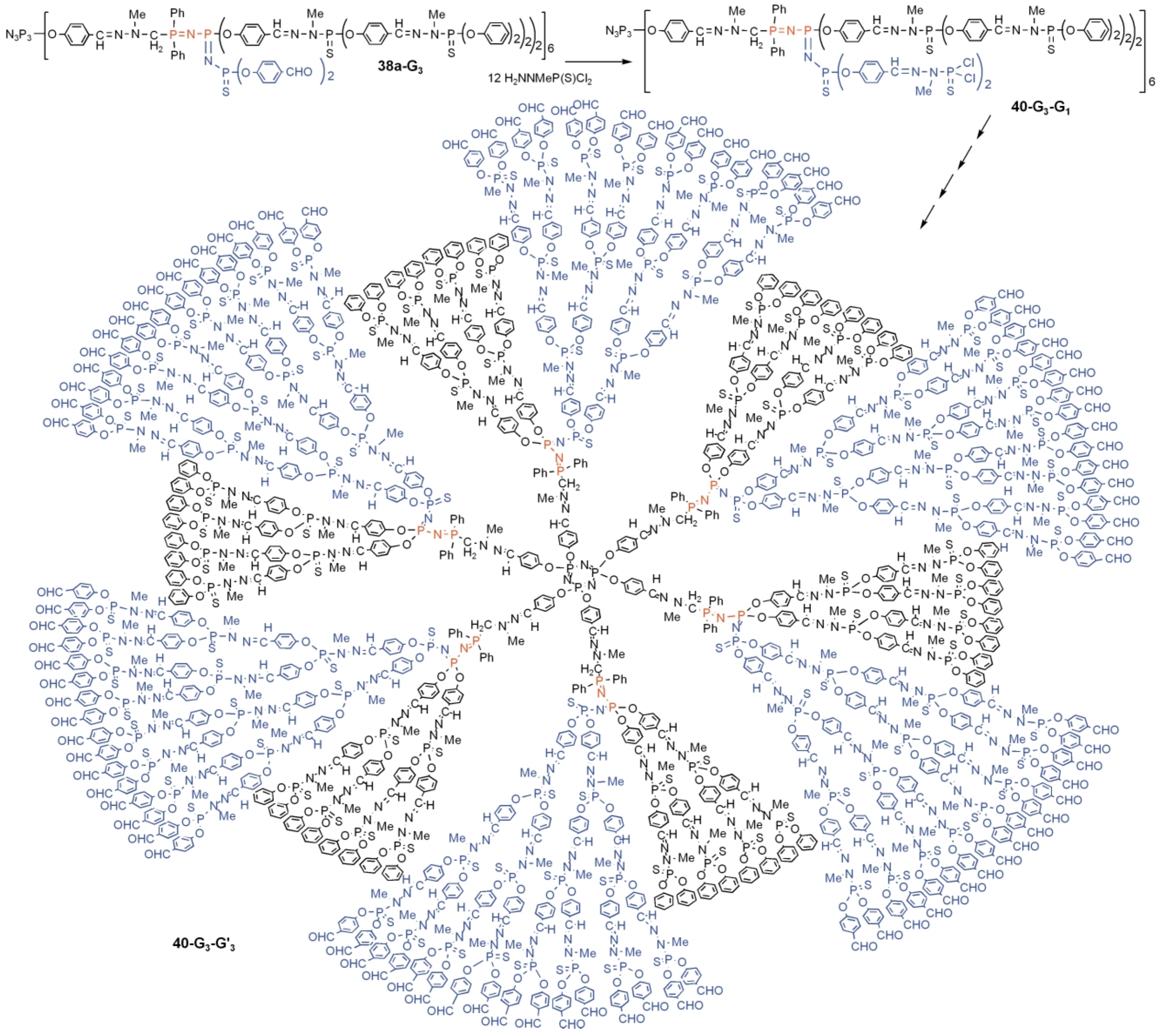
steps process shown in part in Scheme 8, using H_2NNMeH, Ph_2PCH_2OH, and $N_3P(S)(OC_6H_4CHO)_2$.[19] Both methods gave very unusual dendritic architectures. The two-steps process is illustrated in Scheme 20, and the three-steps process in Scheme 21.

At all steps, these compounds have functional internal groups, which can be used for the grafting of other functions. For instance, zwitter-ionic internal groups were grafted for the first time to dendrimers by reaction of **41-G$_3$-G′$_1$** with a zirconium derivative[41] (Scheme 21).

The presence of P=N–P=S linkages as constituents of some branches of compound **41-G$_3$-G′$_3$** allowed the regiospecific complexation of gold by these linkages[42] (Scheme 21). These reactions and many other examples concerning the internal reactivity of dendrimers were previously reviewed.[43]

Reactivity of the core

The vinyl group located at the core of dendron **10-G′$_n$** is activated by the P=N–P=S linkage, which allows Michael-type additions of various functionalized amines and hydrazines.[17] The functions newly grafted, particularly NH_2 functions, were used for further reactions, leading for instance by condensation reactions to the grafting of a diphosphine or an azide at the core of the dendron, such as compound **45-G$_4$** (Scheme 22). The



Scheme 20 Step-by-step growing of new branches in the interior of a dendrimer.

reactivity of these new functions gave rise to new dendritic architectures.[17]

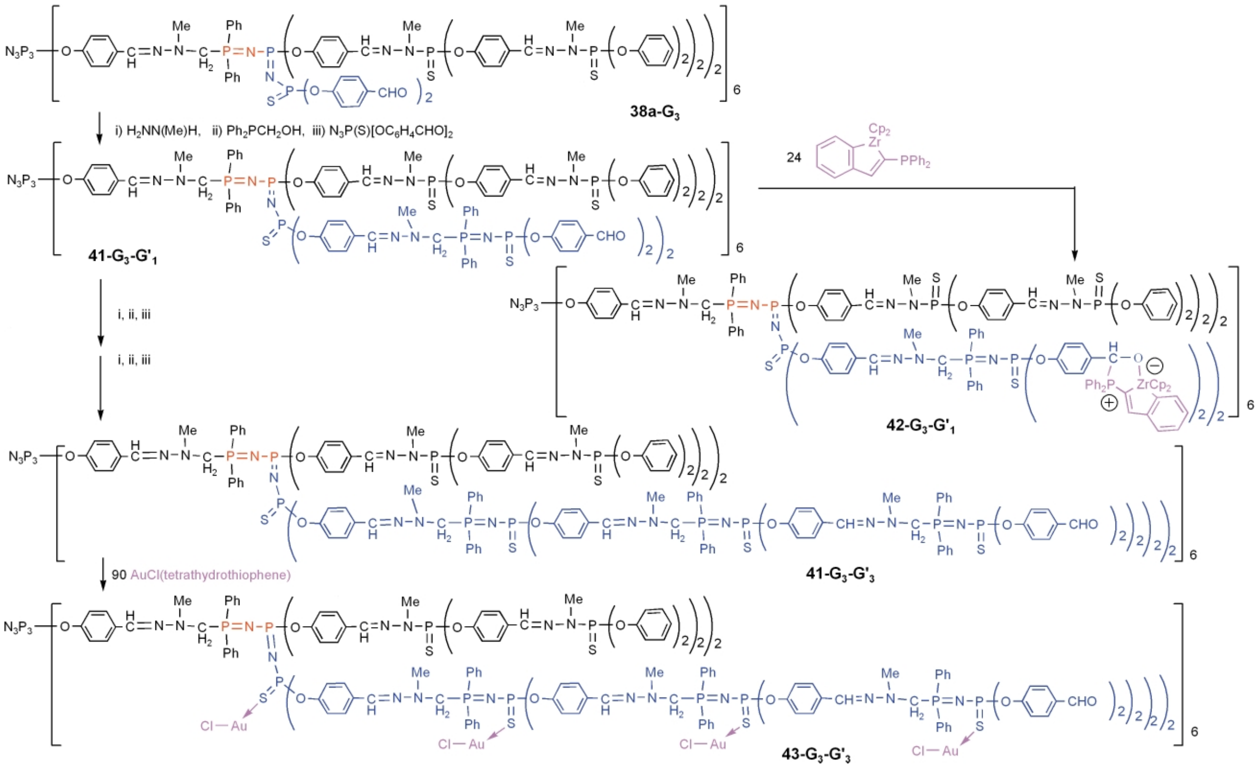
For instance, the ‘layer-block’[44] dendrimer **46-G$_8$**[17] was grown in one step from the third to the eighth generation (Scheme 23). The ‘surface-block’[44] dendrimer **48-G$_3$**[45] was obtained by associating two different dendrons by their core. This compound possesses two different types of end groups located in two different parts of the surface. The dissymmetrical dendrimer **49-G$_3$-G$_8$** (G$_3$ on one side, G$_8$ on the other side), was obtained using the reactivity of half of these end groups[45] (Scheme 24).

Furthermore, dendron **44-G$_3$** can be grafted directly inside dendrimer **38a-G$_3$**, leading in only one step[45] to compound **50-G$_3$-G$_3$**, reminiscent to **40-G$_3$-G′$_3$**, which was previously obtained in 6 steps. It is also possible to grow step by step a new dendron starting from the core of a dendron, in order to have other types of ‘surface-block’ dendrimers.[46] All types of compounds that we obtained starting from dendrons are illustrated in Fig. 5.

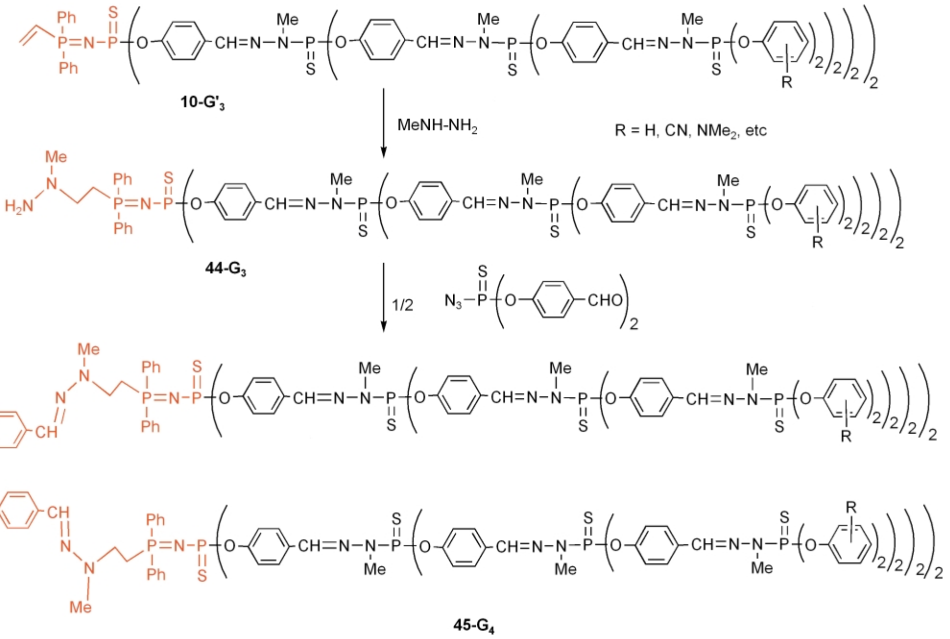
Some particular properties and applications

One original property of dendrimers **6-G$_n$** is their high dipole moment value, due to the presence of thiophosphoryl groups. An exponential increase is observed with increasing generations, up to 320 D for generation 11.[11] This is the highest value reported up to now for a dendrimer, despite the enormous compensation of the elemental vectors constituting the global dipole moment due to the almost spherical structure of these compounds.

However, the most widely studied property of phosphorus-containing dendrimers is catalysis. The presence of tricoordinated phosphorus atoms, generally on the surface, allows the complexation of various organometallic derivatives having catalytic properties. Dendritic catalysts are believed to combine the advantages of homogeneous catalysts, since they are soluble, and the advantages of heterogeneous catalysts since they should be easily recovered and reused, thanks to their large size. Many experiments have been conducted, with various types of dendrimers having phosphorus either at the branching points and the surface, or only on the surface, or at the core. In some cases, the catalytic properties were increased, in other cases decreased, compared to monomeric complexes possessing an analogous structure. For instance, we have carried out experiments using dendrimers **27a-G$_n$** for the catalysis of Stille coupling reactions, and dendrimers **27d-G$_n$** for the catalysis of Knoevenagel condensations.[47] We observed generally a slight increase of activity on going from the monomer to the first, then



Scheme 21 Repetition of a three-steps process to built new branches, and some examples of reactivity of these internal branches.

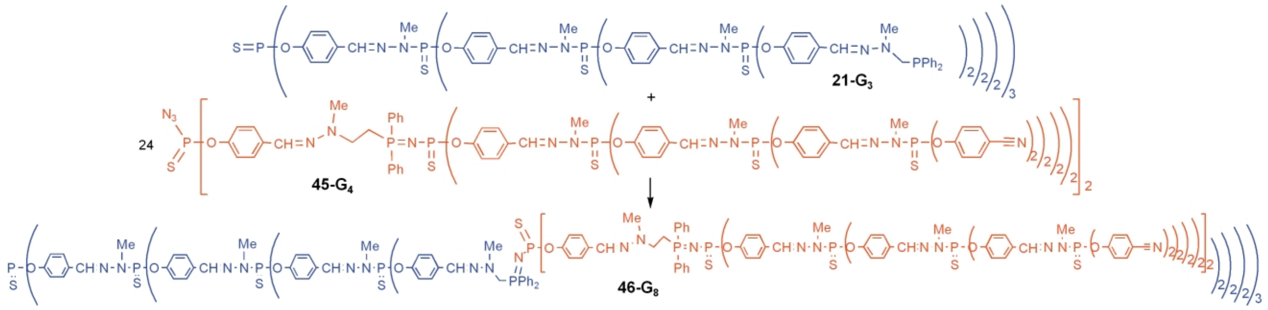


Scheme 22 Reactivity at the core of dendrons.

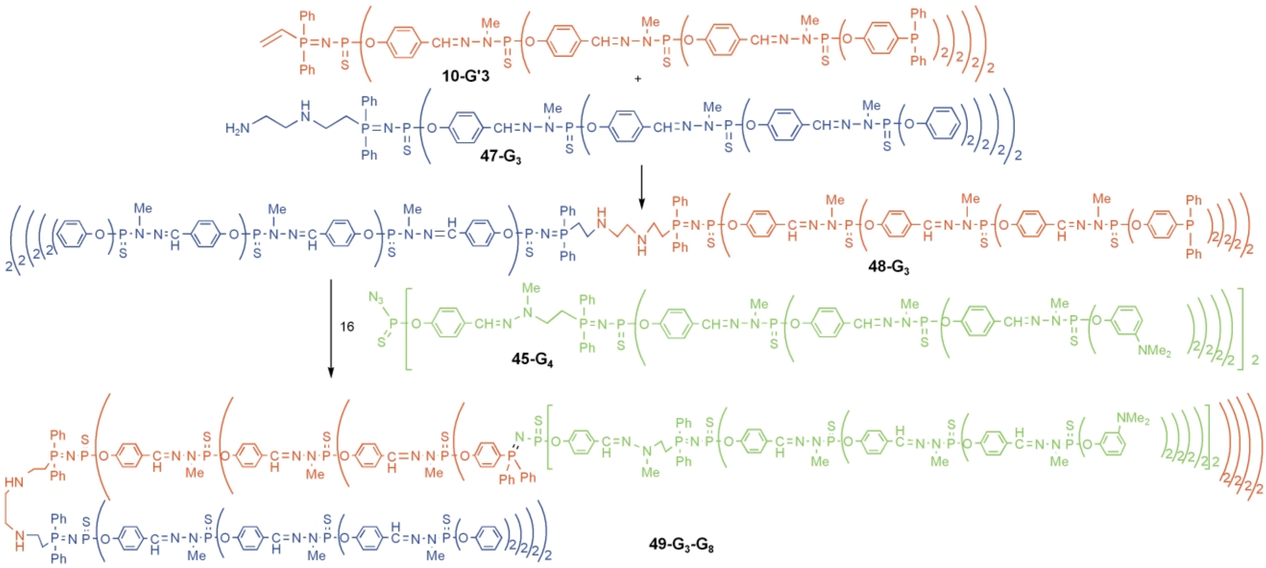
the third generation of the dendrimers. The most important point is that the third generation can be recovered by a simple precipitation with diethyl ether and reused at least three times without significant lost of activity.[47] Most of the catalytic experiments done with dendrimers having phosphorus as constituents of the structure or only as complexing agent were recently gathered as part of reviews,[48] or as the only topic of a review.[49]

Recently, we found an unexpected and so far unique property of some water-soluble phosphorus-containing dendrimers. Compounds **30a,b-G*n*** dissolved in water, even at low concentrations (0.25% in weight) are able to produce solid hydrogels when this solution is heated.[32] Thus, a single molecule of **30b-G$_4$** is able to gel up to 500000 molecules of water! These gels are translucent, they do not flow, and they can even be crushed into pieces. Hydrogen bonding and hydrophilic/hydrophobic interactions seem to play a major role in this phenomenon. During the gelation process, several types of water-soluble substances can be incorporated within the gel. A high loading of these substances can be incorporated, for instance up to 30% of nickel acetate.

Beside these specific properties, phosphorus-containing dendrimers share some properties with other dendrimers. Several types of dendrimers were used for the obtaining of new



Scheme 23 Synthesis of dendrimer **46-G$_8$** in one step from the third to the eighth generation.



Scheme 24 Synthesis of a surface-block dendrimer by associating two dendrons, followed by the synthesis of an unsymmetrical dendrimer.

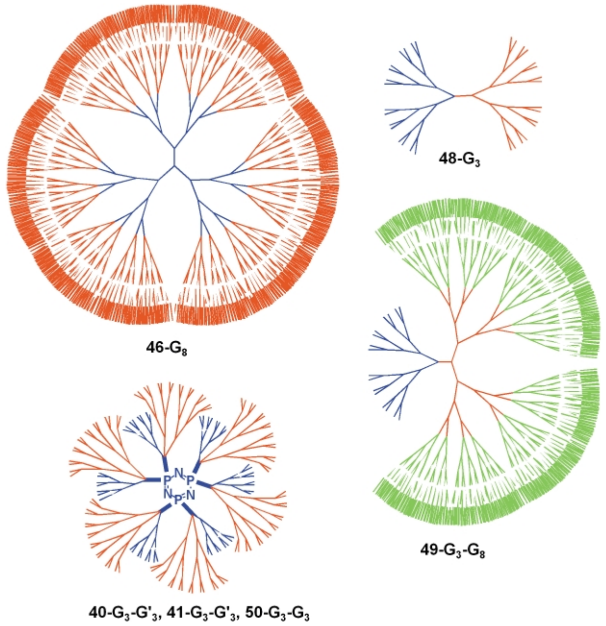


Fig. 5 Various dendritic architectures obtained from dendrons.

materials; we have also shown the usefulness of phosphorus-containing dendrimers in this field. For instance, the reaction of the neutral form of dendrimer **33-G$_1$** (alcohol end groups), or dendrimer **31-G$_1$** (carboxylic acid end groups) with a titanium cluster $Ti_{16}O_{16}(OEt)_{32}$ gives mesostructured solids in which dendrimers act as spacers for the clusters.[33] We also used dendrons having a triethoxysilyl group at the level of the core to build mesoporous functionalized silica.[50] Furthermore, thiol-terminated phosphorus-containing dendrimers were used for obtaining the first network of clusters of naked gold, which might have unusual properties in nanoelectronics.[51]

We have also used dendrimers to modify the surface of materials. For instance, electroactive derivatives such as ferrocenes,[52] TTF-crown ethers,[53] or bithiophenes[54] grafted to the external layer of dendrimers can be used to modify the surface of electrodes. The electrodeposition occurs onto the electrode during the oxidation process. Depending on the type of electroactive derivative, the modification of the electrode is either reversible (ferrocene or TTF end groups) or irreversible (bithiophene). We have shown sensing properties for some of them (TTF-crown ether), in particular for the detection of barium.[53] The surface of quartz plates can be also modified by dendrimers. The covalent grafting of dendrimer **6-G′$_4$** leads to plates usable for the immobilization of proteins, as shown by the aggregation of human serum albumin.[55]

Several types of dendrimers have found biological applications. One of the aims in this field concerns the delivery of active substances in a large sense, whatever the active substances are. Several types of interactions can be envisaged between a dendrimer and a substance to be delivered. The interaction can be (i) strongly covalent (A), (ii) weak through one (B) or several (C) end groups, (iii) in the internal layers, or (iv) through a network of dendrimers (E) (Fig. 6).

The trapping of various substances within the hydrogels obtained from dendrimers **30a,b-G$_n$** constitutes up to now the only examples of type (E) interaction.[32] We have also used types (A) and (B) interactions for the delivery of an insecticide (fipronil).[56] Some water-soluble phosphorus-containing dendrimers are also able to interact with biological substances

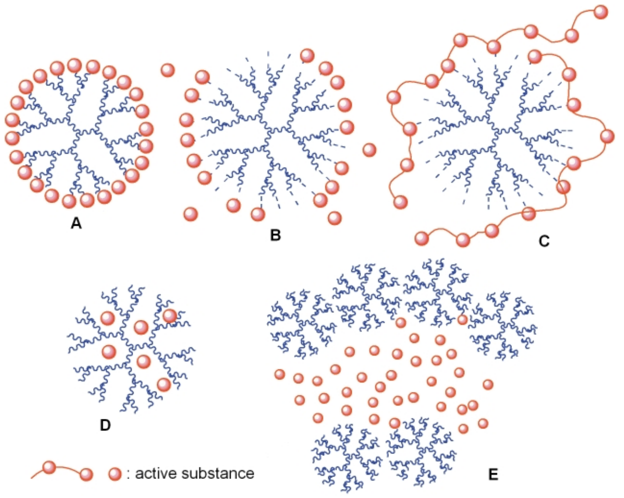


Fig. 6 Various types of interactions between dendrimers and 'active substances'.

through a type (C) interaction. We have shown for instance that dendrimers **28-G$_n$** and **29-G$_n$** can be used for transfection experiments. The efficiency depends on the generation and on the type of end groups; the best results are obtained with **28-G$_4$**.[31]

Finally, the glycol dendrimers **4-G$_n$** were tested as inhibitors of *Vicia villosa* binding to asialglycophorin; an enhanced affinity is observed compared to the efficiency of monomeric species.[7]

Conclusion and outlook

We have shown in this paper that phosphorus-containing dendrimers are not just another series of dendrimers, but that they have their own specificities, whatever the domain considered, synthesis, reactivity or study of properties.

Indeed, several new methods of synthesis were discovered, thanks to the versatile behaviour of phosphorus. The highest generation obtained up to now in dendrimer chemistry (generation 12), one of the most rapid methods of synthesis of dendrimers (multiplication of the number of end groups at each step), and the most environment-friendly method (water and nitrogen as unique by-products), relate to phosphorus-containing dendrimers.

The reactivity of the end groups of these dendrimers is amongst the most versatile and the most widely studied, but the most original reactivity was carried out in the internal layers. Indeed, the presence of P=N–P=S linkages allowed us to develop a so far unique palette of reactions inside the dendrimer, leading to the presence of charges, of several chemical functions such as amines, azides, or fluorescent derivatives, and even to the construction of new branches inside the dendrimer. The reactivity of dendrons synthesized by a divergent method also led to dendritic compounds having particularly original architectures.

Phosphorus-containing dendrimers share several properties with other types of dendrimers, for instance concerning catalysis, creation of new materials, modification of surfaces of materials, or transfection experiments. However, they have also some properties never reported up to now for other dendrimers, such as a high dipole moment value and the ability to form hydrogels even at low concentrations in water.

What is the future for phosphorus dendrimers? The extraordinary versatile chemistry of phosphorus should still lead to more efficient methods of synthesis. However, the most promising fields of research certainly will concern the applications of these compounds in various aspects of chemistry, biology, physics and material science. One can anticipate in particular that compounds having a hydrophobic interior and a hydrophilic surface should have valuable properties.

Notes and references

† Divergent methods consist in grafting small molecules on the surface of the dendrimer at each step. In contrast, convergent processes consist in grafting at least two dendrons[16] on one single molecule. Divergent methods are the most widely used for the synthesis of any type of dendrimers.

1 (*a*) Some very recent reviews concerning dendrimers: G. R. Newkome, F. Vögtle and C. N. Moorefield, *Dendrimers and dendrons*, John Wiley and Sons, 2001; (*b*) J. M. J. Fréchet and D. A. Tomalia, *Dendrimers and other dendritic polymers*, John Wiley and Sons, 2001; (*c*) D. C. Tully and J. M. J. Fréchet, *Chem. Commun.*, 2001, 1229; (*d*) S. M. Grayson and J. M. J. Fréchet, *Chem. Rev.*, 2001, **101**, 3819.
2 J. P. Majoral and A. M. Caminade, *Chem. Rev.*, 1999, **99**, 845.
3 K. Rengan and R. Engel, *J. Chem. Soc., Chem. Commun.*, 1990, 1084.
4 R. Engel, K. Rengan and C. S. Chan, *Heteroatom. Chem.*, 1993, **4**, 181.
5 A. Miedaner, C. J. Curtis, R. M. Barkley and D. L. DuBois, *Inorg. Chem.*, 1994, **33**, 5482.
6 M. Petrucci-Samija, V. Guillemette, M. Dasgupta and A. K. Kakkar, *J. Am. Chem. Soc.*, 1999, **121**, 1968.
7 R. Roy, *Top. Curr. Chem.*, 1997, **187**, 241.
8 G. Salamonczyk, M. Kuznikowski and A. Skowronska, *Tetrahedron Lett.*, 2000, **41**, 1643.
9 G. Salamonczyk, M. Kuznikowski and E. Poniatowska, *Chem. Commun.*, 2001, 2202.
10 N. Launay, A. M. Caminade, R. Lahana and J. P. Majoral, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1589.
11 M. L. Lartigue, B. Donnadieu, C. Galliot, A. M. Caminade, J. P. Majoral and J. P. Fayet, *Macromolecules*, 1997, **30**, 7335.
12 M. L. Lartigue, A. M. Caminade and J. P. Majoral, *Phosphorus, Sulfur Silicon*, 1997, **123**, 21.
13 M. L. Lartigue, M. Slany, A M. Caminade and J. P. Majoral, *Chem. Eur. J.*, 1996, **2**, 1417.
14 M. L. Lartigue, N. Launay, B. Donnadieu, A. M. Caminade and J. P. Majoral, *Bull. Soc. Chim. Fr.*, 1997, **134**, 981.
15 N. Launay, A. M. Caminade and J. P. Majoral, *J. Organomet. Chem.*, 1997, **529**, 51.
16 Dendrons are dendritic macromolecules having one function located at the core and several other functions located on the surface. The first dendrons were synthesized by Fréchet and Hawker using a convergent method: C. J. Hawker and J. M. J. Fréchet, *J. Chem. Soc., Chem. Commun.*, 1990, 1010; C. J. Hawker and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 1990, **112**, 7638.
17 V. Maraval, R. Laurent, B. Donnadieu, M. Mauzac, A. M. Caminade and J. P. Majoral, *J. Am. Chem. Soc.*, 2000, **122**, 2499.
18 C. Galliot, D. Prévoté, A. M. Caminade and J. P. Majoral, *J. Am. Chem. Soc.*, 1995, **117**, 5470.
19 C. Galliot, C. Larré, A. M. Caminade and J. P. Majoral, *Science*, 1997, **277**, 1981.
20 L. Brauge, G. Magro, A. M. Caminade and J. P. Majoral, *J. Am. Chem. Soc.*, 2001, **123**, 6698; L. Brauge, G. Magro, A. M. Caminade and J. P. Majoral, *J. Am. Chem. Soc.*, 2001, **123**, 8446 (erratum).
21 S. Merino, L. Brauge, A. M. Caminade, J. P. Majoral, D. Taton and Y. Gnanou, *Chem. Eur. J.*, 2001, **7**, 3095.
22 N. Launay, A. M. Caminade and J. P. Majoral, *J. Am. Chem. Soc.*, 1995, **117**, 3282.
23 J. P. Majoral and A. M. Caminade, *Top. Curr. Chem.*, 1998, **197**, 79.
24 N. Launay, M. Slany, A. M. Caminade and J. P. Majoral, *J. Org. Chem.*, 1996, **61**, 3799.
25 M. Slany, A. M. Caminade and J. P. Majoral, *Tetrahedron Lett.*, 1996, **37**, 9053.
26 A. M. Caminade, R. Laurent, B. Chaudret and J. P. Majoral, *Coord. Chem. Rev.*, 1998, **178–180**, 793.
27 M. Slany, M. Bardají, M. J. Casanove, A. M. Caminade, J. P. Majoral and B. Chaudret, *J. Am. Chem. Soc.*, 1995, **117**, 9764.
28 M. Slany, M. Bardaji, A. M. Caminade, B. Chaudret and J. P. Majoral, *Inorg. Chem.*, 1997, **36**, 1939.
29 M. Bardají, M. Kustos, A. M. Caminade, J. P. Majoral and B. Chaudret, *Organometallics*, 1997, **16**, 403.
30 M. Bardaji, A. M. Caminade, J. P. Majoral and B. Chaudret, *Organometallics*, 1997, **16**, 3489.

31 C. Loup, M. A. Zanta, A. M. Caminade, J. P. Majoral and B. Meunier, *Chem. Eur. J.*, 1999, **5**, 3644.

32 C. Marmillon, F. Gauffre, T. Gulik-Krzywicki, C. Loup, A. M. Caminade, J. P. Majoral, J. P. Vors and E. Rump, *Angew. Chem., Int. Ed.*, 2001, **40**, 2626.

33 M. K. Boggiano, G. J. A. A. Soler-Illia, L. Rozes, C. Sanchez, C. O. Turrin, A. M. Caminade and J. P. Majoral, *Angew. Chem., Int. Ed.*, 2000, **39**, 4249.

34 R. M. Sebastian, G. Magro, A. M. Caminade and J. P. Majoral, *Tetrahedron*, 2000, **56**, 6269.

35 G. R. Newkome, C. N. Moorefield and F. Vögtle, *Dendritic Molecules, Concepts, Synthesis, Perspectives*, VCH, Weinheim, 1996.

36 C. Larré, A. M. Caminade and J. P. Majoral, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 596.

37 C. Larré, B. Donnadieu, A. M. Caminade and J. P. Majoral, *J. Am. Chem. Soc.*, 1998, **120**, 4029.

38 (*a*) J. Omelanczuk and M. Mikolajczyk, *Tetrahedron Lett.*, 1984, **25**, 2493; (*b*) J. Omelanczuk, *J. Chem. Soc. Chem. Commun.*, 1992, 1718.

39 C. Larré, D. Bressolles, C. Turrin, B. Donnadieu, A. M. Caminade and J. P. Majoral, *J. Am. Chem. Soc.*, 1998, **120**, 13070.

40 L. Brauge, A. M. Caminade, J. P. Majoral, S. Slomkowski and M. Wolszczak, *Macromolecules*, 2001, **34**, 5599.

41 V. Cadierno, A. Igau, B. Donnadieu, A. M. Caminade and J. P. Majoral, *Organometallics*, 1999, **18**, 1580.

42 C. Larré, B. Donnadieu, A. M. Caminade and J. P. Majoral, *Chem. Eur. J.*, 1998, **4**, 2031.

43 J. P. Majoral, C. Larré, R. Laurent and A. M. Caminade, *Coord. Chem. Rev.*, 1999, **190–192**, 3.

44 (*a*) For the definition of 'layer-block' and 'surface-block' dendrimers, see: C. J. Hawker and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 1992, **114**, 8405; (*b*) C. J. Hawker, K. Wooley and J. M. J. Fréchet, *Macromol. Symp.*, 1994, **77**, 11.

45 V. Maraval, R. Laurent, S. Merino, A. M. Caminade and J. P. Majoral, *Eur. J. Org. Chem.*, 2000, 3555.

46 V. Maraval, R. M. Sebastian, F. Ben, R. Laurent, A. M. Caminade and J. P. Majoral, *Eur. J. Inorg. Chem.*, 2001, 1681.

47 V. Maraval, R. Laurent, A. M. Caminade and J. P. Majoral, *Organometallics*, 2000, **19**, 4025.

48 (*a*) R. Kreiter, A. W. Kleij, R. J. M. K. Gebbink and G. van Koten, *Top. Curr. Chem.*, 2001, **217**, 163; (*b*) D. Astruc and F. Chardac, *Chem. Rev.*, 2001, **101**, 2991; (*c*) G. E. Oosterom, J. N. H. Reek, P. C. J. Kamer and P. W. N. M. van Leeuwen, *Angew. Chem., Int. Ed.*, 2001, **40**, 1828; (*d*) L. J. Twyman, A. S. H. King and I. K. Martin, *Chem. Soc. Rev.*, 2002, **31**, 69.

49 A. M. Caminade, V. Maraval, R. Laurent and J. P. Majoral, *Curr. Org. Chem.*, 2002, **6**, 739.

50 C. O. Turrin, V. Maraval, A. M. Caminade, J. P. Majoral, A. Mehdi and C. Reyé, *Chem. Mater.*, 2000, **12**, 3848.

51 G. Schmid, W. Meyer-Zaika, R. Pugin, T. Sawitowski, J. P. Majoral, A. M. Caminade and C. O. Turrin, *Chem. Eur. J.*, 2000, **6**, 1693.

52 (*a*) C. O. Turrin, J. Chiffre, D. de Montauzon, J. C. Daran, A. M. Caminade, E. Manoury, G. Balavoine and J. P. Majoral, *Macromolecules*, 2000, **33**, 7328; (*b*) C. O. Turrin, J. Chiffre, J. C. Daran, D. de Montauzon, A. M. Caminade, E. Manoury, G. Balavoine and J. P. Majoral, *Tetrahedron*, 2001, **57**, 2521; (*c*) C. O. Turrin, J. Chiffre, D. de Montauzon, G. Balavoine, E. Manoury, A. M. Caminade and J. P. Majoral, *Organometallics*, 2002, **21**, 1891.

53 F. Le Derf, E. Levillain, A. Gorgues, M. Sallé, R. M. Sebastian, A. M. Caminade and J. P. Majoral, *Angew. Chem., Int. Ed.*, 2001, **40**, 224.

54 R. M. Sebastian, A. M. Caminade, J. P. Majoral, E. Levillain, L. Huchet and J. Roncali, *Chem. Commun.*, 2000, 507.

55 B. Miksa, S. Slomkowski, M. M. Chehimi, M. Delamar, J. P. Majoral and A. M. Caminade, *Colloid Polym. Sci.*, 1999, **277**, 58.

56 R. Göller, J. P. Vors, A. M. Caminade and J. P. Majoral, *Tetrahedron Lett.*, 2001, **42**, 3587.