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Dendrimers Containing Heteroatoms (Si, P, B, Ge, or Bi)

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I. Introduction

Dendrimers are highly branched regular three-dimensional monodisperse macromolecules with a branch occurring at each monomer unit. Large dendrimers adopt a globular shape. They are characterized by the presence of a large number of functional groups on the surface which results in solubility, viscosity, and thermal behaviors different from those of more classical polymers. They are also characterized by the presence of internal cavities which can be functionalized and by a core that does or does not bear functional groups (Figure 1).

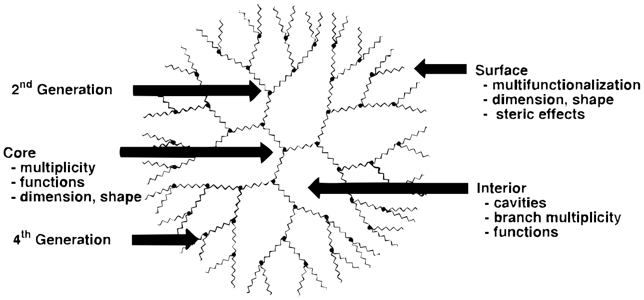

Figure 1. Representation of a dendrimer of generation 4.

Dendrimers are generally prepared using either a divergent method or a convergent one. In the divergent method dendrimers are built stepwise from a small polyfunctional core and through the reiteration of a sequence of reactions. This sequence of reactions allows one to build dendrimers layer after layer, i.e., generation after generation. The divergent approach should suffer from defects on the surface because of the high number of branches when the generation number increases. Excess reagent is needed and the required elimination of this excess may be a problem. The convergent method consists of the branching of dendrons (branched polymeric arms) using the reactivity of their core. The convergent method suffers from steric constraints when the dendrons supposed to be linked to the core become too large.

Historically, the first synthesis was reported in 1978 by Vögtle and co-workers[1] who prepared oligomeric nitrile terminated polyamines via a sequence of two reactions: Michael addition and then reduction of nitrile functions. The preparation was restricted to the synthesis of a dendrimer of generation 2 because of the formation of unwanted side products and the low yield of the reduction step. Later on two distinct synthetic strategies were used for the synthesis of dendrimers: the first is the divergent growth approach developed independently by the group of Tomalia[2] and the group of Newkome[3] in 1985, and the second one is a convergent synthesis proposed by Hawker and Fréchet in 1990.[4] Both methods consist of the reiteration of a sequence of reactions which allows to build the dendrimers generation after generation. Three patents between 1981 and 1983 from Denkewalter et al.[5] disclosed the synthesis of poly(lysine) dendritic macromolecules.

Following these pioneering works, studies on dendrimers increased exponentially: a number of reviews appeared in the last 5 years.[6] Most of these reviews are concerned with dendrimers with organic skeletons; a few are devoted to main group element-containing dendrimers.[7,8] The extraordinary diversity

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Jean-Pierre Majoral was born in Montauban, France, studied chemistry at the University Paul Sabatier in Toulouse, France, and received his Ph.D. in 1972. In 1972–1973 he worked with Prof. A. Katritzky, University of East Anglia, Norwick, U.K. He became Directeur de Recherche at the Centre National de la Recherche Scientifique in Toulouse in 1978. His research interests mainly focus on all aspects of main group elements chemistry with an emphasis on phosphorus chemistry. During the latter years, he has been 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 the recipient of several national and international awards and is the author of more than 250 papers, reviews, and patents.

Anne-Marie Caminade was born in 1958 in Carmaux, France. She received her 3rd cycle doctoral degree in 1984 and her Doctorat d'Université in 1988 from the Université Paul Sabatier, Toulouse, France. She became Chargée de Recherche at the Centre National de la Recherche Scientifique in 1985 in Dr. Jean Pierre Majoral's group. She joined Prof. Michael Veith's group in 1988–1989 in Saarbrücken, Germany, as a postdoctoral fellow of the Alexander von Humboldt Foundation. She was awarded a bronze medal from the CNRS in 1989. She has been Directeur de Recherche at the CNRS in Toulouse since October 1997. Her research interest focuses on main group elements, especially phosphorus. She developed several aspects of the chemistry of phosphorus, including low-coordinated compounds, transition metal coordination, reactivity with metallic hydrides, phosphorus-containing macrocycles, and cryptands. Her current research interest is the synthesis, reactivity, and study of the properties of main group elements containing dendrimers.

of the chemistry of silicon and phosphorus was expected to stimulate similar research work, but surprisingly dendrimers incorporating these elements have attracted attention only in the late 1980s although the corresponding linear polymers have been found to present useful properties for industrial applications.

This review covers the literature concerning the synthesis, reactivity, properties, and applications of dendrimers incorporating main group elements (inorganic elements), i.e., not only silicon or phosphorus, but also boron, germanium, and bismuth, up to the middle of 1998. Papers concerning dendrimers incorporating nitrogen or transition metals at the branching point as well as hyperbranched polymers are not reported here.

II. Silicon-Containing Dendrimers

Silicon-based dendrimers were the first heteroatom-containing dendrimers being synthesized as far back as 1989.[9] Three types of linkages are used at the branching points: siloxane (Si−O), carbosilane (Si−C), or silane (Si−Si) groups. The first examples described in 1989 were polysiloxane type dendrimers, containing SiO_3C linkages.[9] Carbosilane type dendrimers containing SiC_4 linkages at all the branching points were synthesized in and after 1992 and are the most important class of silicon-containing dendrimers, due to their excellent chemical and thermal stability and to the possibility of synthesizing these molecules to high generations (up to generation 7). Polysilane type dendrimers containing $SiSi_4$ linkages are known since 1995 and have been synthesized only for low generations (generations 1 and 2).

This section concerns first the methods of synthesis of silicon-containing dendrimers. The reactivity, which has been carried out mainly with surface functional groups of carbosilane type dendrimers, is reviewed after the methods of synthesis. Finally the characterization and study of properties of these macromolecules will be described.

A. Methods of Synthesis

Most of the methods used to synthesize silicon-containing dendrimers are divergent methods, only a few examples concern convergent syntheses.

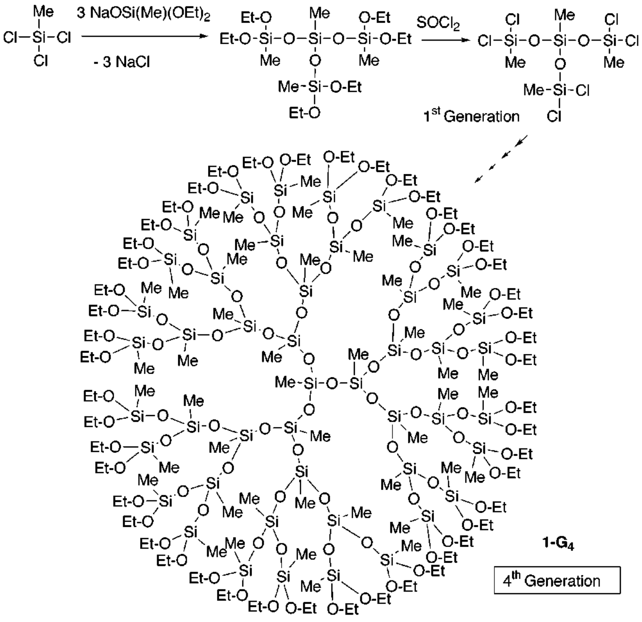
1. Synthesis of Siloxane Type Dendrimers

The first heteroelement-containing dendrimers were synthesized by Rebrov et al. up to the fourth generation.[9] The synthesis consists of the repetition of two steps starting from a trifunctional core such as methyltrichlorosilane: the first step is a nucleophilic substitution of the chlorosilyl groups by diethoxyhydroxymethylsilane sodium salt, and the second step is the reaction of $SOCl_2$ with the ethoxysilane end groups to yield Si−Cl end groups (Scheme 1). The repetition of these two steps has been accomplished up to the fourth generation (**1-G$_4$**) which possesses 48 ethoxy end groups.

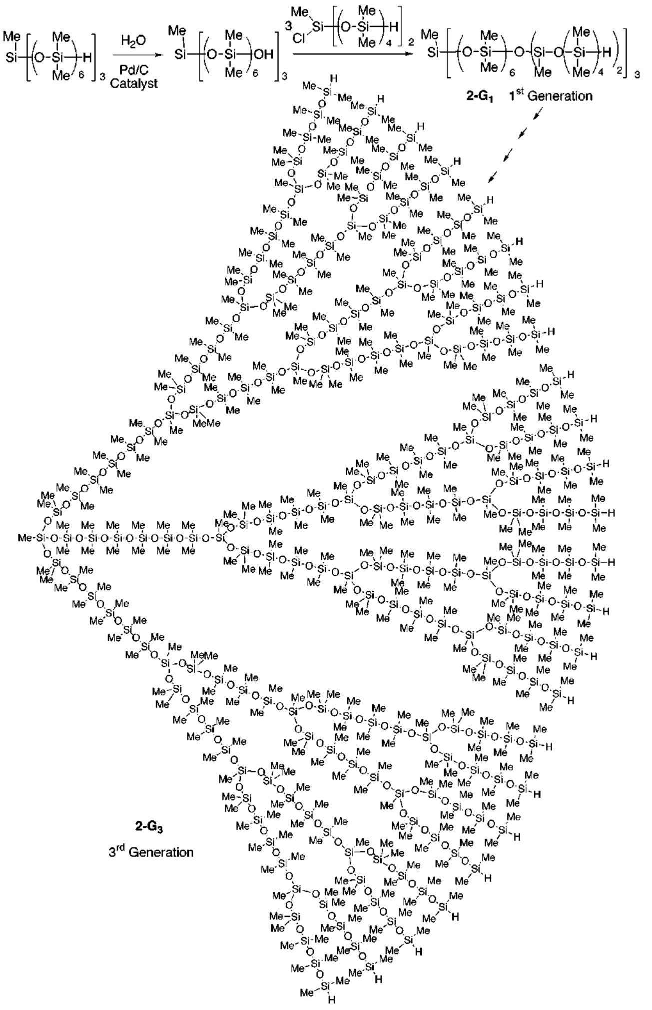
A series of oligosiloxane dendrimers with longer branches was developed in 1990.[10] These dendrimers are also built by the repetition of two steps from a trifunctional core (Scheme 2). The first step is a catalytic oxidation of Si−H linkages to Si−OH linkages; the second step is a substitution of OH groups by a silane. The reiteration of these two steps has been carried out up to the third generation, **2-G$_3$**.

Analogous siloxane dendrimers can be obtained by repetition of a sequence of three reactions from a trifunctional core:[11,12] (i) reaction of bromine with phenylsilane end groups to give bromosilanes, (ii)

Scheme 1

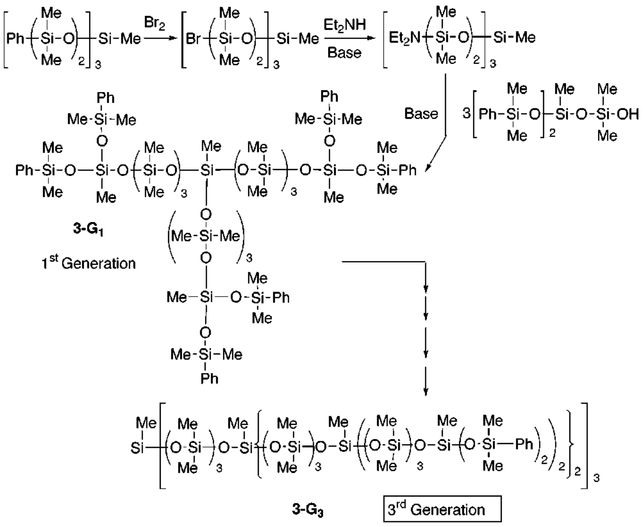


Scheme 2



reaction of diethylamine with bromosilane end groups, and (iii) coupling of diethylaminosilane end groups with a silanol which bears two phenylsilane groups (Scheme 3). This synthesis has been carried out up to the third generation, **3-G$_3$**.

Scheme 3

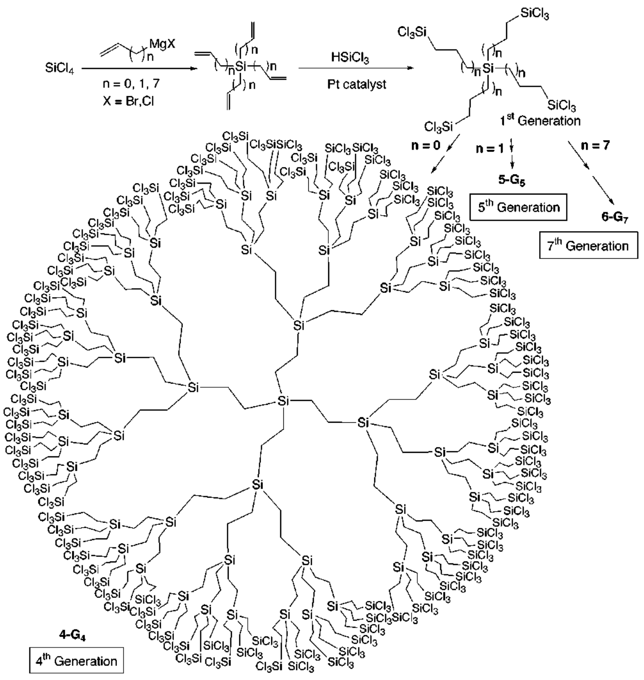


2. Synthesis of Carbosilane Type Dendrimers

All carbosilane dendrimers are synthesized in very good yields by using alternate alkenylation with Grignard reagents and hydrosilylation. Side reactions such as α-addition of hydrosilylation or dehydrogenation are generally avoided by a careful control of the temperature and the choice of the solvent used during the hydrosilylation. However, a tendency of polyallylic systems, beginning with the fourth generation, to cross-link on aging is observed.[13] Several types of carbosilane dendrimers have been obtained: the branch length depends on the length of the alkyl chain of the Grignard reagent used, and the branching multiplicity depends on the type of hydrosilylating agent, such as $HSiCl_3$ or $HSiCl_2Me$, that is used.

$SiCl_4$ is used as core in most cases to react with an alkenylmagnesium derivative. The alkene groups thus grafted are hydrosilylated, for example, with $HSiCl_3$ (Scheme 4). van der Made et al. have carried

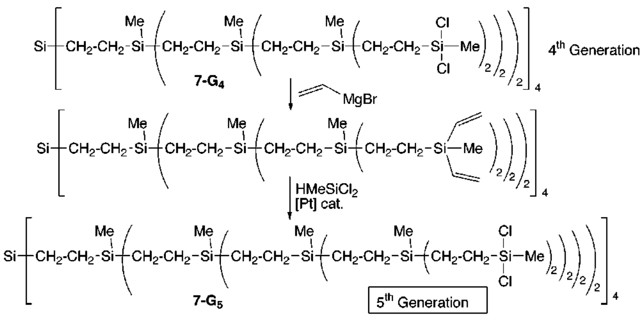
Scheme 4



out these reactions with several alkenyl derivatives having various chain lengths and have shown that the highest generation obtainable in each case depends on the length of the alkenyl group.[14] The seventh-generation dendrimer **6-G$_7$** is the largest; it has been obtained only with the decenyl derivative. The allyl derivative allows the synthesis of the dendrimer up to the fifth generation (**5-G$_5$**), whereas the synthesis with the vinyl derivative has been carried out up to the third generation by van der Made et al.[15] and to the fourth generation (**4-G$_4$**) by Seyferth et al.[16]

This method of synthesis allows several types of modifications. For instance, dichloromethylsilane can be used instead of trichlorosilane.[17,18] Scheme 5 describes the last steps of the synthesis which has been carried out up to the fifth generation, **7-G$_5$**. Several other types of carbosilane dendrons[19] and dendrimers are gathered in Figure 2. Dendrimer **8-G$_2$** is obtained using allyl derivatives;[20] dendrimer **9-G$_3$**[21] has been built up to the third generation with $HSiMeCl_2$ and $BrMgCH_2CH{=}CH_2$ from the hexaallyl core $[CH_2Si(CH_2CH{=}CH_2)_3]_2$. The synthesis has been also carried out up to the fourth generation using Cl_3SiH, $BrMgCH_2CH{=}CH_2$, and the diallyl core $PhMeSi(CH_2CH{=}CH_2)_2$ to afford dendrimer **10-G$_4$** (Figure 2).[22]

Scheme 5



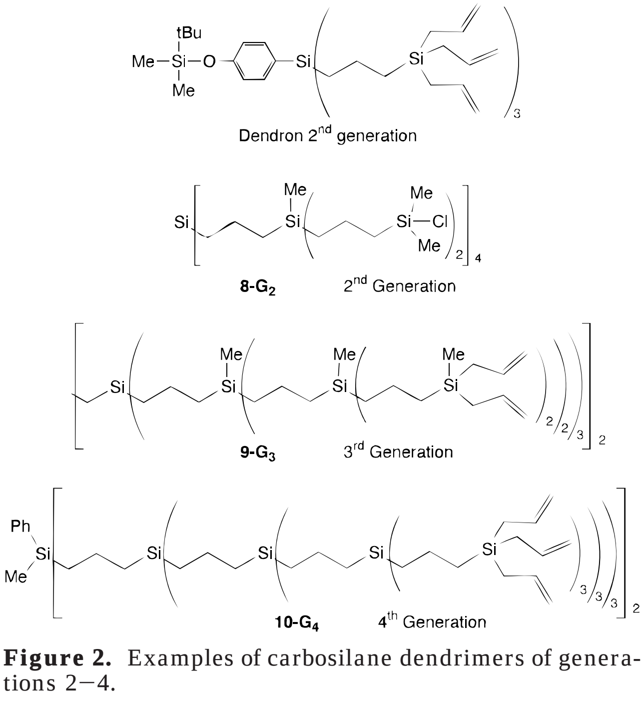


Figure 2. Examples of carbosilane dendrimers of generations 2−4.

Another modification of this process consists of using alkynyl groups instead of allyl or vinyl groups. Thus, the successive reactions of $HSiMe_2Cl$ and $LiC{\equiv}CPh$, starting from $Si(C{\equiv}C{-}Ph)_4$, lead to the formation of the third generation, **11-G$_3$** (Figure 3).[23] The first generation of another type of carbosilane dendrimer composed of 16 thiophene rings has been prepared recently. Treatment of tetra-2-thienylsilane with 4 equiv of BuLi and then with 4 equiv of methyl tri-2-thienylsilyl ether gives a complex mixture from which the first generation (**12-G$_1$**) is recovered in 19% yield by chromatography (Scheme 6).[24]

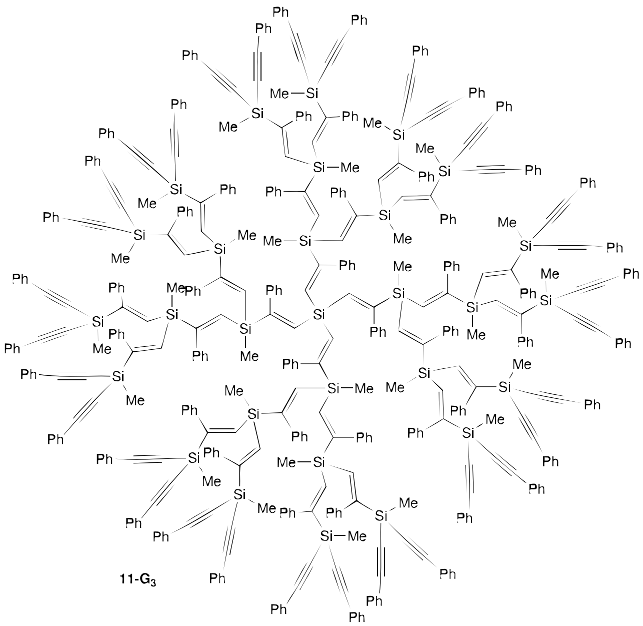
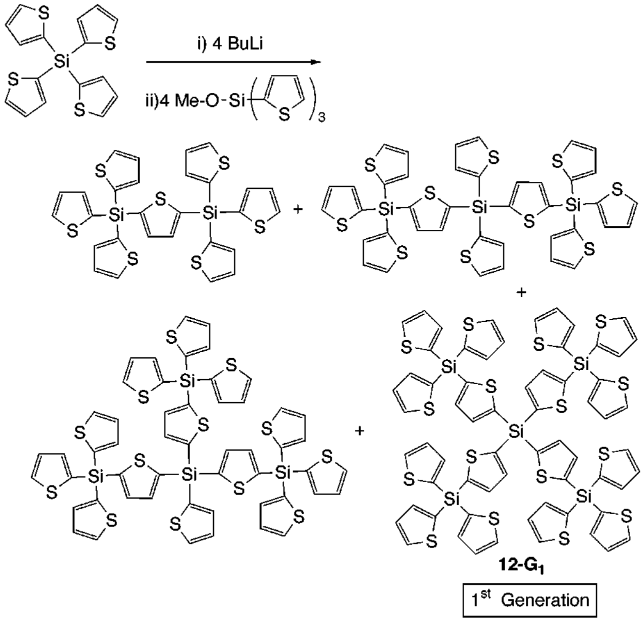


Figure 3. Third generation of an unsaturated dendrimer.

Scheme 6

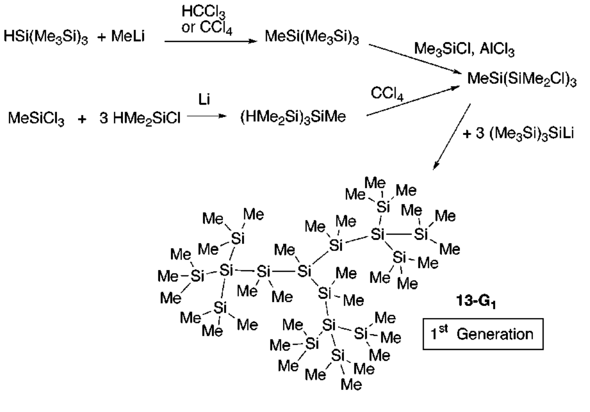


3. Synthesis of Silane Type Dendrimers

The first polysilane dendrimer **13-G$_1$** was described independently by Lambert et al.[25] and Suzuki et al.[26]

in 1995. In both cases, the last step is a coupling between methyl[tris(chlorodimethylsilyl)]silane and tris(trimethylsilyl)silyllithium which affords the dendrimer of generation **1** that contains 15 Si atoms (Scheme 7). Lambert et al. have also developed the synthesis of other first- and second-generation polysilane dendrimers **14-G$_2$** and **15-G$_1$**, respectively (Figure 4), that contain Si–Si bonds.[27] The branches of polysilane dendrimers **16-G$_1$**[28] and **16-G$_2$**[29] also contain Si–Si bonds. **16-G$_2$** is synthesized by the repetition of two steps: (i) cleavage of Si–Me bonds with triflic acid and (ii) formation of Si–Si bonds (Scheme 8).

Scheme 7



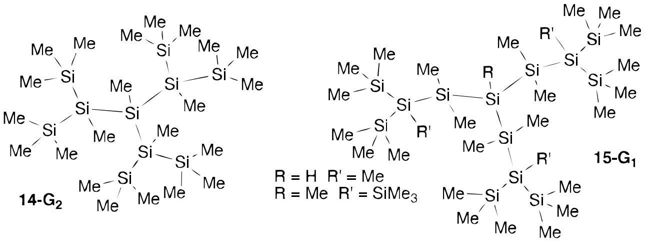
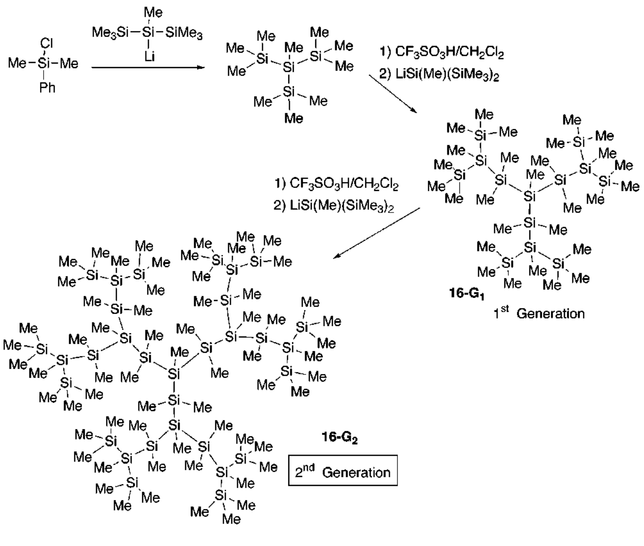


Figure 4. Silane type dendrimers.

Scheme 8

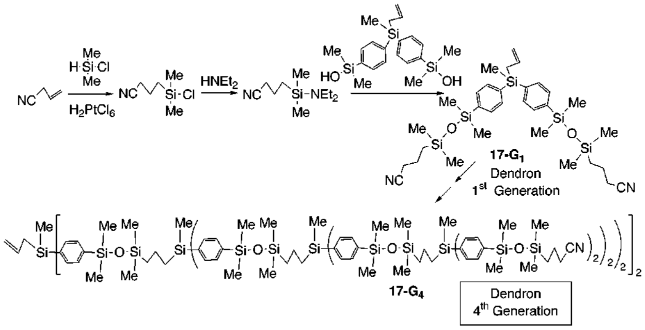


4. Synthesis of "Hybrid" Dendrimers

Several silicon-containing dendrimers contain either two types of silicon units, such as siloxane and carbosilane, or two different elements, such as silicon and phosphorus or silicon and germanium; these are "hybrid" dendrimers.

a. Siloxane–Carbosilane. Kakimoto and co-workers[30] have described the first siloxane–carbosilane dendrimer, obtained by a convergent method. In this case, the branching points are constituted of carbosilane groups, and the branches include linear Si–O–Si linkages. The synthetic sequence has three reaction steps: (i) hydrosilylation with chlorodimethylsilane, (ii) grafting of diethylamine, and (iii) coupling between the diethylaminodimethylsilyl groups with Si–OH groups. Reiteration of these three steps was carried out up to the formation of the fourth-generation dendron **17-G$_4$** (Scheme 9). Three equivalents of the third-generation dendron have been grafted on a trifunctional core to afford a third-generation dendrimer **18-G$_3$** which bears 24 nitrile functions on the surface (Scheme 10).

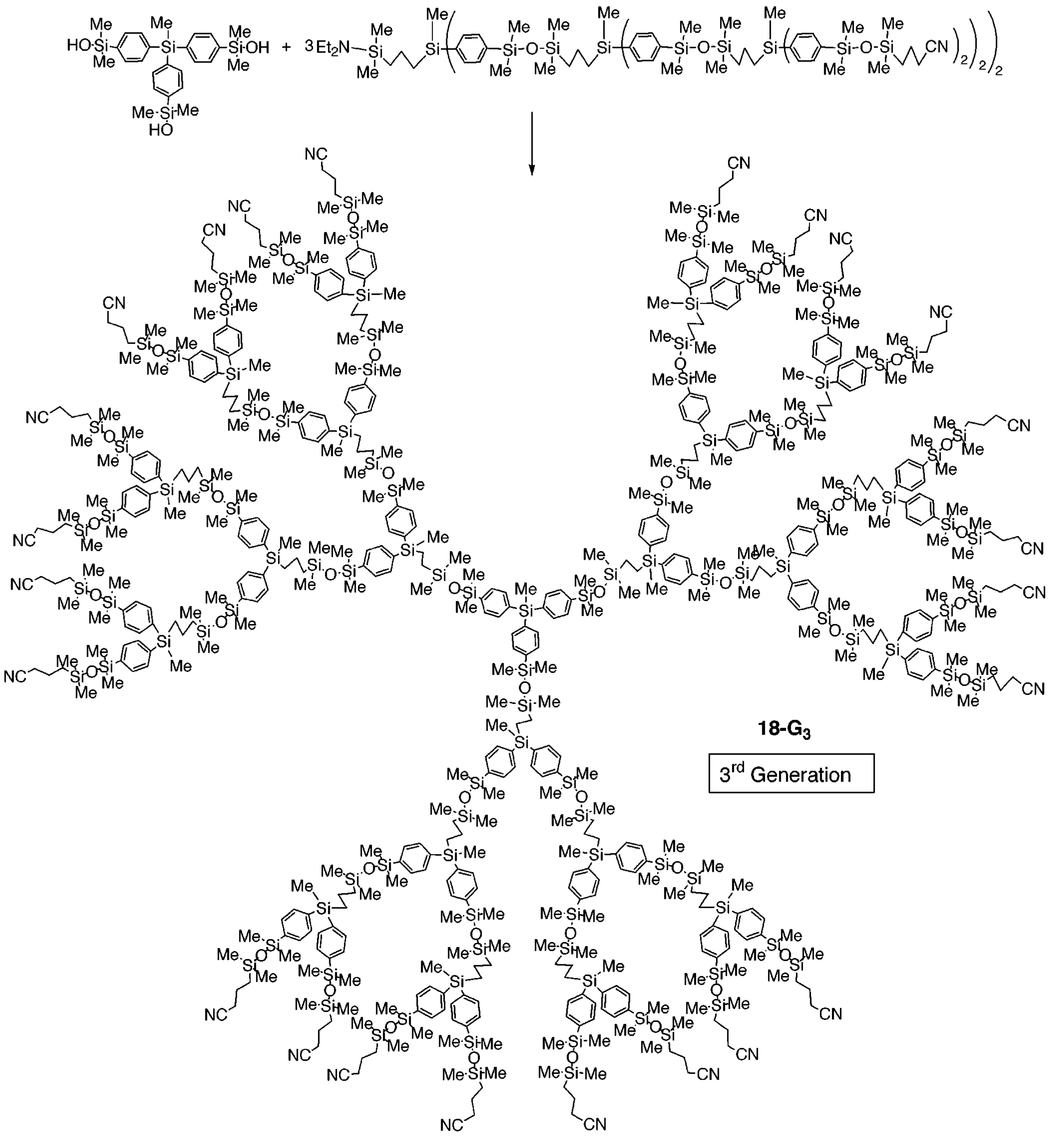
Scheme 9



Combination of convergent and divergent methods leads to the formation of another type of siloxane–carbosilane dendrimer.[31] The last step of the synthesis is the coupling of 8 equiv of a siloxane dendron on a carbosilane core by hydrosilylation (Scheme 11). The final dendrimer **19-G$_3$** possesses two types of branching points: carbosilane groups for the core and the first generation and siloxane groups for the other branching points and in the branches. An analogous hydrosilylation reaction carried out with siloxane dendrons on a trifunctional carbosilane core linked to a pyrenyl moieties leads to the formation of **20-G$_2$** (Scheme 12).[32,33] Recently, the formation of carbosilane dendrimers grown up to the third[34] or fourth[35] generation such as **21-G$_4$** from a siloxane tetramer core by the alternative use of hydrosilylation and alkenylation reactions already described for carbosilane dendrimers has been reported (Scheme 13). Small dendrimers have been obtained from another siloxane type core, silsesquioxane. The reaction has been carried out with $H_2C{=}CH(CH_2)_3OSiMe(OSiMe_3)_2$ on $H_8Si_8O_{12}$, leading to the first generation,[36] and with $HSiCl_3$ and $CH_2{=}CHMgBr$ on $Si_8O_{12}(CH{=}CH_2)_8$, leading to the second generation (**22-G$_2$**) (Scheme 14).[37]

b. Silicon–Other Heteroelement. The first dendrimer incorporating both silicon and another heteroelement was obtained by DuBois and co-workers.[38] The last step of the synthesis is a hydrophosphorylation reaction of the tetravinylsilane core with 4 equiv of a triphosphine dendron leading to the second

Scheme 10

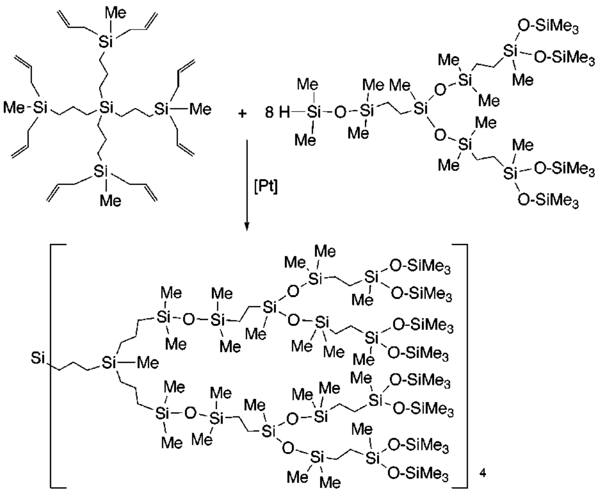


generation of the dendrimer which contains silicon only at the core (Scheme 15). This dendrimer reacts with $[Pd(CH_3CN)_4](BF_4)_2$ to produce **23-G$_2$** which contains four square-planar palladium complexes bound to a central silicon atom.[38] Another type of silicon−phosphorus-containing dendrimer, **24-G$_2$**, was recently described.[39] The last step of the synthesis is the quaternization of eight phosphino groups linked to a silsesquioxane core by eight organic benzyl bromide dendrons (Scheme 16). In this case also only the core contains silicon.

Very recently, a dendrimer with alternating silicium and germanium atoms, **25-G$_1$**, was synthesized.[40] This dendrimer was obtained by a divergent method analogous to those already described for polysilane type dendrimers (Scheme 17).

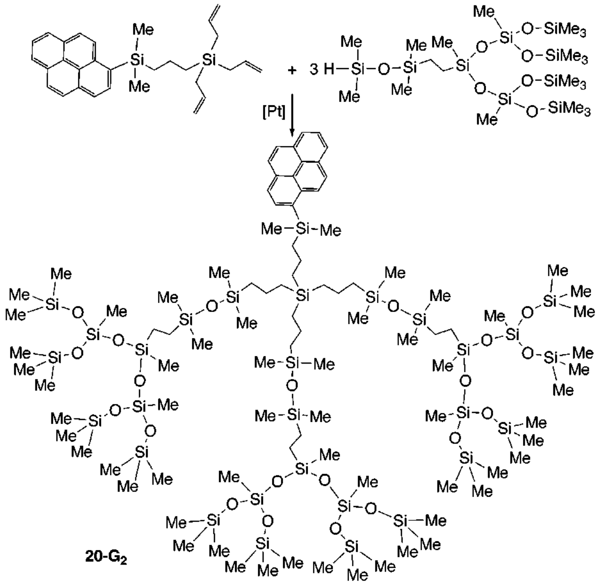
c. Silicon and Organic Dendrimers. Several silicon derivatives have been grafted on the surface of purely organic dendrimers. Two methods for the siliconization of polyaminoamide dendrimers, in most cases of generation 3 (32 NH_2 end groups), have been reported.[41] A Michael addition of silicon-containing acrylates or haloalkylation with silane or siloxane derivatives leads to the formation of radially layered copoly(aminoamide−organosilicon) dendrimers **26-G$_3$** and **27-G$_3$** which possess hydrophilic interiors and

Scheme 11



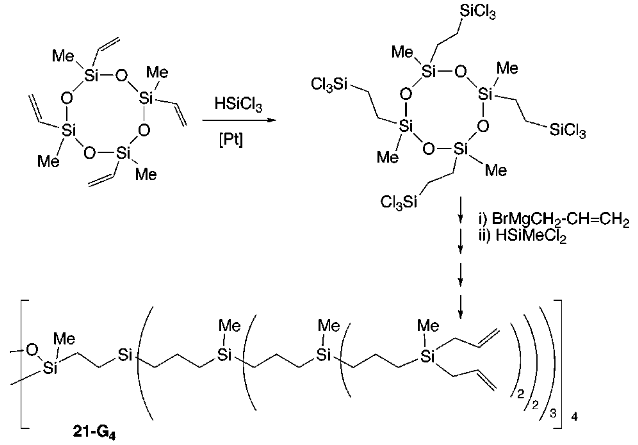
19-G$_3$

Scheme 12



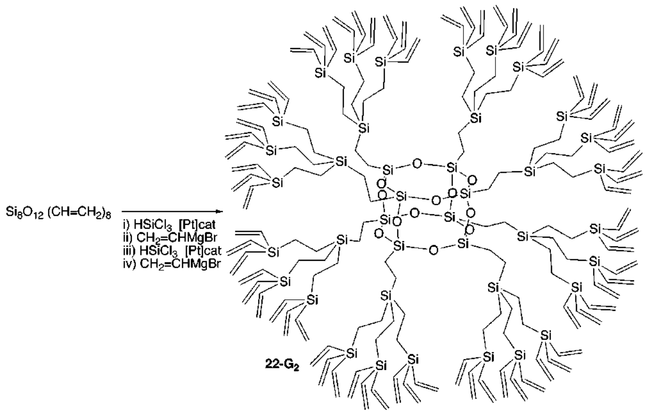
20-G$_2$

Scheme 13

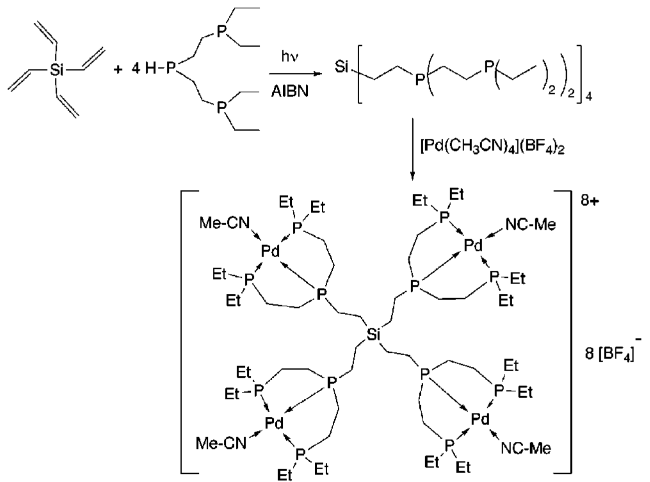


21-G$_4$

Scheme 14



Scheme 15



23-G$_2$

hydrophobic exteriors (Scheme 18). Isocyanate trisiloxane derivatives have been grafted on the surface of the fourth generation of polyamine dendrimers bearing 32 NH_2 end groups[42,43] leading to dendrimer **28-G$_4$**. This isocyanate trisiloxane derivative has been used alone (Scheme 19) or together with several other isocyanate derivatives to afford combinatorial-based, i.e., peripherally heterogeneous, dendrimers.

Organic dendrimers incorporating silicon only at the core have also been described. The method for synthesis of poly(amido)amine PAMAM dendrimers[2] has been applied to a silsesquioxane core derivatized with aminopropyl groups: the reaction with methyl acrylate and then with an excess of ethylenediamine produces the first generation of the dendrimer **29-G$_1$** (Scheme 20).[44] Very recently, the axial chloro ligands of dichloro(phthalocyaninato)silicon have been substituted by the first, second, and third generations of poly(aryl ether) dendrons[4] leading to silicon phthalocyanines with axial dendritic substituents, **30-G$_n$** ($n = 1-3$) (Scheme 21).[45]

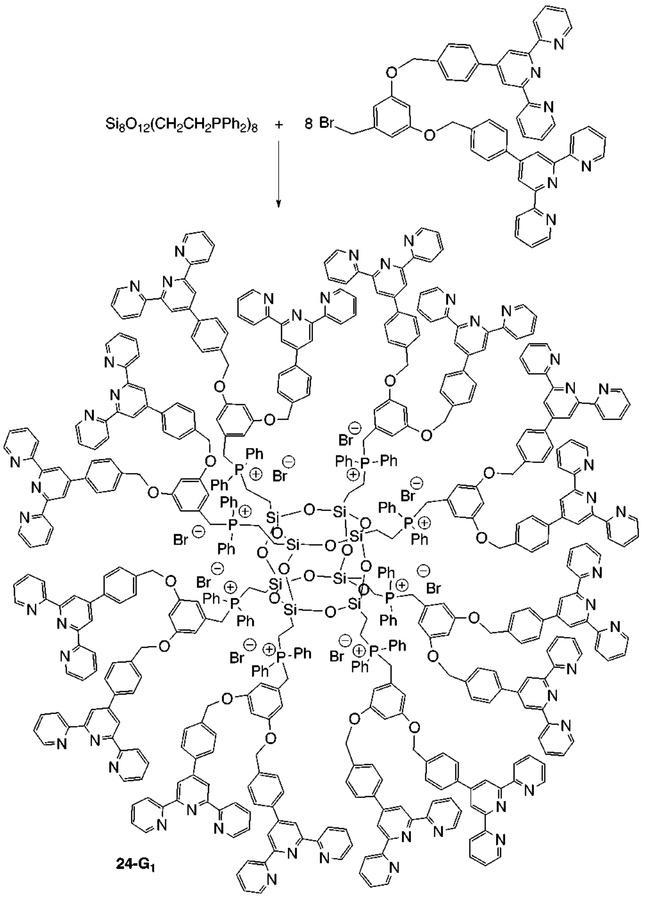
B. Reactivity

The reactivity of surface functional groups has been studied only for carbosilane dendrimers and in most cases for low generations. The reactivity concerns either the substitution of the chlorine atom of the Si−Cl end groups by various reagents or the addition of compounds with labile hydrogen to Si−allyl end groups.

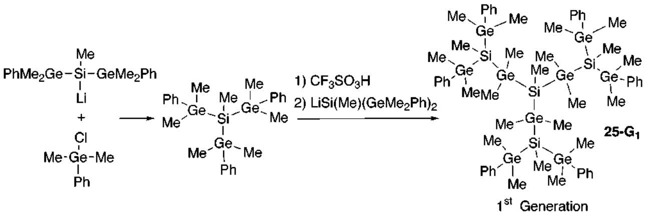
1. Reactions of Si–X End Groups (X = Cl, Br)

a. With Lithium or Sodium Salts or Grignard Reagents. The first example concerning the reactivity of

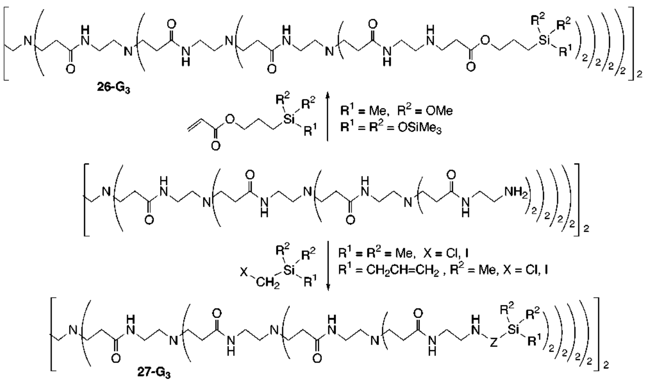
Scheme 16



Scheme 17

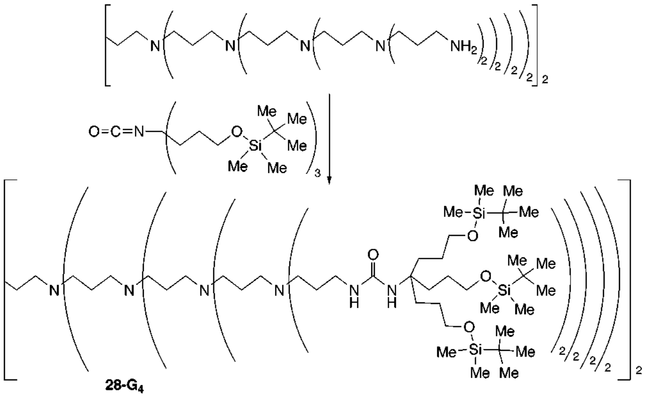


Scheme 18

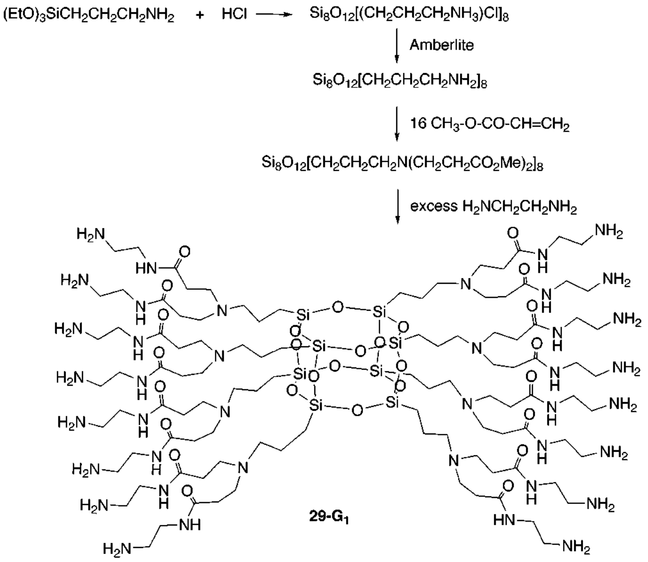


carbosilane dendrimers was the grafting of polybutadiene. This reaction has been carried out with living poly(butadienyl)lithium and the third,[46] fourth, and fifth generations[47,48] of dendrimers having terminal $SiMeCl_2$ groups. This led in the last case, i.e., with **7-G$_5$** to formation of a regular star polymer **31-G$_5$** with 128 arms after 8 weeks (Scheme 22). Analogous reactions occur with the third generation of the dendrimer and living monolithium derivatives of polystyrene, polyisoprene, and poly(dimethylsiloxane).[49]

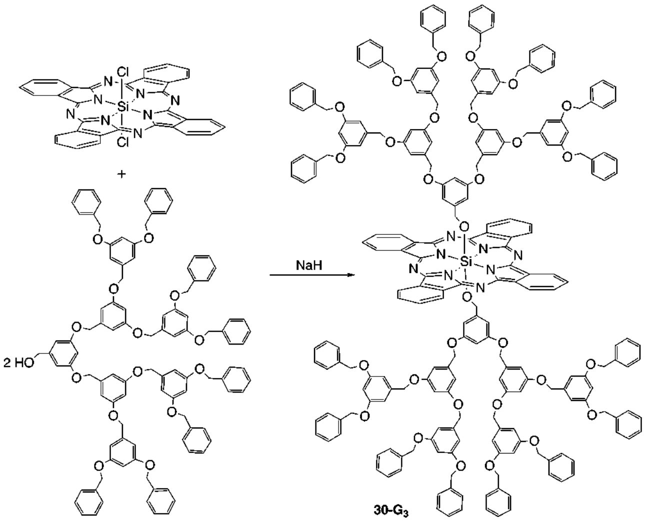
Scheme 19



Scheme 20

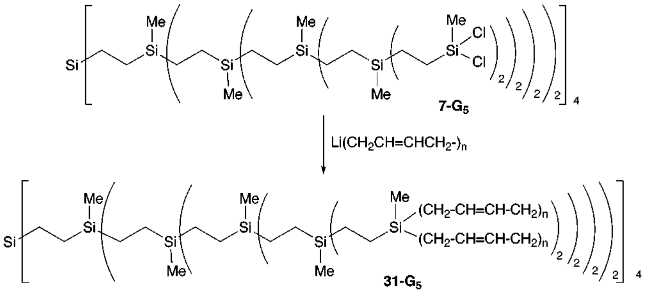


Scheme 21

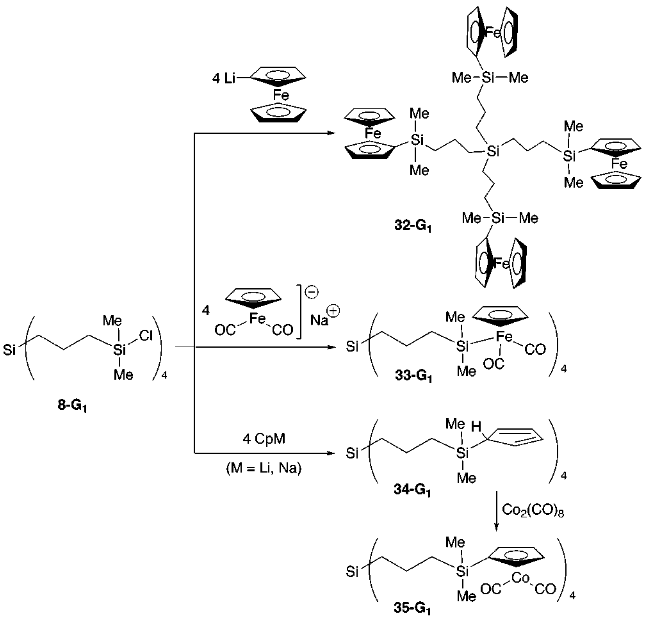


The reaction of lithium or sodium salts has been also used to graft several types of organometallic derivatives. These reactions have been mainly carried out with small carbosilane dendrimers. The first example involves the use of ferrocenyllithium with the first and second generations of dendrimer **8-G$_n$**,

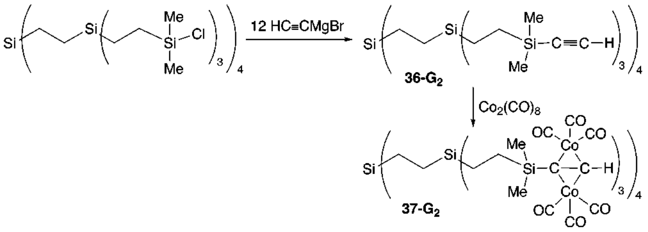
Scheme 22



Scheme 23



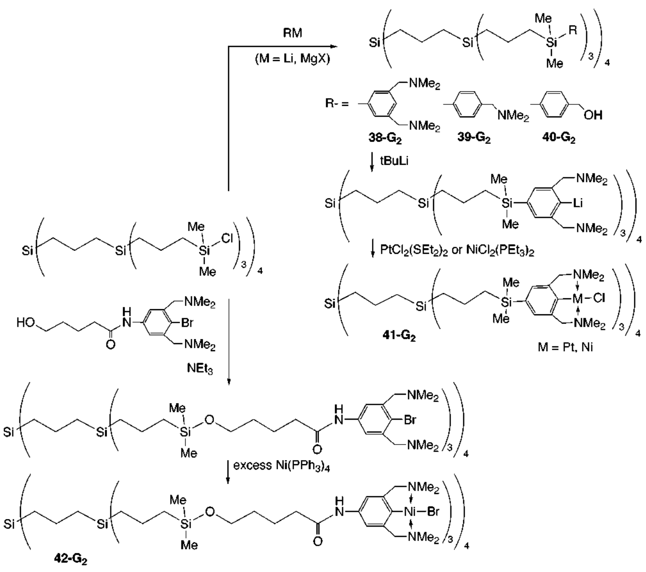
Scheme 24



affording dendrimer **32-G$_n$** ($n = 1, 2$)[20,50] (Scheme 23). Direct silicon–iron bonds are obtained for **33-G$_1$** from the carbonyl anion Na[CpFe(CO)$_2$],[50,51] whereas cobalt derivatives can be grafted in two steps: reaction of alkaline cyclopentadienides with Si–Cl groups leading to **34-G$_1$** and then complexation with octacarbonyldicobalt (Scheme 23).[50,51] The same cobalt derivative has been linked to the triple bonds of dendrimer **36-G$_2$**, obtained by reaction of HC≡CMgBr with Si–Cl end groups (Scheme 24).[52] The reaction of lithium phenylacetylide on the SiCl$_2$ end groups of the third generation of a carbosilane dendrimer based on a siloxane tetramer as a core leads also to a dendrimer with acetylide end groups (32 Ph–C≡C–).[34]

Other organometallic derivatives have been grafted on the second generation of carbosilane dendrimers via the use of organolithiums or Grignard reagents.[53] Dendrimers **38-G$_2$**, **39-G$_2$**, and **40-G$_2$** with tertiary amine or alcohol end groups are obtained in this way (Scheme 25). Lithiation of **38-G$_2$** with tBuLi followed by transmetalation with PtCl$_2$(SEt$_2$)$_2$ or NiCl$_2$(PEt$_3$)$_2$ affords the polytransition metal derivative **41-G$_2$**.[53]

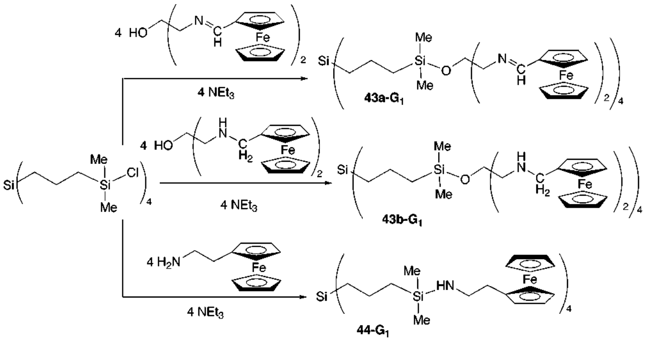
Scheme 25



b. With Alcohols or Amines. Various types of alcohols have been grafted on the surface of silicon dendrimers. For instance, *p*-bromophenol reacts in the presence of tetramethylethylenediamine (TMEDA) to afford [OSiMe(CH$_2$)$_2$Si((CH$_2$)$_3$SiMe$_2$OC$_6$H$_4$-Br)$_3$]$_4$, the second generation of a dendrimer based on a siloxane tetramer.[54] This type of reaction has mainly been applied to the grafting of organometallic species on the surface of dendrimers. Reaction of the first or second generation of a carbosilane dendrimer that has Si–Cl end groups with an alcohol that has terminal diaminoaryl bromide moieties, in the presence of NEt$_3$, followed by the reaction with the zerovalent nickel complex Ni(PPh$_3$)$_4$ gives the oxidative addition product **42-G$_n$** (n = 1, 2) (Scheme 25).[55,56]

Two types of ferrocenyl derivatives have been grafted on Si–Cl groups using alcohols or amines. Thus, the ferrocenylimine dinuclear compound derived from 1,3-diaminopropan-2-ol and ferrocene carbaldehyde leads to the formation of compound **43a-G$_1$**, whereas compound **43b-G$_1$** is obtained after reduction of CH=N bonds of the alcohol derivative (Scheme 26).[50] The reaction of β-aminoethylferrocene

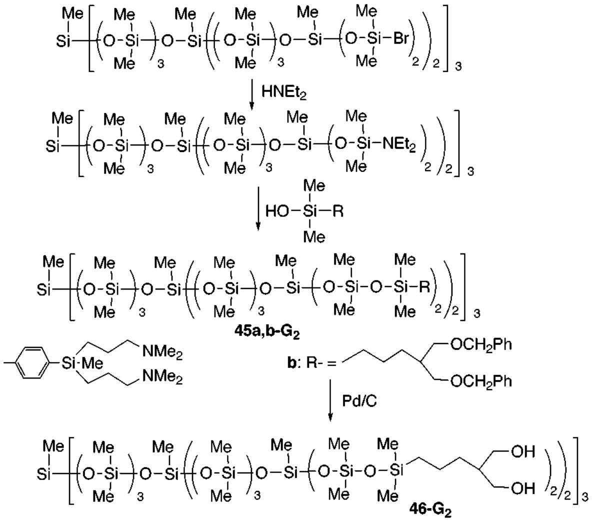
Scheme 26



with a first- or second-generation dendrimer leads to the formation of **44-G$_n$** ($n = 1,2$) which possess four or eight ferrocene units on the surface (Scheme 26).[20]

The SiBr end groups of polysiloxane dendrimers have been reacted first with diethylamine and then with difunctionalized silanols to yield dendrimers **45a,b-G$_2$**, possessing 24 dimethylamino or benzyloxy groups, respectively. The latter compound was converted to the polyol **46-G$_2$** upon treatment with H_2 in the presence of palladium on carbon (Scheme 27).[12]

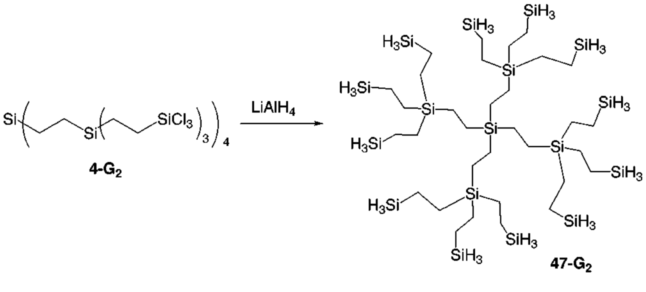
Scheme 27



It was found that the solubility of the dendrimer was remarkably affected by the nature of the functional groups.

c. Reduction. The Si−Cl bond can readily be reduced to a Si−H bond with $LiAlH_4$. This reaction was applied first to dendrimer **4-G$_n$** ($n = 1-4$) leading to compound **47-G$_n$** (Scheme 28).[16] The reduced dendrimers are also precursors of organometallic molecules. For instance, the reduced species $Si((CH_2)_3SiMe_2H)_4$ (**48-G$_1$**) reacts with $Co_2(CO)_8$ to afford $Si((CH_2)_3SiMe_2Co(CO)_4)_4$ (**49-G$_1$**).[51] It is also used for the hydrosilylation of various vinylferrocene derivatives leading to compounds **50-G$_1$**,[57] **51-G$_1$**, and **52-G$_1$**[58] (Scheme 29). The first reaction has been applied to the second generation, leading to compound **50-G$_2$**, possessing eight ferrocene units.[57]

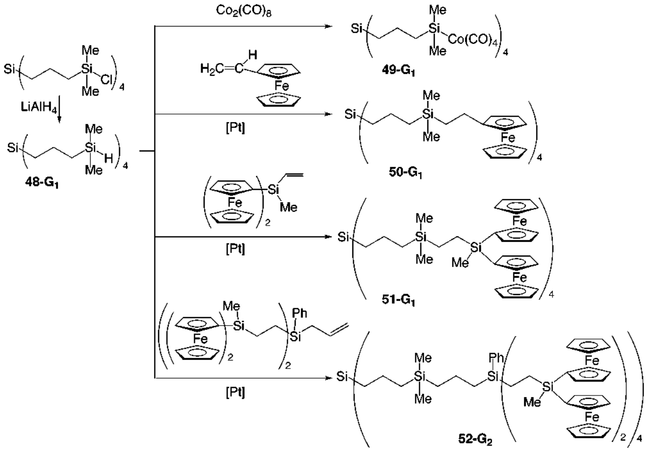
Scheme 28



2. Reactions of Si–Allyl or Si–Vinyl End Groups

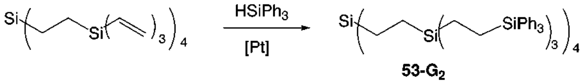
All the reactions carried out with allyl or vinyl end groups concern the addition of compounds with labile hydrogen such as silanes, mercaptans, and boranes to the C=C bond.

Scheme 29

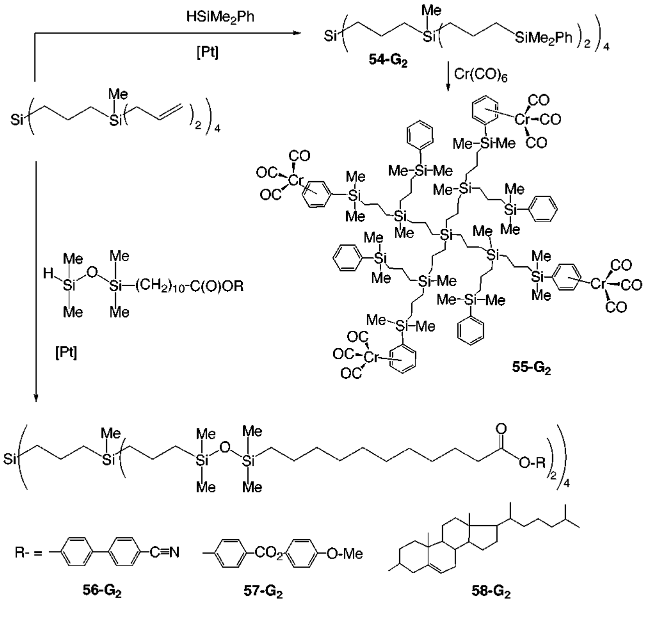


a. Hydrosilylation. Hydrosilylations described in this paragraph are reactions with silane derivatives different from those used during the construction of the dendrimer. For instance, triphenylsilane has been grafted on the vinyl groups of the first and second generation of a carbosilane dendrimer leading to compounds **53-G$_n$** ($n = 1, 2$) (Scheme 30).[59] The reaction of dimethylphenylsilane leads to the analogous dendrimer **54-G$_2$** which reacts later with $Cr(CO)_6$ to afford as the major product dendrimer **55-G$_2$** in which only four of the eight phenyl groups are complexed to $Cr(CO)_3$ units (Scheme 31).[60]

Scheme 30

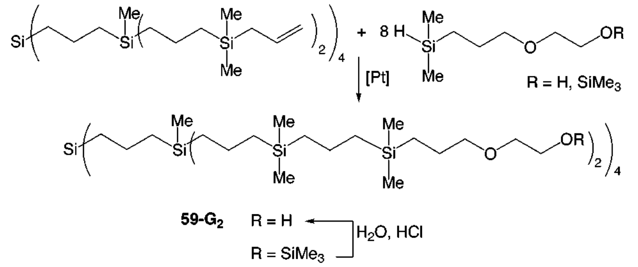


Scheme 31



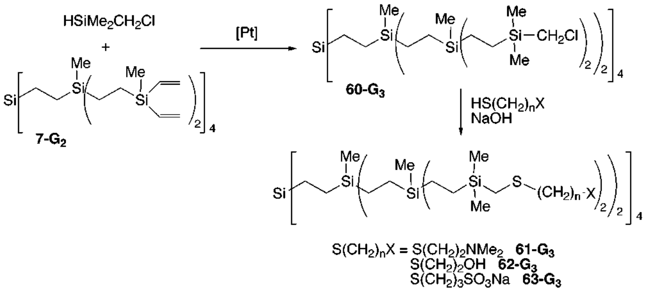
Long chain silanes have also been grafted on the surface of carbosilane dendrimers by hydrosilylation. Cyanobiphenyl, methoxyphenylbenzoate, and cholesteryl moieties linked by a C_{10} spacer to a silane group react with the eight allyl groups of a dendrimer to afford the liquid crystal dendrimers **56-G$_2$**, **57-G$_2$**, and **58-G$_2$**, respectively (Scheme 31).[61] The use of dimethyl(6-hydroxy-4-oxahexyl)silyl groups leads to the attainment of alcohol functions on the surface of the dendrimer **59-G$_2$**. This compound is also obtained in two steps, using a trimethylsilyl derivative which is hydrolyzed in the last step (Scheme 32).[62,63]

Scheme 32



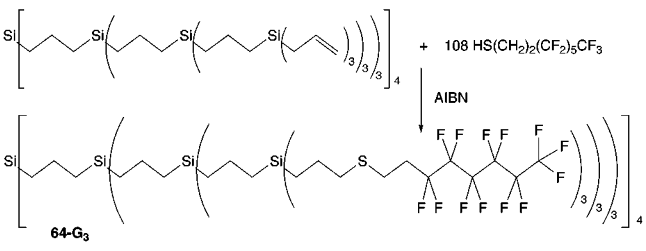
Water-soluble carbosilane dendrimers have been obtained in two steps.[64] The first step is the hydrosilylation of dendrimers **7-G$_n$** ($n = 0-2$) with HSiMe$_2$CH$_2$Cl, which gives dendrimers **60-G$_{n+1}$** possessing (chloromethyl)silyl groups on their terminal branches (Scheme 33). In the second step, a nucleophilic reaction between mercapto-substituted amphiphiles and these end groups leads to the formation of dendrimers **61-G$_{n+1}$**, **62-G$_{n+1}$**, and **63-G$_{n+1}$** ($n = 0-2$) possessing dimethylamino, alcohol, and sulfonate end groups, respectively. Dendrimers **63-G$_{n+1}$** and positively charged dendrimers **61-G$_{n+1}$** are water-soluble.

Scheme 33



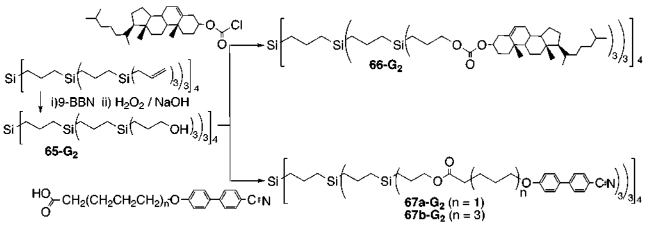
The hydrosilylation reactions have been recently extended to “hydrosulfuration”. The reaction of tridecafluoro-*n*-octylmercaptan on dendrimers from the zeroeth to the third generation with up to 108 allyl end groups in the presence of AIBN as catalyst affords the polyfluorinated dendrimers **64-G$_n$** ($n = 0-3$) (Scheme 34).[65]

Scheme 34

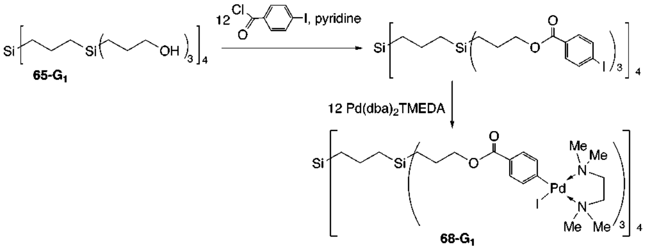


b. Other Addition Reactions. Most of the addition reactions on the C=C end groups of dendrimers other than hydrosilylation are hydroboration reactions. They are generally carried out using 9-borabicyclo[3.3.1]nonane (9-BBN) with subsequent oxidation by H$_2$O$_2$/OH$^-$ leading to the quantitative transformation of allyl groups to alcohols. This reaction has been applied to carbosilane dendrimers with allyl end groups from the zeroeth to the third generation (Scheme 35).[66] Frey and co-workers have developed several reactions from these alcohol end groups; for instance, the reaction of cholesteryl chloroformiate has been carried out up to the third generation, leading to dendrimer **66-G$_3$** (Scheme 35).[67-69] The alcohol end groups of the first and second generations (**65-G$_1$** and **65-G$_2$**) also react with carboxylic acids such as 5-((4′-cyano(1,1′-biphenyl)-4-yl)oxy)valeric acid or 11-((4′-cyano(1,1′-biphenyl)-4-yl)oxy)undecanoic acid to afford dendrimers **67a-G$_n$** and **67b-G$_n$** ($n = 1$, 2) (Scheme 35).[70] Dendrimers **67a-G$_n$** have also been obtained using the corresponding acid chloride in the presence of pyridine.[71,72] 4-Iodobenzoyl chloride reacts, also in the presence of pyridine, with the zeroeth and first generations (**65-G$_0$** and **65-G$_1$**) leading to dendrimers with peripheral iodoarene groups (Scheme 36).[73] Oxidative addition of the iodoarene groups to Pd(dba)$_2$ in the presence of TMEDA leads to the formation of the palladated dendrimers **68-G$_0$** and **68-G$_1$**.

Scheme 35

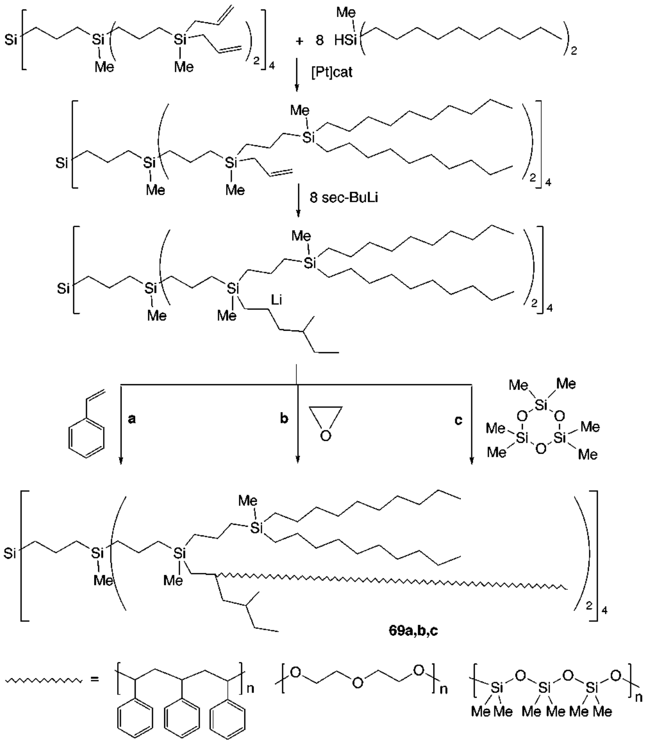


Scheme 36



Very recently, addition of s-BuLi on allyl groups located in the inner area of a special dendrimer was accomplished. The first step consists of reacting 8 equiv of didecylmethylsilane on the second generation of a dendrimer possessing 16 allyl end groups. The sterical demand of the didecyl groups causes a partial screening of the remaining allyl groups; ^{29}Si NMR is consistent with the grafting of only one SiMe(C$_{10}$H$_{21}$)$_2$ group on each SiMe(CH$_2$CH=CH$_2$)$_2$ end group. In the second step, s-BuLi is added on the remaining allyl groups leading to a dendrimer possessing eight Li atoms. The location of the Li atoms in the inner part of the dendrimer prevents the problems of solubility and aggregation generally encountered with polylithium compounds. Thus, this compound is used for the anionic polymerization of styrene, ethylene oxide, and hexamethylcyclotrisiloxane, leading to the multiarm star-shaped polymers **69a**, **69b**, and **69c**, respectively (Scheme 37).[49,74]

Scheme 37



C. Characterization and Properties

1. Methods of Characterization

Silicon-containing dendrimers are characterized by classical methods such as NMR that have been used to characterize organic dendrimers. In addition to ^{1}H and ^{13}C NMR, most of the silicon-containing dendrimers, including oligosilane dendrimers, have been characterized by ^{29}Si NMR.[28,75] Only a few structures have been determined by X-ray diffraction. In all cases, these determinations concern only small dendrimers: first generation (**13-G$_1$**,[25,26] **15-G$_1$**,[27] **22-G$_1$**,[37] **25-G$_1$**,[40] **37-G$_1$**,[52] **53-G$_1$**[59]) or second generation (**14-G$_2$**,[27] **16-G$_2$**,[29] **30-G$_2$**,[45] **47-G$_2$**[16]). Furthermore, most of these molecules are rather small, even for the second generation, due to the fact that branches generally contain only one (**14-G$_2$**), two (**16-G$_2$**), or three (**47-G$_2$**) atoms. In addition, fluorescence spectra of pyrenyl-labeled dendrimers such as **20-G$_2$** allows a sensitive investigation of the flexibility of the skeleton, based on excimer formation peculiarities.[32,33]

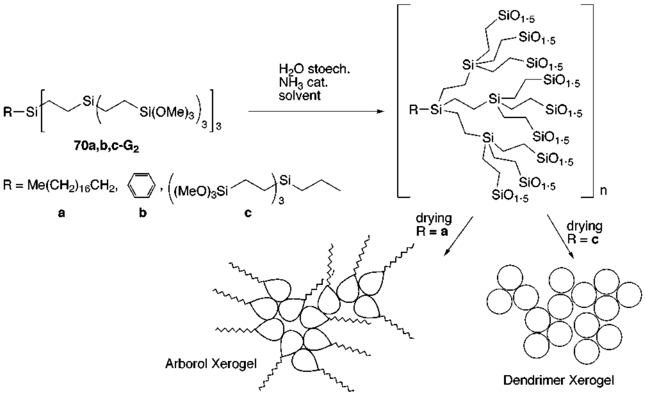
Other methods of dendrimer characterization include the determination of molecular weight by mass spectrometry using electrospray[39] and mainly MALDI-TOF (matrix-assisted laser desorption ionization−time-of-flight) technique, which has already found broad application for the analysis of peptides, proteins, and synthetic macromolecules; slight structural defects are often observed.[31,44,66,69,76] In adddition, techniques developed for polymer analysis can be used but often have to be adapted since they are based on linear polymer standards and are not directly suitable for the characterization of dendrimers. Thus, GPC (gel permeation chromatography),[17,30] size exclusion chromatography,[17,66] laser light scattering,[17,48] or osmometry[17,48] have been also used to characterize silicon dendrimers. DSC-TGA (differential scanning calorimetry−thermogravimetric analysis)[41] and glass transition temperatures (T_g)[17,65,66] have also been measured. The T_g of carbosilane dendrimers lies under 0 °C, indicating that the framework is highly flexible; a linear relationship between T_g and n_e/M (n_e = number of end groups; M = molecular weight of the dendrimer) is observed.[65,66] The intrinsic viscosity is also an important characteristic of polymer molecules, which is expected to be lower for dendrimers than for linear polymers, since dendrimers are more compact; experiments have confirmed this asumption.[11,17,30]

2. Study of Properties

a. Properties in Solution. The star-branched polybutadiene **31-G$_n$** ($n > 3$) in semidilute solutions has macrocrystalline ordering which leads to the formation of physical gels.[77] These compounds ($n > 2$) have characteristic properties of hard sphere molecules in dilute solution[46,48] and represent good model polymers for polymeric micelles.[47]

Hybrid organic−inorganic gels are obtained by sol−gel polycondensation of the second-generation arborols **70a,b** or dendrimer **70c** with a stoichiometric amount of water and NH_3 as catalyst (Scheme 38).

Scheme 38



Drying the gels induces the formation of xerogels obtained as insoluble powders. Dendrimer xerogels are porous materials, while arborol xerogels form porous or nonporous materials, depending on their structure and on the gelation conditions. Removal of the organic part by thermal oxidation leads to the formation of microporous silica, but no control of the porosity could be achieved.[78]

Carbosilane dendrimers with hydrophilic surface such as **63-G$_3$** enhance the solubility of lipophilic alkyl-substituted benzene derivatives in water. They are able to solubilize two or three alkylbenzene molecules per dendrimer molecule, indicating that these dendrimers with lipophilic interior and hydrophilic surface exhibit micelle-like solution behavior.[64] The host properties of carbosilane dendrimers with various branch lengths have been also studied using molecular dynamics, which gave dimensions of the inner cavities in the range of 5−15 Å.[79] Organic dendrimers with hydrophilic interior and hydrophobic organosilicon surface (**27-G$_n$**) exhibit considerable surface activity: compounds with the best water solubility lower the surface tension of water, whereas hydrophobic compounds form spread monolayers on water, capable of sustaining much higher surface pressures than poly(dimethylsiloxane) (over 40 mN/m).[80]

b. Properties of Neat Dendrimers. Essentially two types of properties of neat dendrimers have been studied, depending on the type of end groups: the formation of liquid crystal phases and the formation of thin films on surfaces. The use of carbosilane dendrimers as ceramic precursors has been investigated but appears to be too expensive.[16] Dendrimers bearing terminal mesogenic groups should present a conflict situation between anisotropic ordering behavior of the mesogenic groups and the isotropic shape of the dendrimer core. However, it has been shown variously by polarizing microscopy, wide-angle X-ray scattering (WAXS),[65] or DSC that all of them are liquid crystals. Dendrimers **56-G$_2$**, **57-G$_2$**, and **58-G$_2$** give different mesophases of the smectic type, depending on the chemical nature of the eight mesogenic groups.[61] Broad smectic A phases are also observed when a larger number of mesogen groups is linked to dendrimer **67a-G$_n$** (n = 1−3).[71,72] The influence of the spacer length between the dendrimer and the mesogen has also been studied; comparison between **67a-G$_n$** and **67b-G$_n$** indicates that the longer spacer facilitates the development of layered mesophases.[70] The dependence of the formation of mesophases on the generations is also illustrated by the behavior of dendrimers **64-G$_n$**: **64-G$_0$** is crystalline, and **64-G$_1$** forms a highly ordered smectic mesophase, whereas **64-G$_2$** and **64-G$_3$** do not form mesophases.[65]

The possibility of forming thin films on mica surface has also been studied by atomic or scanning force microscopy. Several behaviors have been observed. Cholesteryl-ended dendrimers **66-G$_n$** (n = 1−3) form liquid crystal films for n = 1 and 2. Depending on the initial concentration, irregular monolayer films or flat homogeneous films of 2−4 dendrimer layers are obtained.[68] The carbosiloxane dendrimer **19-G$_3$** displays a complex aggregation process: single molecules coagulate to clusters and fluid droplets, which slowly spread into lamellae with a thickness of two molecular layers.[31] The hydroxyl-terminated carbosilane dendrimer **59-G$_2$** deposited on a mica surface forms droplets of thickness about 14 Å, which is approximately one-half the hypothetical diameter of a single dendrimer, indicating that the molecules lying on the surface are deformed.[62]

c. Properties of Metal-Containing Dendrimers. The most straightforward use of organometallic complexes linked to the surface of dendrimers is catalysis. Indeed, these dendrimers should present advantages of homogeneous catalysts (solubility, accessibility of the reagents to catalytic sites) and heterogeneous catalysts (possibility to recover the catalyst by ultrafiltration). Two groups (van Koten[55] and DuBois[38]) have carried out simultaneously experiments in this field in 1994, starting from silicon-containing dendrimers.

Diaminoarylnickel(II) complexes anchored to siloxane dendrimers are effective for catalysis of the Kharasch addition of halogenoalkanes to olefinic C═C double bonds. The catalytic activity of each metal site in dendrimers **42-G$_1$** and **42-G$_2$** for the reaction of methyl methacrylate with CCl_4 is 20% and 30% less, respectively, than that of a monomeric organometallic complex having an analogous catalytic site.[55,56] Dendrimer **41-G$_2$** (M = Ni) is also an active catalyst in the Kharasch addition.[53]

Studies of the electrochemical behavior of dendrimer **23-G$_2$** show that it catalyzes the electrochemical reduction of CO_2 to CO in acidic dimethylformamide. An estimate of the average activity of each site in the dendrimer indicates that it is similar to those observed for monomeric analogous complexes.[38]

The electrochemical behavior of ferrocenylsilicon-based dendrimers has also been studied in detail for compounds **32-G$_n$**,[20,50,57,82] **44-G$_n$**,[20,50] **50-G$_n$**[50,57] (n = 1,2), **51-G$_1$**, and **52-G$_2$**.[58] A simultaneous four- or eight-electron transfer is observed for **32-G$_n$**, **44-G$_n$**, and **50-G$_n$** as expected for an independent reversible one-electron process of four or eight ferrocenyl units at the same potential; therefore, in these compounds, the ferrocenyl moieties are noninteracting redox centers. These dendrimers deposit onto electrode surfaces as they become oxidized. Thus, modified electrodes with films of dendrimers as electroactive materials persistently attached to the electrode surface have been obtained.[82] Electrodes derivatized with dendrimers **44-G$_n$** are sensitive to the presence of anions, particularly $H_2PO_4^-$; thus these modified electrodes could be used for the electrochemical recognition of anions.[50] Carbon paste electrodes containing the dendrimer **32-G$_n$** or **50-G$_n$** and glucose oxidase have been used as biosensors for glucose.[57]

A different electrochemical behavior is observed for dendrimers **51-G$_1$** and **52-G$_2$**. In these cases, the ferrocenyl units linked together in close proximity are in electronic communication with each other. The existence of significant interactions between the two ferrocenyl units which are linked together by a bridging silicon atom leads to the presence of two well-separated and reversible oxidation waves of equal intensity in the cyclic voltammograms.[58]

III. Phosphorus-Containing Dendrimers

In pioneering work Rengan and Engel[83] reported in 1990 the preparation of a new category of cascade molecules in which the initiator core and subsequent branch points are quaternary phosphonium ion sites. The first neutral phosphorus-containing dendrimers possessing either P−N and P−O bonds[84] or P−C bonds[38] were described in 1994. Since that time synthesis and chemistry of these new macromolecules has been blossoming.

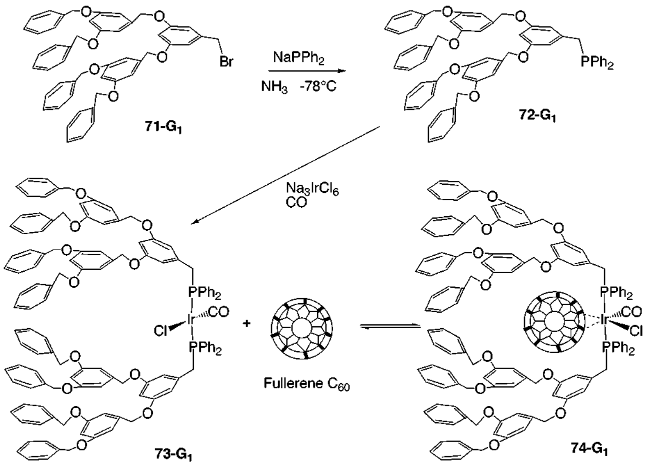
This review covers the preparation of dendrimers in which phosphorus can be located exclusively at the core, on the surface, at the core and at each generation, or at the core at each generation and on the surface. Reactivity will be presented too: it will demonstrate the specificity of phosphorus-containing dendrimers.

A. Methods of Synthesis

1. Phosphorus at the Core

The dendron **72-G₁** (generation 1) containing a phosphino group at the core is prepared according to the reactions outlined in Scheme 39. The transition metal complex [*trans*-Ir(CO)Cl (**72-G₁**)$_2$] (**73-G₁**) is obtained in good yield by carbon monoxide reduction of $Na_3IrCl_6{\cdot}6H_2O$ in methoxyethanol. The species **73-G₁** shows reversible binding with C_{60} to afford **74-G₁** (Scheme 39).[85]

Scheme 39

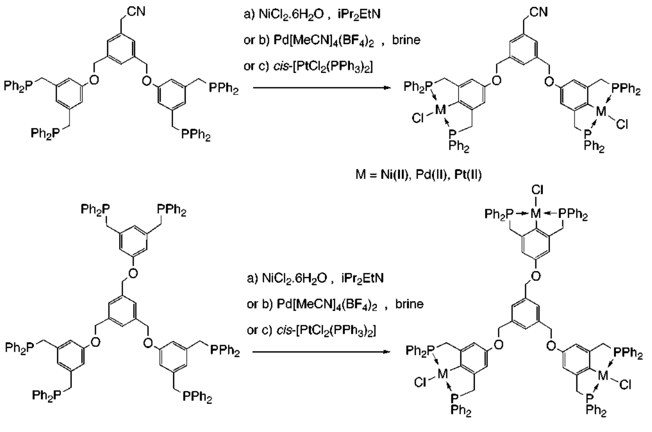


A phosphane-substituted polyhedral octasilsesquioxane $Si_8O_{12}(CH_2CH_2PPh_2)_8$ has been used as a core for building new types of dendritic macromolecules incorporating eight phosphonium centers,[39] as already shown in sectopm A.4.b (Scheme 16).

2. Phosphorus on the Surface

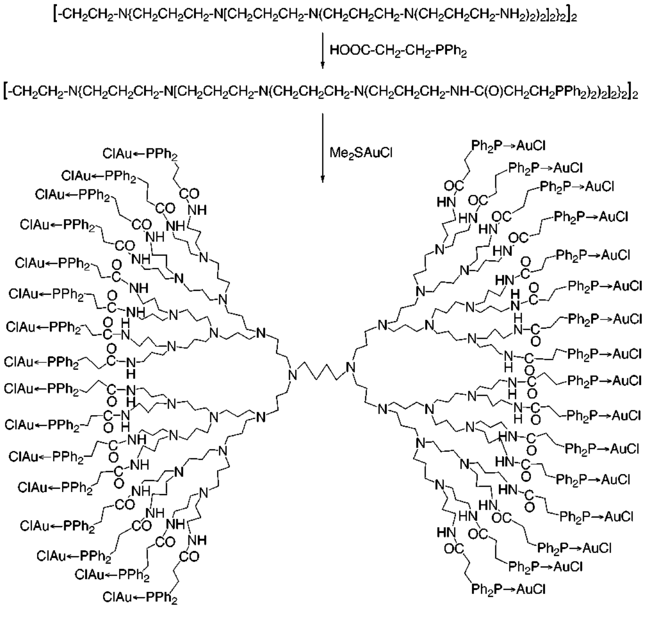
The coupling of [3,5-bis[(diphenylphosphinyl)methyl]phenyl]oxy groups to bi- and trifunctional spacers followed by cyclometalation of the ligand precursor compounds with $[NiCl_2{\cdot}6H_2O]$, $Pd[CH_3CN]_4(BF_4)_2$, or *cis*-$[PtCl_2(PPh_3)_2]$ gives Ni, Pd, and Pt complexes (Scheme 40).[86] The resulting pincer ligand complexes might be used as building blocks for the controlled assembly of both homo- and heteromultinuclear metalladendrimers.

Scheme 40



Diaminobutane–poly(trimethyleneamine) dendrimers of generations 2 and 3 have been reacted with α-(diphenylphosphino)acetic acid and *p*-(diphenylphosphino)benzoic acid.[87] Up to 32 peripheral diphenylphosphino groups have been grafted, and the corresponding polynuclear gold complexes have been prepared (Scheme 41).

Scheme 41

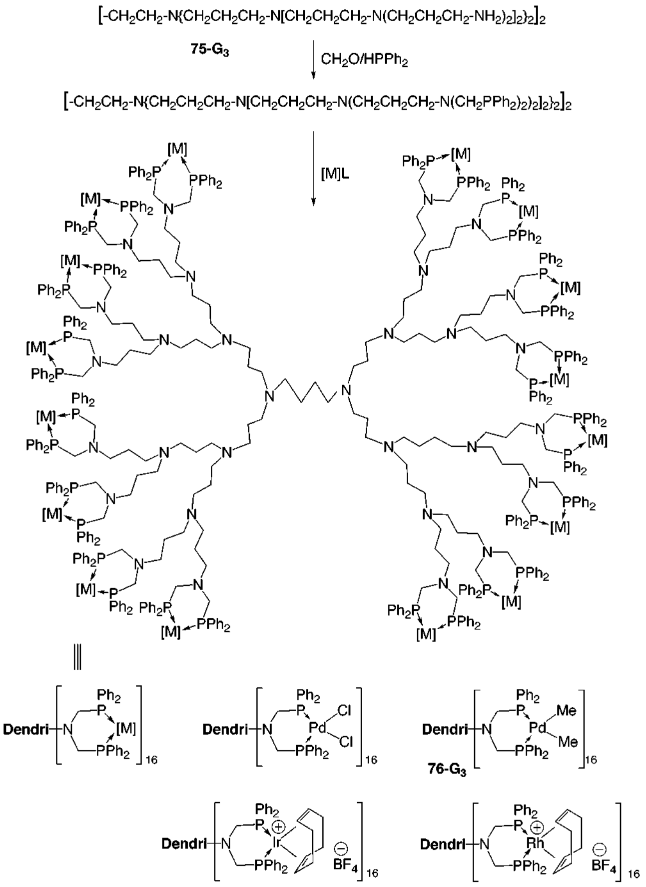


The double phosphinomethylation of the 1,4-diaminobutane-based polyamino dendrimer **75-G₃** (generation 3, 16 terminal NH_2 groups) using Ph_2PCH_2OH[88] allows the incorporation of 16 terminal $N(CH_2PPh_2)_2$ groups which appear to be excellent ligands toward $[Pd(CH_3)_2(tmeda)]$, $[Ni(CH_3)_2(tmeda)]$, $[Ir(cod)_2BF_4]$, and $[Rh(cod)_2BF_4]$ (Scheme 42).[89] The Pd-containing dendrimer **76-G₃** is an excellent catalyst in the Heck reaction of bromobenzene and styrene with formation of stilbene. For the first time a significantly higher activity is observed for a dendritic complex compare to the corresponding monomer (typically turnover numbers (TON) of 50 for the complex **76-G₃** versus 16 for the parent compound $[R\text{-}N(CH_2PPh_2)_2Pd(CH_3)_2]$ ($R = nC_3H_7$, C_6H_5)).

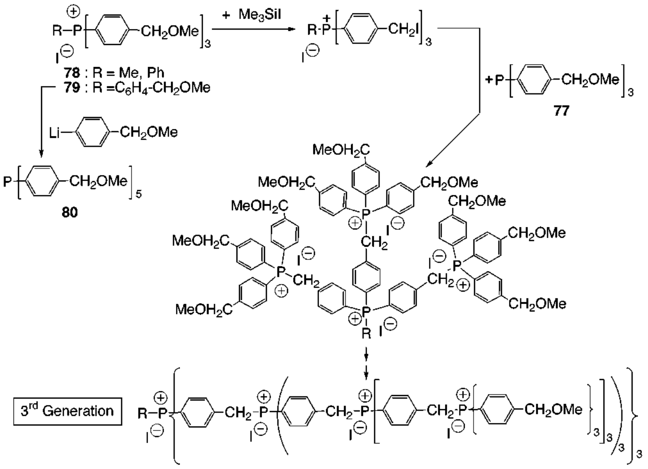
3. Phosphorus at the Core, within the Cascade Structure, and on the Surface

Rengan and Engel prepared the first charged dendrimers bearing phosphorus at the core and at branching points.[83] Up to 40 phosphonium groups can be incorporated (Scheme 43). The strategy consists of the quaternization of tris(*p*-methoxymethyl)phenylphosphane ($P(C_6H_4CH_2OMe)_3$, **77**) with an alkyl halide to generate the primary core $[RP(C_6H_4CH_2OMe)_3]^+$ (**78**) or with *p*-methoxymethylbromobenzene in the presence of nickel bromide to form the primary core $[P(C_6H_4CH_2OMe)_4]^+$ (**79**). A neutral quinquedirectional core $P(C_6H_4CH_2OMe)_5$ (**80**) can also be easily prepared from **79** and 4-(methoxymethyl)-

Scheme 42



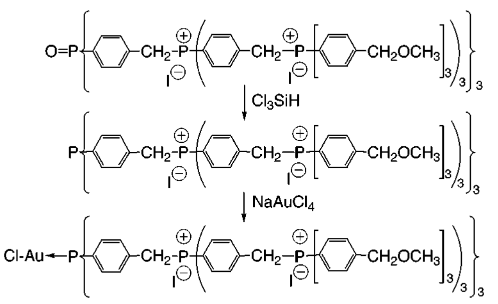
Scheme 43



phenyllithium. The synthesis of tri-, tetra-, or pentadirectional dendrimers can be carried out starting from **78**, **79**, or **80**, respectively, via the selective cleavage of the benzylic ether linkages with iodotrimethylsilane: the resulting benzylic iodides treated with **77** give rise to dendrimers of generation 1 with phosphonium salts at the periphery.[90] Such a strategy has been conducted up to generation 3 with a phosphane or a phosphonium core (Scheme 43).

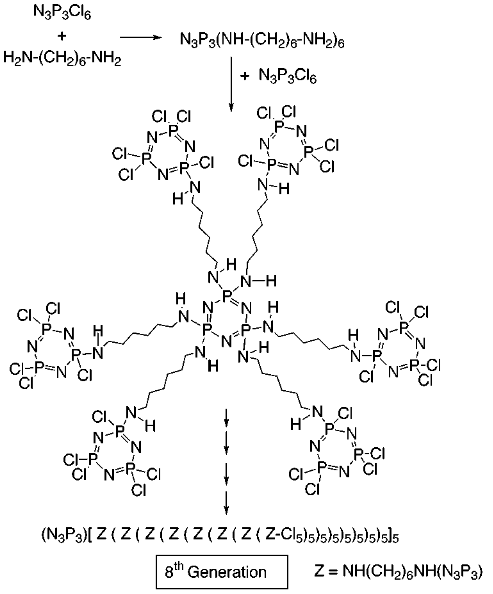
The same reactions can be conducted starting from $(O)P(C_6H_4CH_2OMe)_3$ as the core. Reduction of the P=O moiety leads to a polycationic dendrimer having at the core a phosphino group which can be coordinated to gold (Scheme 44).

Scheme 44



A D_{3h} cyclophosphazene formed by a regiospecific peraminolysis of hexachlorocyclotriphosphazene is a suitable core for generating spherical dendrimers built up to generation 8; although with increasing molecular size an increasing amount of incompletely substituted side products was noted[91] (Scheme 45).

Scheme 45

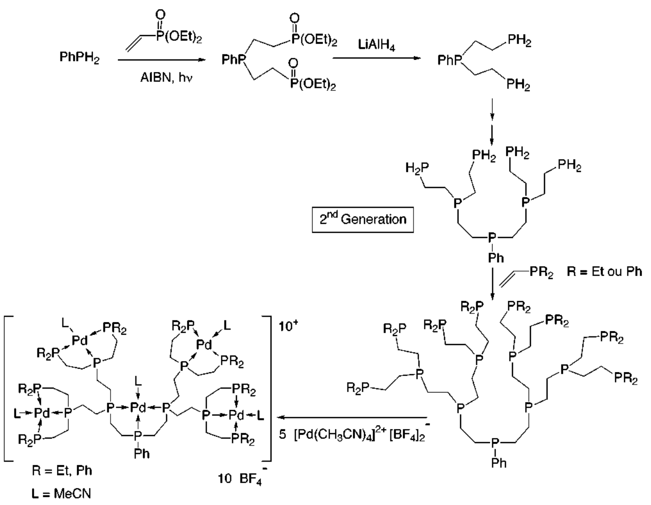


Risk of impurities resulting from incomplete reactions as well as cross-linking reactions are claimed to be minimized by modified reaction sequences and experimental conditions. However, this synthetic approach seems to violate about every rule for the synthesis of perfect dendrimers since one would expect unavoidable cross-linking reactions.

DuBois and co-workers[38,92] describe the synthesis of organophosphane dendrimers via the sequential addition of diethylvinyl phosphonate to primary phosphanes followed by reduction with lithium aluminum hydride (Scheme 46). Metalation of some of these dendrimers containing 12 and 15 phosphorus atoms with $[Pd(MeCN)_4](BF_4)_2$ gives rise to complexes exhibiting catalytic activity for electrochemical CO_2 reduction. A similar approach for synthesizing a phosphorus-containing dendrimer with a silane core has also been applied (see section A.4.b, Scheme 15).

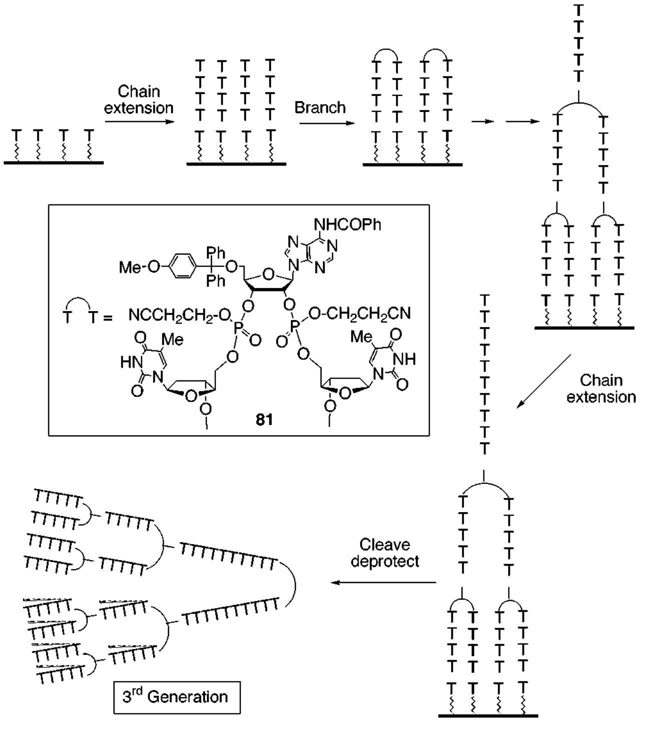
A general convergent synthesis of nucleic acid dendrimers has been reported by Hudson and Damha.[93] This method involves thymidines anchored to a long chain alkylamine-controlled pore glass. Chain

Scheme 46



extension is obtained with an automated DNA synthesizer. An activated adenosine 2′,3′-bis(phosphoramidite) derivative **81** allows the coupling of two adjacent polymer-bound nucleotide chains (Scheme 47). Repetitive chain elongation and branching steps lead to the formation of various dendrimers based on thymidine and adenosine building blocks including an 87-unit long dendrimer having a molecular weight of ca. 25 000 Da with 6 branch points and 12 terminal ends. A divergent approach for the construction of branched nucleic acids mimicking naturally occurring lariat and forked introns is also described.[93]

Scheme 47



Methods for the preparation of neutral phosphorus-containing dendrimers using hydrazono derivatives have been intensively studied these last 5 years. The formation of dendrimers up to generation 3 using the reiteration of a sequence of three reactions has been developed.[94] The core can be the hexapodant N_3P_3-$(OC_6H_4CHO)_6$. The first step is a Schiff reaction between the core and methylhydrazine leading to the hexahydrazone **82**. The treatment of **82** with a chlorophosphane like chlorodiphenylphosphane or chlorodiazaphospholane in the presence of base affords the hexahydrazone phosphane **83** which upon treatment with the azide $N_3P(S)(OC_6H_4CHO)_2$ leads to the dendrimer of generation 1, **84-G$_1$**. Reiteration of such a sequence of three reactions allows one to obtain dendrimers of generation 2 (**84-G$_2$**) and generation 3 (**84-G$_3$**) (Scheme 48). These reactions can be extended to other cores such as $(X)P(OC_6H_4CHO)_3$ (X = S or O).[94]

This strategy allows introduction of inorganic P=N–P fragments which are useful probes for controlling branch assembly and alternatively three different reactive groups (e.g., aldehyde, hydrazone, and hydrazonophosphane) on the surface. However, this method suffers from two drawbacks: it necessitates the repetition of a sequence of three reactions, and the lack of solubility of dendrimers of generation 3 prevents construction of higher generations.

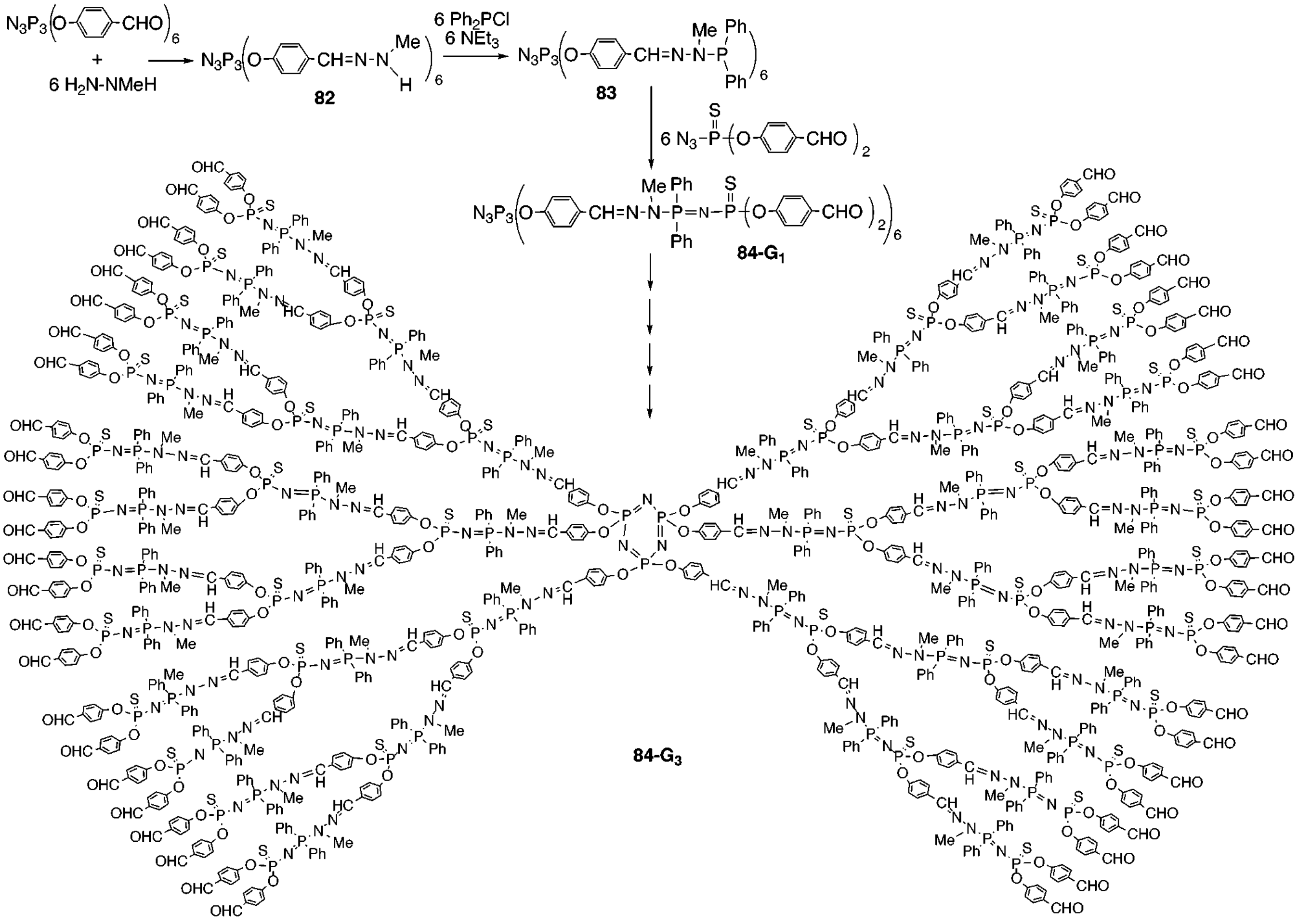
Three different synthetic routes for small phosphorus dendrimers using in all cases the phosphotrihydrazide $(S)P(NCH_3NH_2)_3$ have also been reported.[95] These multifunctionalized species have on the periphery functionalities such as aldehyde, primary amine, phenoxy, phosphane, or P–Cl (up to 12 for the largest compound), but none of them permits the preparation of large dendrimers.

A simple and general strategy involving the reiteration of only two reactions appears to be up to now the most efficient way to prepare neutral phosphorus-containing dendrimers up to the highest generation reported till now in dendrimer chemistry, i.e., generation 12.[84, 96]

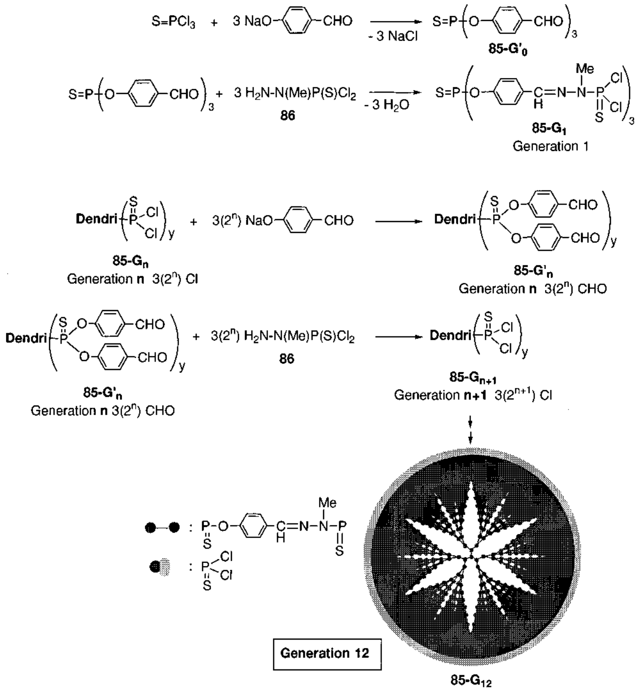
The first step consists of the reaction of $SPCl_3$ with the sodium salt of 4-hydroxybenzaldehyde in a 1/3 ratio to give **85-G′$_0$**. Further addition of the hydrazine derivative $H_2NN(CH_3)P(S)Cl_2$ (**86**) to **85-G′$_0$** affords quantitatively **85-G$_1$**, a first-generation dendrimer possessing six P–Cl bonds (Scheme 49).

Elaboration to second, third, and up to the twelfth generation is accomplished by repetition of these two steps. In each reaction cycle terminal aldehyde groups and terminal dichlorothiophosphoryl groups are introduced quantitatively and remain available for continued reactions. Remarkably no protection/deprotection procedure is necessary, and the only byproducts of the reactions are sodium chloride and water. Up to generation 11 dendrimers are very soluble in a variety of solvents such as THF, $CHCl_3$, CH_2Cl_2, etc. The dendrimer of generation 12 (theoretical molecular weight > 3 000 000 Da, more than 12 000 terminal P–Cl bonds) has poor solubility in these solvents, and this has prevented further construction to higher generations (see paragraph characterization and properties hereafter). A variety of cores can be used as starting material. As an example a dendrimer of generation 8 having 1536 aldehyde chain ends can be easily prepared from $N_3P_3Cl_6$ (Scheme 50).[97] Dendrimers were characterized by NMR, IR spectroscopy, and elemental analysis. Mass spectrometry (FAB) is useful for dendrimers up to generation 3.

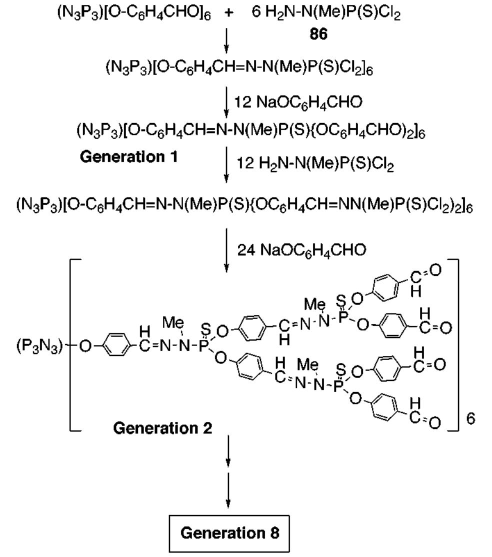
Scheme 48



Scheme 49



Scheme 50



Two dendrimers of generation 1 have been characterized by X-ray diffraction studies (Figure 5).[96,98] The data (length of each arm = 9 Å, distance between terminal P=S or P=O groups 17 Å, molecule resembles a three-bladed propellor when examined in the direction of the central P=S group) allow one to understand why steric congestion does not disturb the construction of dendrimers even for the highest generations and why terminal groups are readily available for further reactions.

Alternation of P=O and P=S groups can be easily realized when moving from one generation to another. Indeed it is possible, for example, to build a

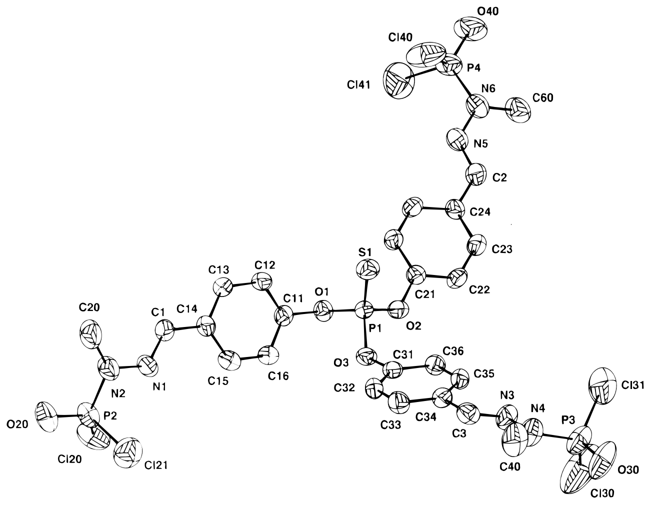


Figure 5. CAMERON drawing of a phosphorus-containing dendrimer of generation 1.

dendrimer of generation 4 bearing alternatively P═S or P═O groups at each generation or to build a dendrimer of generation 4 with P═S units at the core and within the cascade structure and P═O groups on the surface (Figure 6).[98]

Another very efficient way of construction of dendrimers should be emphasized. It is outlined in Schemes 51 and 52. Dendrimers **87-G$_1$**−**87-G$_4$** and **87-G′$_1$**−**87-G′$_4$** can be prepared in high yield.[99] They possess a number of P═N−P═S groups, and the O−C_6H_4CH═N−N(CH_3)P(S) fragment functions as the linker between each generation in all these macromolecules. From **87-G′$_4$** a new repeat unit at the surface can be introduced via addition of methylhydrazine to the 64 terminal aldehyde groups and then treatment of the resulting polyhydrazone with the phosphane Ph_2PCH_2OH: under these conditions the dendrimer **87-G‴$_4$** is formed. The last step of the construction of this new surface layer consists of the reaction of **87-G‴$_4$** with the azide $N_3P(S)(OC_6H_4\text{-}CHO)_2$, leading to the dendrimer of generation 5 (**88-G′$_5$**) with 128 terminal aldehyde groups. The application of the methodologies shown in Schemes 55 and 56 leads to the formation of dendrimers **89-G′$_6$** and **90-G′$_7$**.[99]

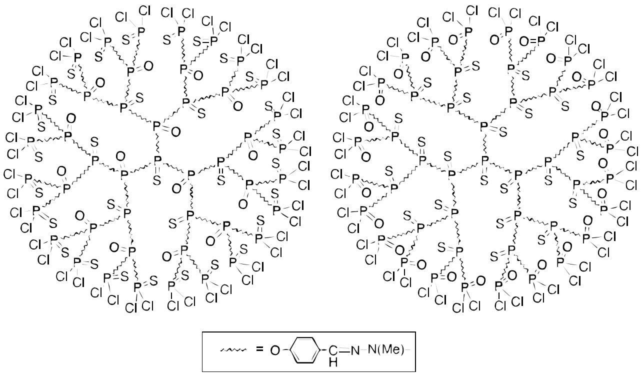


Figure 6. Dendrimers of generation 4 with P═O and P═S groups.

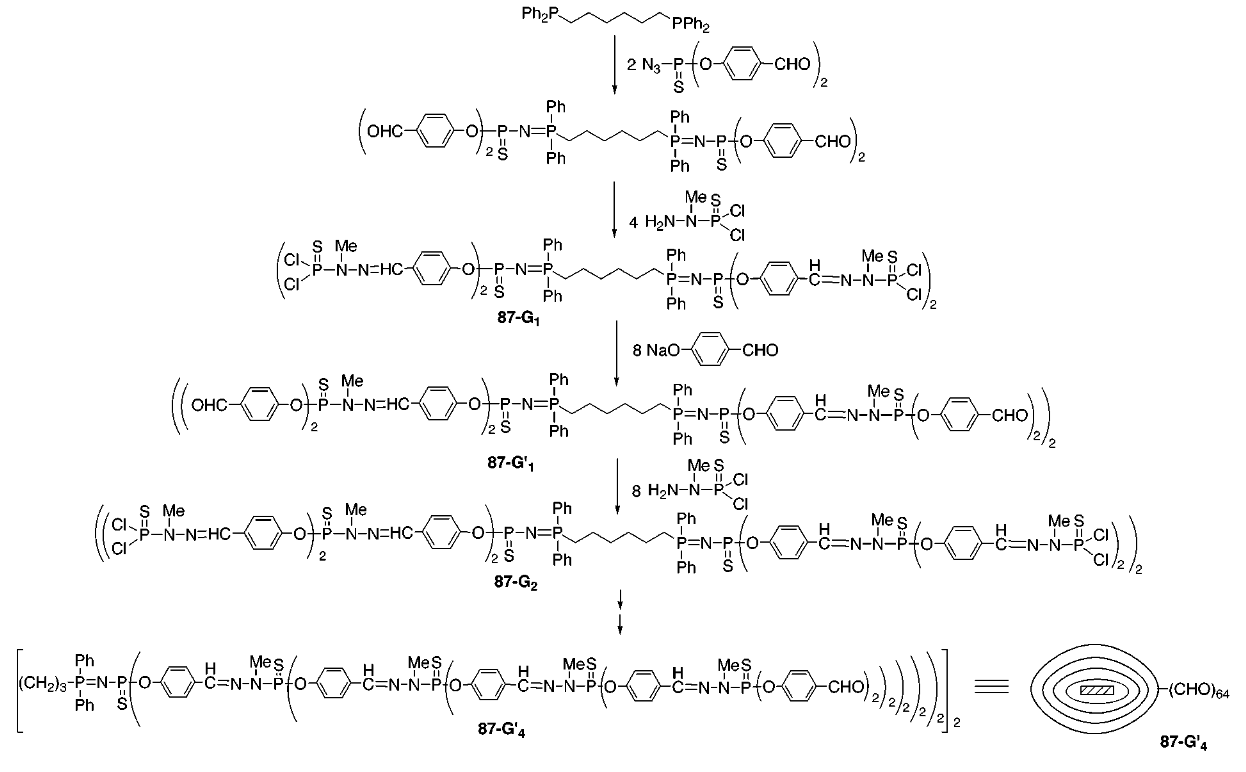
B. Reactivity

All the examples reported in this section concern the reactivity of hydrazono-containing dendrimers.

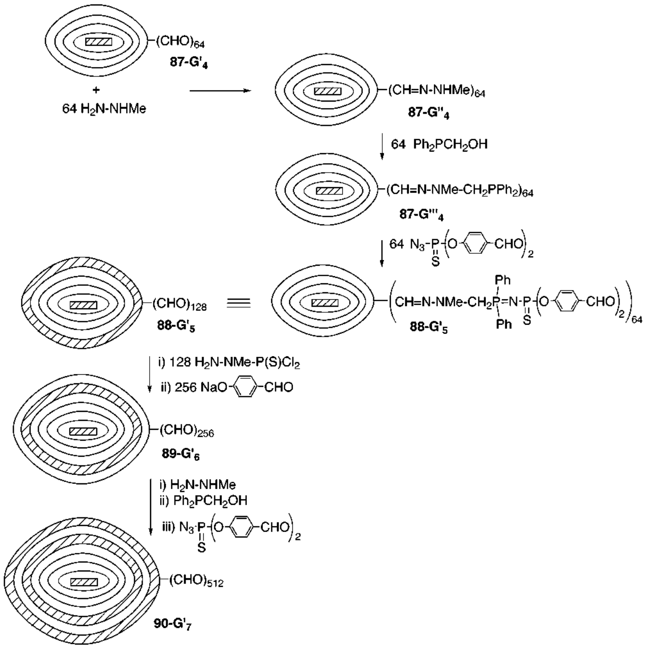
1. Reactivity on the Surface

a. Reactions on Terminal P(X)Cl$_2$ Groups. *Monosubstitution Reactions.* Addition of bisallylamine to dendrimers **85-G$_1$**−**85-G$_4$** (generations 1−4) possessing 3, 6, 12, and 24 terminal P(S)Cl$_2$ groups, respectively, led selectively to monosubstitution of the P(S)Cl$_2$ moieties, regardless of the number of

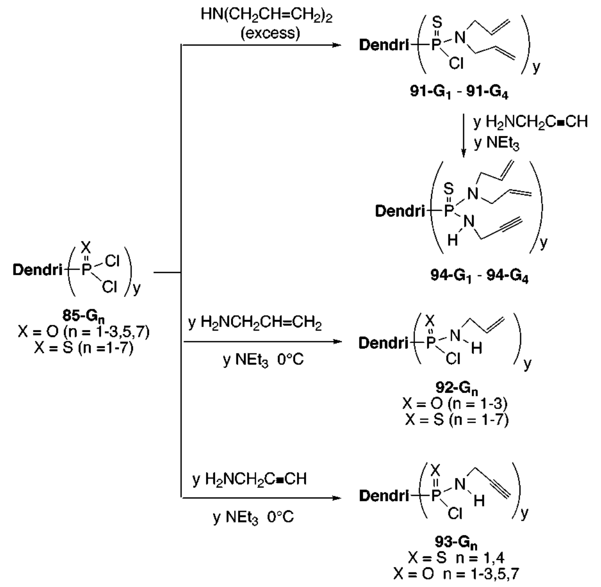
Scheme 51



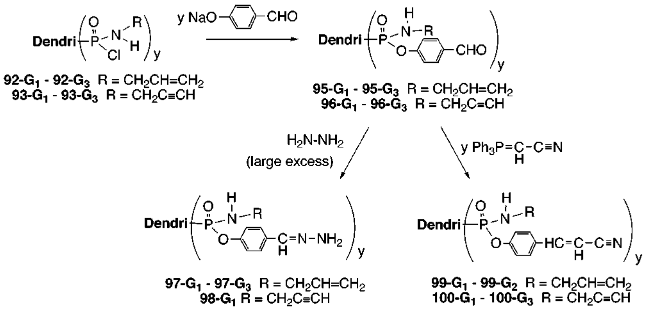
Scheme 52



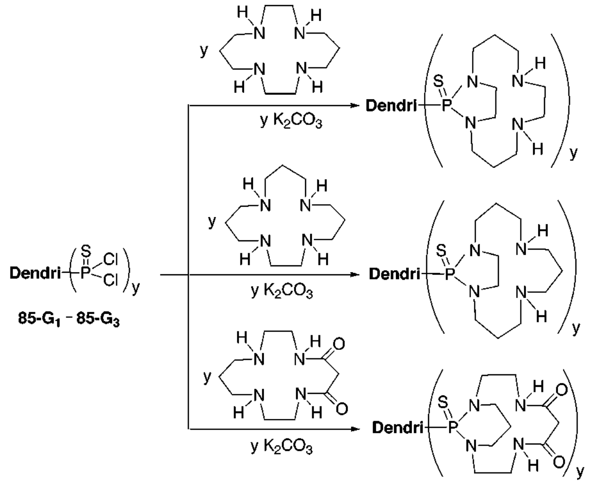
Scheme 53

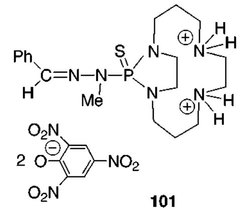


Scheme 54



Scheme 55





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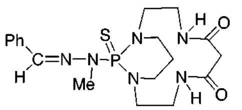

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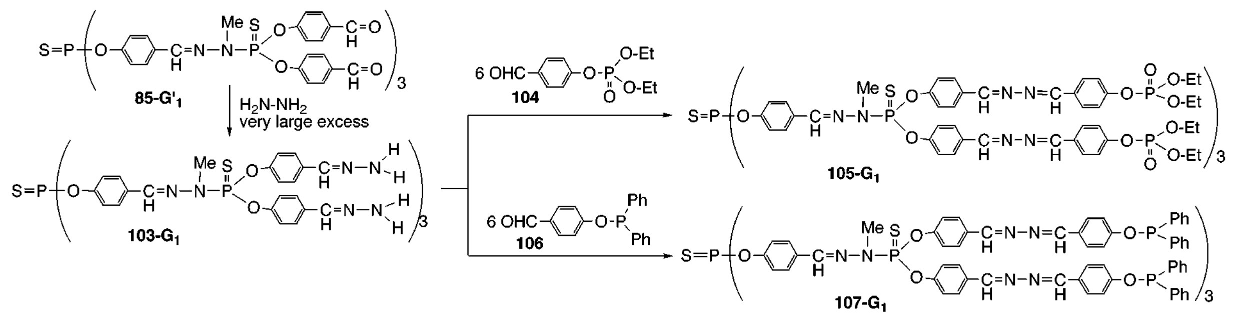
equivalents of bisallylamine used, with the formation of derivatives **91-G$_1$**–**91-G$_4$** (Scheme 53), possessing three different types of functionalities on the surface. Trifunctionalization of dendrimers via monosubstitution reactions was also attempted by reacting **85-G$_1$** with 3 equiv of allylamine in the presence of 3 equiv of base (generally triethylamine) in THF at 0 °C for 3 h. A selective and quantitative monosubstitution took place affording **92-G$_1$** possessing at each chain end three functionalities, namely, N–H bond, P–Cl bond, and allyl group.[100] Such a selective reaction can be extended to dendrimers of generations 2–7 allowing the grafting of up to 192 NH(allyl) moieties. In all cases each P(S)Cl$_2$ group behaved as a monomeric species and reactions could be controlled to avoid disubstitution reactions on each P(S)Cl$_2$ group, regardless of the generation considered (Scheme 53). This useful and convenient entry to multiply "trifunctionalized" dendrimers can be extended to a variety of dendrimers with P(S)Cl$_2$ or P(O)Cl$_2$ terminal groups, and it was also successfully applied in the reaction of propargylamine with dendrimers **85-G$_n$** having terminal P(X)Cl$_2$ (X = O, S) groups (Scheme 53).

Disubstitution Reactions. While attempts to disubstitute dendrimers **85-G$_1$**–**85-G$_4$** with bisallylamine failed, the corresponding monosubstituted compounds **91-G$_1$**–**91-G$_4$** were still reactive toward amines such as propargylamine. The addition of this amine to **91-G$_1$** and **91-G$_4$** led to compounds **94-G$_1$** and **94-G$_4$**, respectively, that incorporate both bisallylamino and propargylamino groups on the same phosphorus atom (Scheme 53).[100]

The remaining P–Cl bond on each terminal P(X)(NHR)Cl (R = allyl or propargyl) group is still reactive and addition of the sodium salt of 4-hydroxybenzaldehyde led clearly to other new multiply trifunctionalized dendrimers, **95-G$_1$**–**95-G$_3$** and **96-G$_1$**–**96-G$_3$** (Scheme 54).

Macromolecules **95-G$_n$** and **96-G$_n$** are good models for the preparation of dendrimers possessing four different functionalities at each chain end. Indeed reaction of hydrazine to **95-G$_1$** and **95-G$_3$** afforded dendrimers **97-G$_1$** and **97-G$_3$**, respectively, bearing compatible functionalities: NH, NH$_2$, allyl, and hy-

Scheme 56



drazono groups (Scheme 54). The same reactions can be performed with derivatives **96-G$_1$**.[100]

A Wittig reaction involving the phosphonium ylide $Ph_3P{=}CH{-}CN$ and dendrimers **95-G$_n$** and **96-G$_n$** allowed the preparation of other multiply "tetrafunctionalized" species, **99-G$_n$** and **100-G$_n$** (Scheme 54).[100]

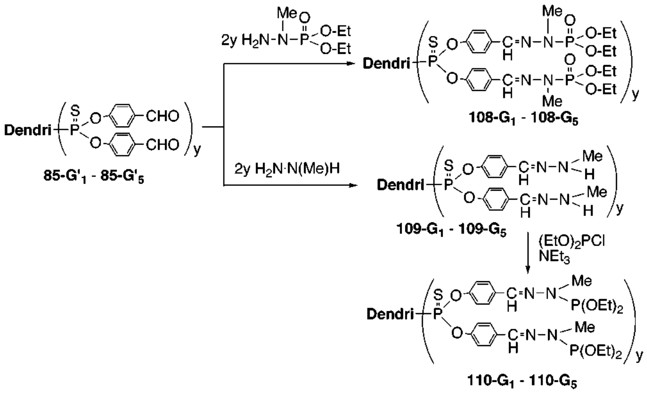
Disubstitution reactions can be performed directly from the $P(X)Cl_2$ chain ends with, for example, allyl- or propargylamines, and this leads to dendrimers with terminal $P(X)(NHR)_2$ groups (X = S, O; R = allyl or propargyl).[101] Such disubstitution reactions can be conducted also with cyclic polyamines such as tetraazacyclotetradecane or pentadecane and tetraazacyclotetradecanedione and $P(S)Cl_2$ chain ends of dendrimers of generations 1 and 3 in the presence of K_2CO_3. Up to 12 of these nitrogen macrocycles can be grafted, and the way of grafting was corroborated by X-ray crystallography studies performed on the monomers **101** and **102** (Scheme 55).

Therefore all these experiments conducted on terminal $P(X)Cl_2$ (X = S or O) groups corroborate the unique specificity of the substitution reactions of phosphorus-containing dendrimers. All these results suggest that attachment of several active substances showing different properties can be envisaged and that grafting of dendrimers to a second polymer by means of a suitable functionality leaving other functional groups available for further reactions may also be possible.

b. Reactions of Terminal Aldehyde Groups. *Phosphate-, Phosphite-, Ylide-, and Phosphonate-Terminated Dendrimers.* Phosphate units can be grafted on the surface of a dendrimer of generation 1 **85-G′$_1$** via a sequence of two reactions: (i) condensation of **85-G′$_1$** with hydrazine and (ii) condensation of the resulting hexahydrazone **103-G$_1$** with the aldehyde **104** (Scheme 56).[102] Extension of this reaction to higher generations (2−5) failed because of lack of solubility of the final products. Similarly the hexahydrazone **103-G$_1$** can be condensed with the phosphinite **106** to form the hexaphosphinite **107-G$_1$**. Here again solubility prevents the formation of higher generations (Scheme 56).

Hydrazonophosphate-terminated dendrimers **108-G$_1$−108-G$_5$** can be readily prepared by reacting the dendrimers **85-G′$_1$−85-G′$_5$** with $H_2NNMeP(O)(OEt)_2$. Up to 96 hydrazonophosphate groups can be anchored on the surface (Scheme 57).[102] Many types of phosphorus derivatives can be grafted on the surface either using this strategy or using the two-step methodology described in Scheme 56, in which the anchorage of P(III) units such as hydrazinophosphites is shown.

Scheme 57



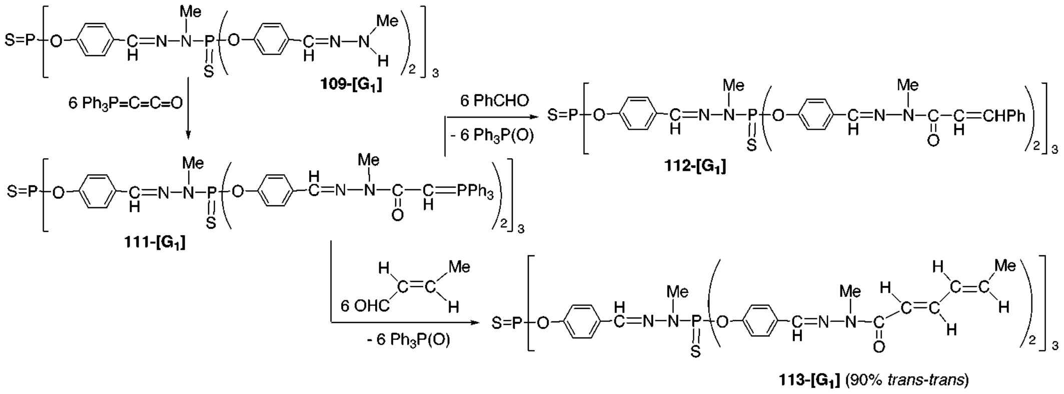
Methods allowing the grafting of various phosphorus units through the formation of phosphorus−carbon bonds should also be noted. Dendrimers **109-G$_n$** can be used as the starting material for the grafting of ylides. Treatment of triphenylphosphoranylidene ethenone ($Ph_3P{=}C{=}C{=}O$) with **109-G$_1$** affords **111-G$_1$** formed by addition of the terminal acidic hydrogen onto the C=C bond. The resulting hexaylide reacts with benzaldehyde or crotonaldehyde in a classical Wittig reaction to give the dendrimers **112-G$_1$** and **113-G$_1$**, respectively (Scheme 58).[102]

Phosphonate units can be also grafted on the surface. In all cases the method used consists of the addition of P−H bonds on polar double bonds of the dendrimer (aldehyde or imine end groups) (Scheme 59). The anchorage of phosphonate groups can be extended to high generations without any problem of solubility. Addition of phosphonates $(EtO)_2P(O)H$ on a dendrimer with α,β-unsaturated aldehydes as end groups can also be performed.[102]

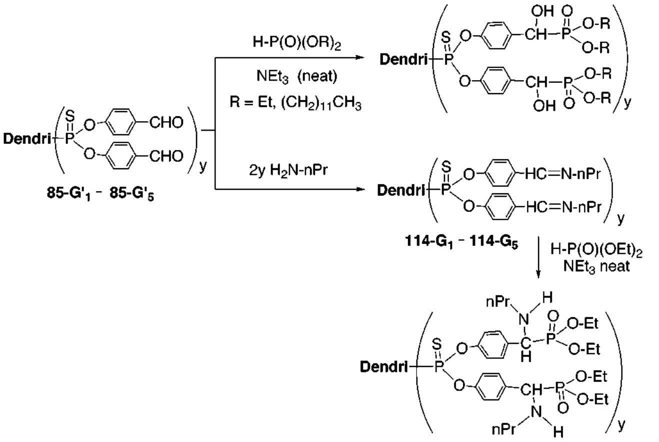
Several remarks can be made concerning all these dendrimers with phosphorus-containing chain ends. Solubility of the dendrimers depends essentially on the type of substituents grafted on the surface. Thus, azine phosphate, azine phosphinite, and ylide linkages on the periphery reduce significantly the solubility of dendrimers possessing more than six end groups, whereas the grafting of long chain hydrocarbons increases the solubility in organic solvents. Each end group behaves independently as far as the reactivity is concerned.

Other Condensation Reactions. A classical Schiff reaction between dendrimers of generations 1, 2, and 4 (**85-G′$_1$**, **85-G′$_2$**, and **85-G′$_4$**) and 4-aminobenzo-15-

Scheme 58



Scheme 59



crown-5 takes place to afford dendrimers in which the surface is covered by 6, 12, or 48 crown ether units (Scheme 60) (Figure 7).[103] Reactions conducted

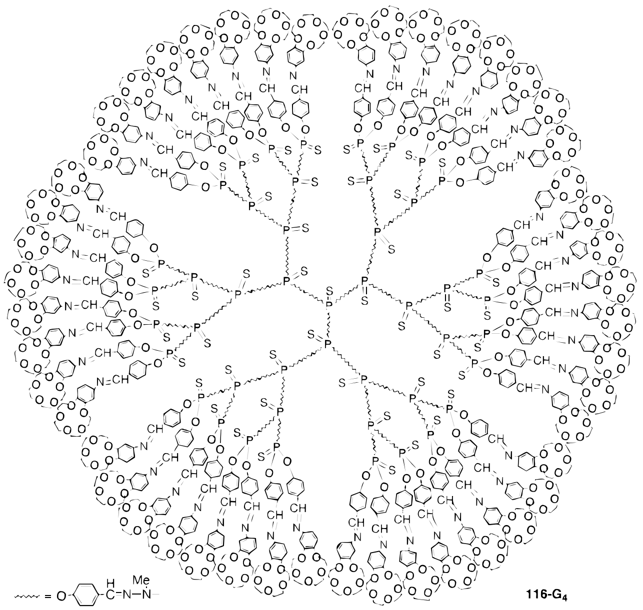
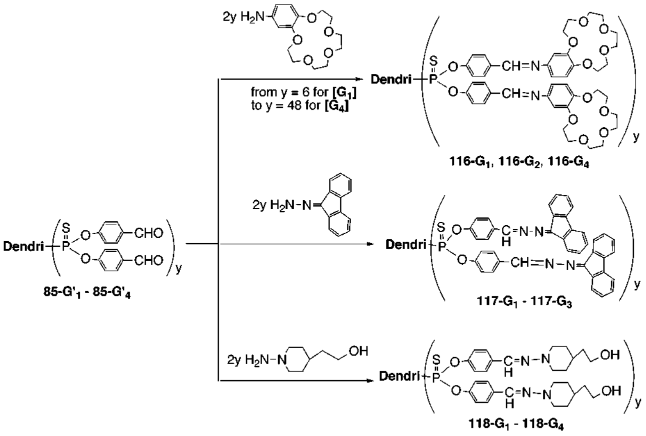


Figure 7. Phosphorus-containing dendrimer (generation 4) decorated with 48 crown ether units.

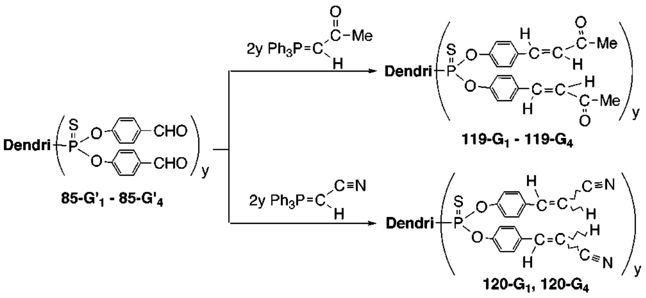
with aldehyde-terminated dendrimers **85-G′$_1$–85-G′$_4$** and fluorenone hydrazone or 1-amino-4-(2-hydroxyethyl)piperazine occur as expected leading to fluorenone- and hydroxy-terminated dendrimers (Scheme 60).

Scheme 60



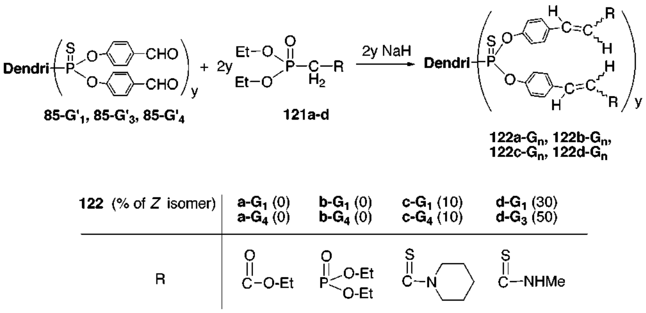
Wittig and Horner–Wadsworth–Emmons Reactions. Wittig reactions with dendrimers having aldehyde chain ends were also investigated. Dendrimers **85-G′$_1$–85-G′$_4$** react with (acetylmethylene)triphenylphosphorane in THF at reflux for 48 h to give the new dendrimers **119-G$_1$–119-G$_4$** that were isolated in high yields. A similar experiment performed with (cyanomethylene)triphenylphosphorane gave the new macromolecules **120-G$_1$** or **120-G$_4$** possessing either 6 or 48 terminal cinnamonitrile type groups (Scheme 61).[101] Trans configuration for the terminal olefinic chain ends was found for **119-G$_1$–119-G$_4$**, while a mixture of trans/cis isomers in a 4/1 ratio was obtained for **120-G$_1$** as well as for **120-G$_4$**. Remarkably no difference of reactivity was detected when moving from dendrimer of generation 1 to dendrimers of generations 2–4.

Scheme 61

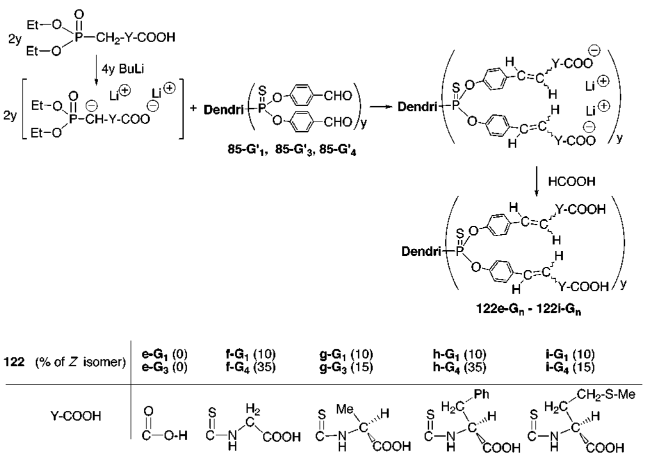


The Horner–Wadsworth–Emmons reaction applied to aldehyde-terminated dendrimers has been conducted with the salts of the ester, phosphonate, thioamide, and carboxylic acid derivatives of phosphonates. It leads to dendrimers bearing various α,β-unsaturated functional groups on the surface, and these species were isolated after workup in moderate yields.[104] Depending on the starting phosphonate it was found that there was either solely formation of the *E* isomer detectable by ^1H NMR or formation of a mixture of *E* and *Z* configuration of the resulting double bond (Scheme 62). This reaction was extended to the phosphonate derivative of amino acids such as glycine, L-alanine, L-phenylalanine, and L-methionine. In all cases water-soluble dendrimers with $HC{=}CHC(S)NHCHR'COOLi$ ($R' = H$, Me, CH_2Ph, CH_2CH_2SMe) are obtained but not isolated: when acidified these species give in moderate yields dendrimers **122-G$_1$–122-G$_4$** (Scheme 63). Both *E* and *Z* isomers of the CH=CH bond for all the dendrimers having thioamide functions were identified.

Scheme 62



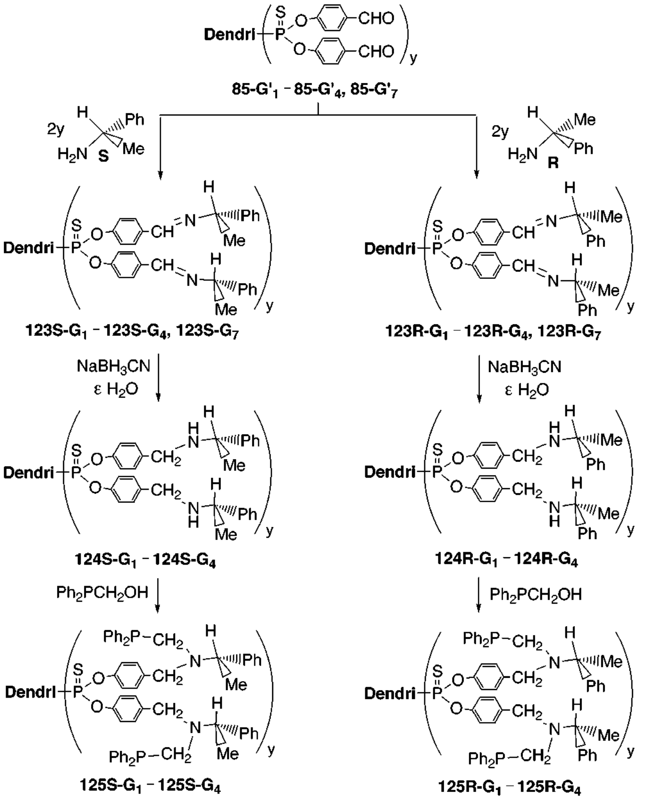
Scheme 63



Introduction of Charges on the Surface. As stated above Engel et al. reported the synthesis of polycationic phosphorus-containing dendrimers (see section III.A.3). Polycationic dendrimers can also be formed by reacting the $P(S)Cl_2$ chain ends of dendrimers with $H_2N(CH_2)_2NEt_2$.[105] Polyanionic species are isolated in good yield by a Horner–Wadsworth–Emmons reaction involving aldehyde groups (see above). These types of charged polymers are water-soluble.

Chiroptical Properties of Dendrimers with Chiral End Groups. Several papers have reported the chiroptical properties of organic dendrimers with chiral substituents on the surface. Six series of dendrimers with stereogenic end groups have been reported. The first one was obtained via condensation reactions between dendrimers of generations 1–4 (**85-G′$_1$–85-G′$_4$**) and the dendrimer of generation 7 (**85-G′$_7$**) bearing terminal aldehyde groups and with methylbenzylamine *S* or *R*. The resulting stereogenic dendrimers with imine end groups (**123*S*-G$_n$** and **123*R*-G$_n$** ($n = 1$–4, 7)) are precursors to two new series of stereogenic dendrimers (**124*S*-G$_n$** and **124*R*-G$_n$**) obtained by selective reduction of the imine bonds. The reaction of Ph_2PCH_2OH with **124*S*-G$_n$** and **124*R*-G$_n$** ($n = 1$–4) occurs at room temperature and affords in good yield the corresponding stereogenic phosphino-terminated dendrimers **125*S*-G$_1$–125*S*-G$_4$** and **125*R*-G$_1$–125*R*-G$_4$** (Scheme 64).[106]

Scheme 64



Study of the chiroptical properties of all these derivatives was undertaken. It was found that the value of the molar specific rotation of these dendrimers depends only and linearly on the number of stereogenic groups, whereas the value of the specific rotation depends linearly on the weight percentage contribution of the stereogenic groups to the molecular weight of the stereogenic dendrimer (see Figure 8 as an illustration). It can be inferred from these results that each terminal stereogenic group of nonhindered dendrimers behaves like an isolated molecule.

c. Metalladendrimers. During the past few years some attention has been focused on the use of dendrimers as multidendate ligands. These macromolecules have been found to incorporate easily on

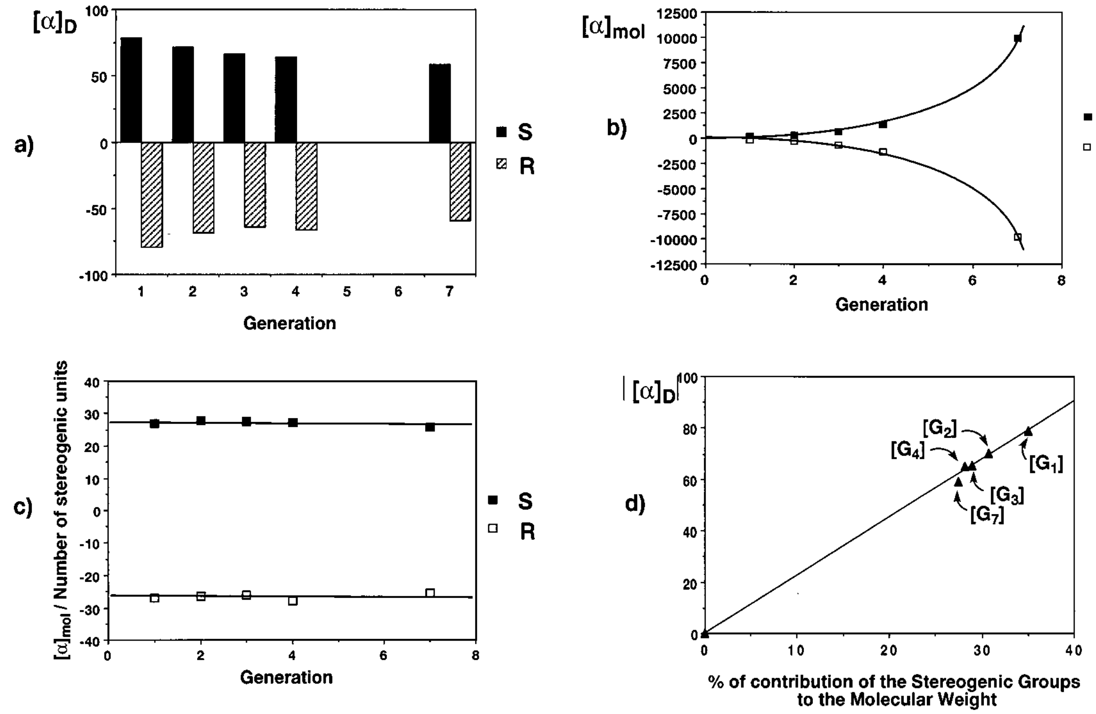
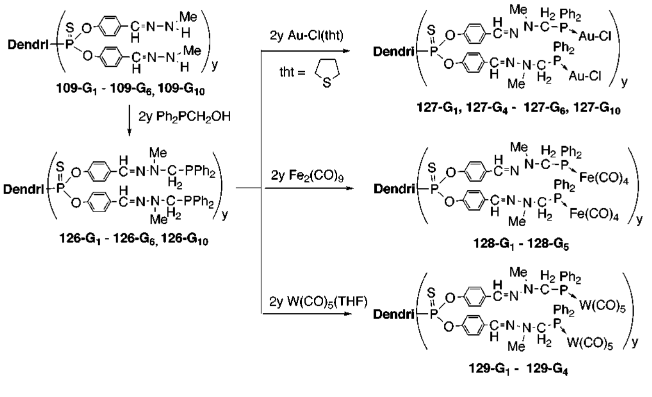


Figure 8. (a) Specific rotation $[\alpha]_D$ versus generation for dendrimers **123*S*-G*n*** and **123*R*-G*n***; (b) molar rotation $[\alpha]_{mol}$ versus generation for dendrimers **123*S*-G*n*** and **123*R*-G*n***; (c) molar rotation $[\alpha]_{mol}$ divided by the number of stereogenic groups versus generation for dendrimers **123*S*-G*n*** and **123*R*-G*n***; (d) absolute value of the specific rotation $|[\alpha]_D|$ versus the percentage of contribution of the stereogenic groups to the molecular weight for dendrimers **123*S*-G*n*** and **123*R*-G*n***.

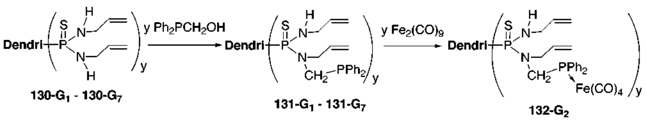
the surface, or within the cascade structure, metals such as ruthenium, osmium, platinum, palladium, iron, cobalt, gold, tungsten, nickel, copper, etc. Some applications of these metalladendrimers have already been found in different areas. A few metallaphosphorus-containing dendrimers have been used in catalysis (see sections III.A.2 and III.A.3).

A way to graft phosphino groups on the surface consists of the treatment of aldehyde-terminated dendrimers of generations 1−10 first with methylhydrazine and then with the phosphane Ph_2PCH_2OH (Scheme 65). This last reaction needs 3 days at 65 °C to go to completion for all the generations, including the tenth generation. The dendrimer of generation 10 **126-G$_{10}$** possesses more than 3000 phosphino groups and can be considered to be the largest polyphosphane of defined structure ever synthesized.[107] Another way to introduce phosphino groups on the surface has been reported: it is the selective monoaddition of Ph_2PCH_2OH to dendrimers **130-G*n*** bearing allylamino groups (Scheme 66).[108]

Scheme 65



Scheme 66



Complexations were first attempted with M(I) compounds and phosphane-terminated dendrimers of generations 1, 4, 6, and 10 (Scheme 65). The absence of any trace of free phosphane in ^{31}P NMR spectra confirms the complete complexation of all the terminal groups within the limits of NMR sensitivity. The presence of gold atoms on the surface allows the visualization of these molecules by high-resolution electron microscopy.[107] As an example, dendrimer **127-G$_{10}$** appears as a bowl-shaped molecule with a diameter of 155 Å (Figure 9).[96]

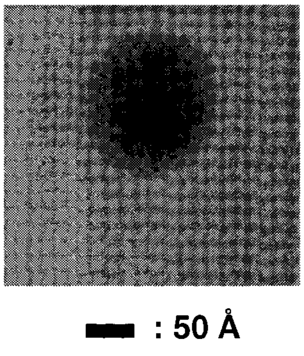
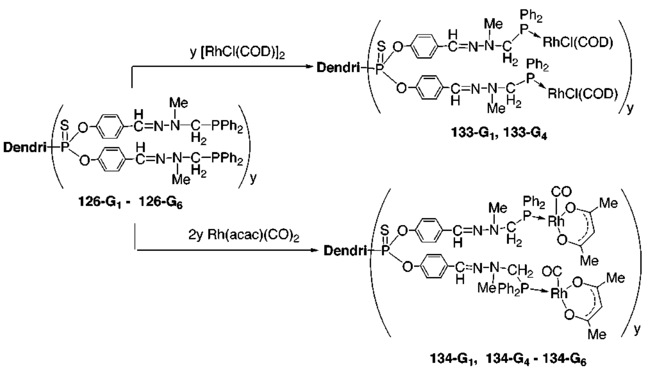
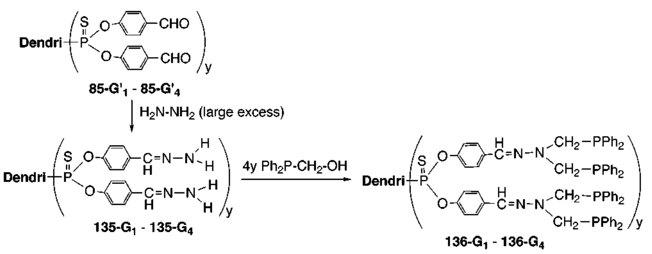


Figure 9. Electron micrograph of the dendrimer **127-G$_{10}$**.

Scheme 67



Scheme 68



Complexation ability of dendrimers **126-G$_n$** was extended to $Fe_2(CO)_9$ and $W(CO)_5$ THF. In all cases complexation occurs in a few hours to give the iron(0) and tungsten(0) derivatives **128-G$_n$** and **129-G$_n$** (Scheme 65).[107,108,109]

The reaction of Rh(I) derivatives such as Rh(acac)$(CO)_2$ (acac: acetyl acetonate) with dendrimers **126-G$_n$** ($n = 1, 4, 6$) leads as expected to the metalladendrimers **134-G$_n$**. Similar reactions can be done with $[Rh(\mu\text{-}Cl)(cod)]_2$ (cod: cyclooctadiene) (Scheme 67).[109,110]

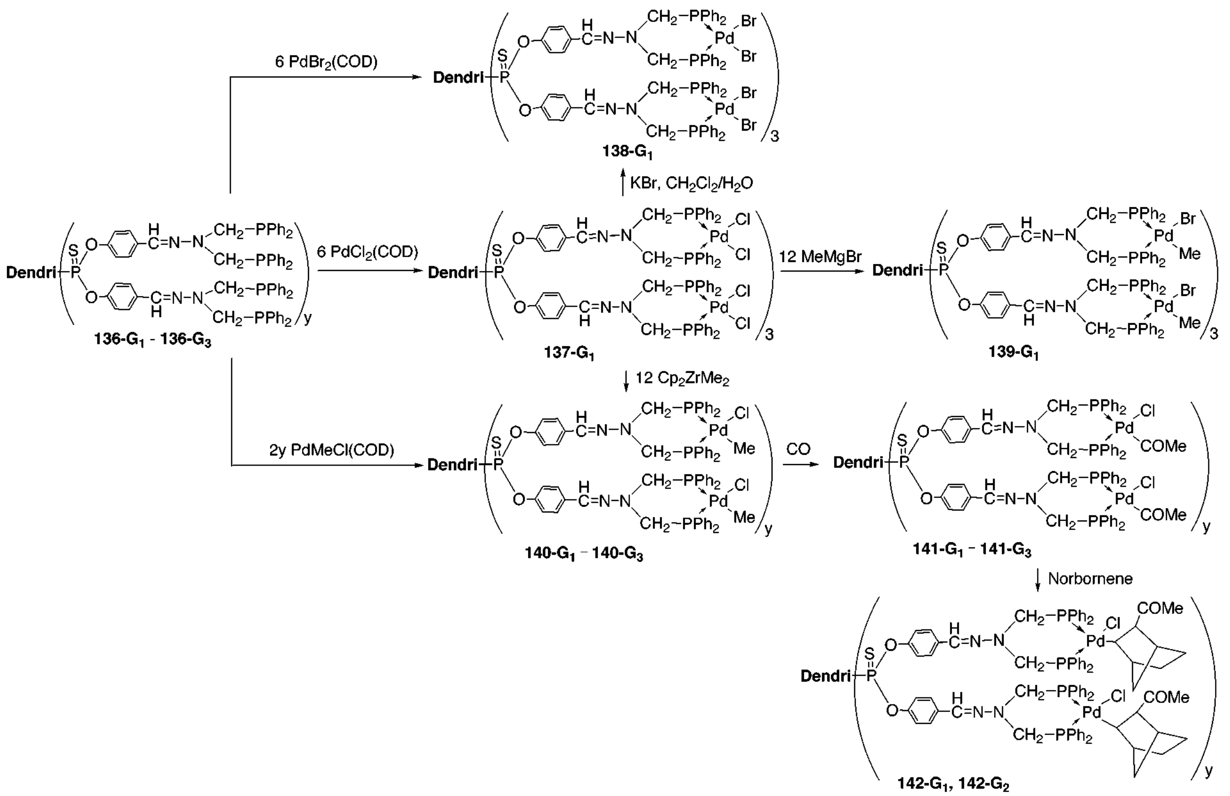
Analogous experiments can be envisaged with multidentate dendrimers possessing diphosphino groups on the surface. Addition of hydrazine to aldehyde-terminated dendrimers of generations 1−4, **85-G′$_1$−85-G′$_4$**, followed by treatment of the resulting hydrazono chain ends with Ph_2PCH_2OH affords the desired multidentate macromolecules possessing from 6 to 48 $N(CH_2PPh_2)_2$ terminal groups (Scheme 68).[111]

A variety of palladium complexes can be prepared from reaction of these species with $PdCl_2(COD)$, $PdBr_2(COD)$, and PdMeCl(COD). Some of these metallacomplexes react with CO to give the expected insertion products. The insertion of norbornene into Pd−acetyl bonds was also shown (Scheme 69).[111]

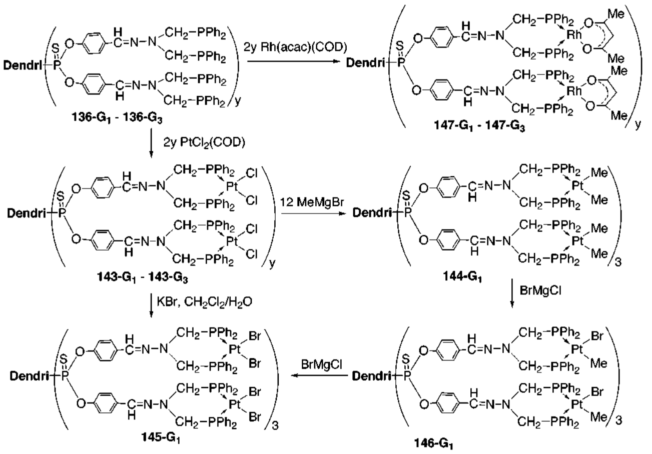
Isolation of complexes **143-G$_1$**, **143-G$_2$**, and **143-G$_3$** incorporating 6, 12, and 24 $PtCl_2$ moieties, respectively, on the dendrimer surface was successfully performed (Scheme 70). Diphosphinorhodium complexes **147-G$_1$**, **147-G$_2$**, or **147-G$_3$** are also prepared in good yield from the reaction of the rhodium complex Rh(acac)(COD) and the corresponding dendrimers.[111]

The reaction of the ruthenium polyhydrides $RuH_2(PPh_3)_4$ and $RuH_2(H_2)_2(PCy_3)_2$ with the dendrimers of generations 1−3 possessing terminal diphosphino groups leads to the new metalladendrimers with $N(CH_2PPh_2)_2RuH_2(PPh_3)_2$ and $N(CH_2PPh_2)_2RuH_2(H_2)(PCy_3)$ chain ends (Scheme 71, Figure 10).[112] The compounds with $P(Cy)_3$ groups exist as a mixture of isomers. These compounds were shown to possess a stretched dihydrogen ligand and to display a high temperature for the minimum of the T_1 relaxation time, in agreement with their binding to the dendrimer in solution. These metalladendrimers react with CO leading to new dihydridocarbonylruthenium complexes.

Scheme 69



Scheme 70



2. Reactivity within the Cascade Structure

a. Polycationic Dendrimers. It has been demonstrated that the incorporation of charges either at each generation during the construction of the dendrimer or only on the surface can be performed by taking advantage of the high reactivity of terminal groups (see sections III.A.3 and III.B).

A strategy for the synthesis of phosphorus-containing dendrimers with generations of different constitution was developed in order to be able to incorporate selectively charges in different layers of the dendrimer: at the core, at the core and on the surface, within the cascade structure (core and internal generations), or even within the cascade structure and on the surface. Up to 322 charges can be chemoselectively incorporated in the skeleton. Remarkably the resulting macromolecules are fairly soluble in several solvents.

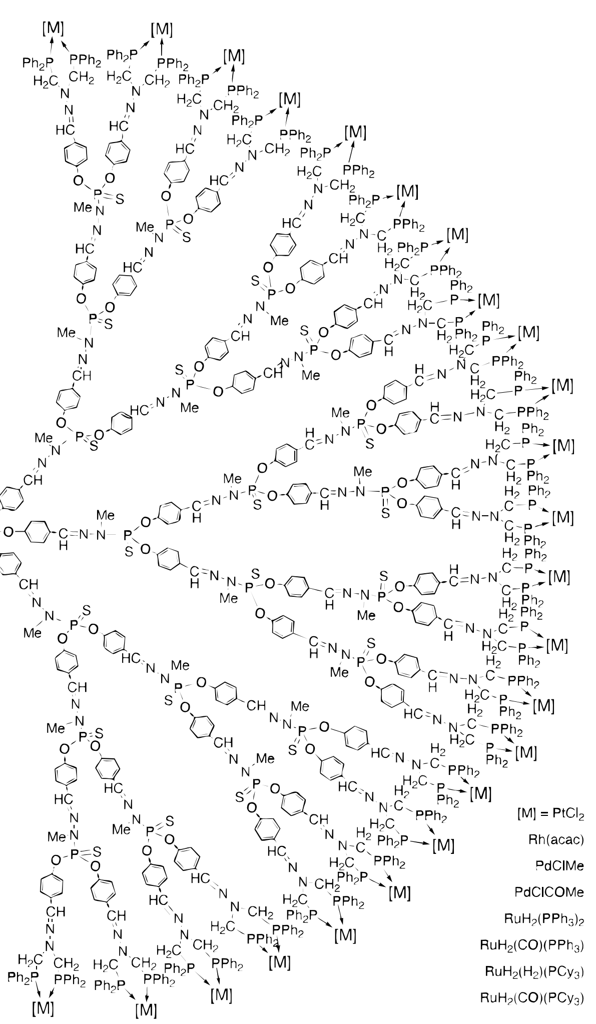
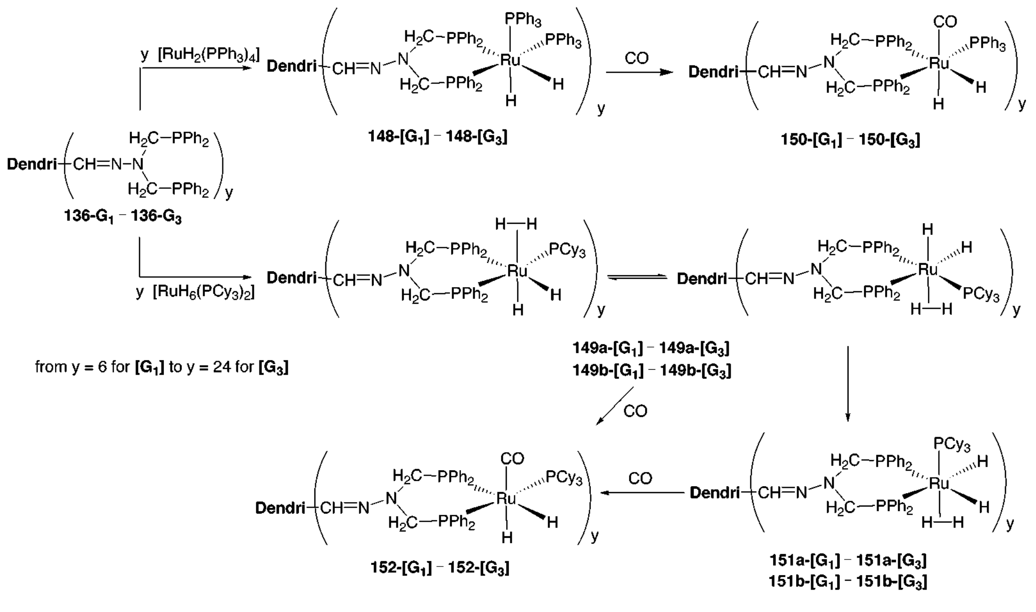


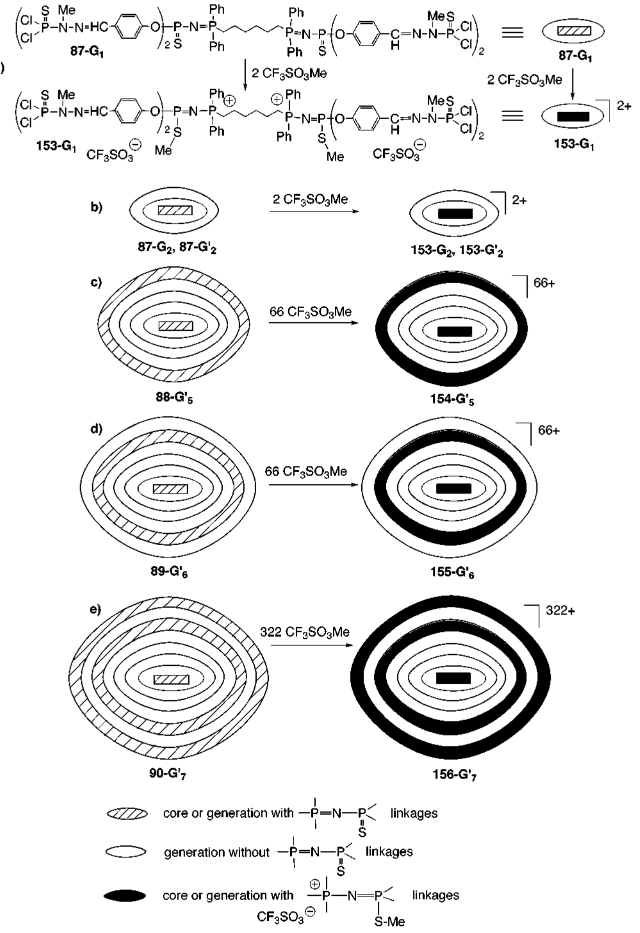
Figure 10. Phosphorus-based dendrimer of generation 3 with 24 terminal metal complex functionalities.

The respective polycationic dendrimers were readily prepared by selective alkylation of the thiophosphoryl groups of the $(Ph)_2P{=}N{-}P(S)$ units (Scheme 72).[99] As an example, alkylation of the core of the dendrimer **89-G′$_6$** (sixth generation: two $(Ph)_2P{=}N{-}P{=}S$ linkages at the core, 64 for the fifth generation, and an upper generation incorporating 256 terminal aldehyde groups) can be cleanly performed and was monitored by ^{31}P NMR spectroscopy. The bisalkylation of the core is accompanied by alkylation of the 64 internal $P{=}N{-}P{=}S$ fragments giving rise to the

Scheme 71



Scheme 72



polycationic macromolecule **155-G′$_6$**. This demonstrates that the core of this sixth-generation dendrimer is available for certain reactions and that the porosity of these dendrimers is very high.

Chemoselective grafting of up to 18 allyl or propargyl groups, at the core and within the cascade structure of a dendrimer of generation 4 possessing 18 P=N−P=S units, has also been reported.[113] The reaction proceeds instantaneously when allyl or propargyl triflates are used and gives quantitatively the polycationic dendrimers **157-G$_4$** and **158-G$_4$**, respectively (Scheme 73). The same reaction conducted with a dendrimer of generation 1 (**87-G$_1$**) allows the incorporation of two allyl or propargyl units with the formation of **157-G$_1$** or **158-G$_1$**, respectively. The molecular structure of **157-G$_1$** has been confirmed by X-ray crystallographic analysis which clearly shows that alkylation takes place selectively on the sulfur atom of each P=N−P=S fragment (Figure 11). **157-G$_1$** transforms slowly and quantitatively at room temperature for three months into a new functionalized macromolecule **159-G$_1$** incorporating two allenic systems instead of two propargylic ones. X-ray crystallography studies of **159-G$_1$** confirm the presence of two allenic units grafted on the P=N−P=S units.[113]

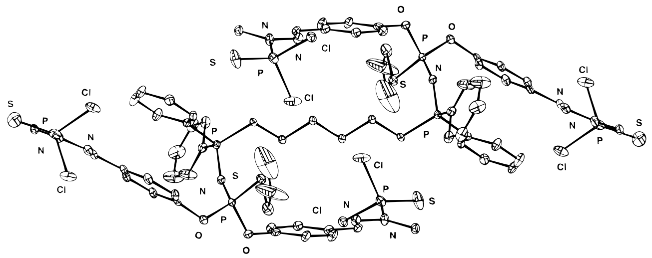


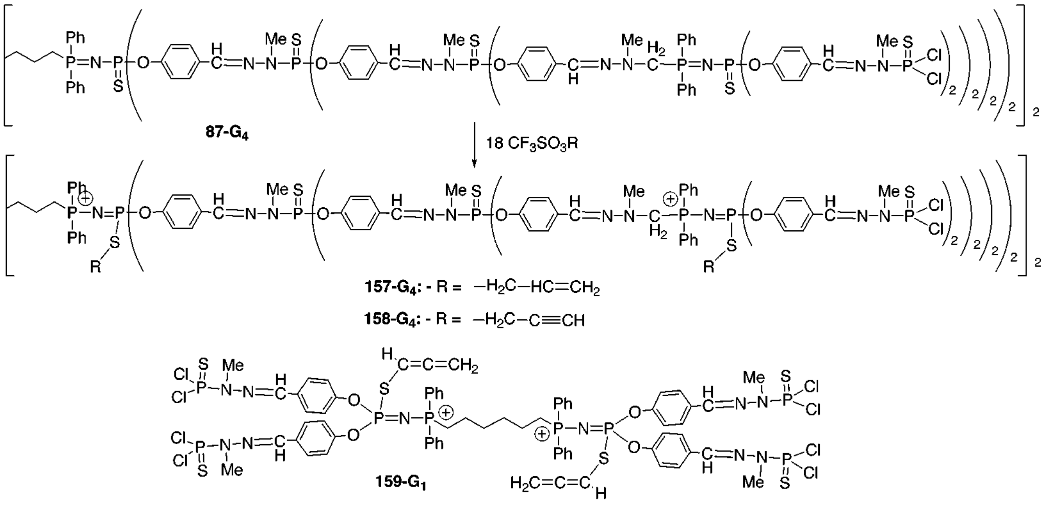
Figure 11. CAMERON drawing of a dendrimer of generation 1 with internal allyl groups.

Therefore the presence of P=N−P=S units in the internal layers of dendrimers allows functionalization, where and when desired into the internal voids, and this opens new routes for the preparation of well-defined molecular objects and devices for a number of applications.

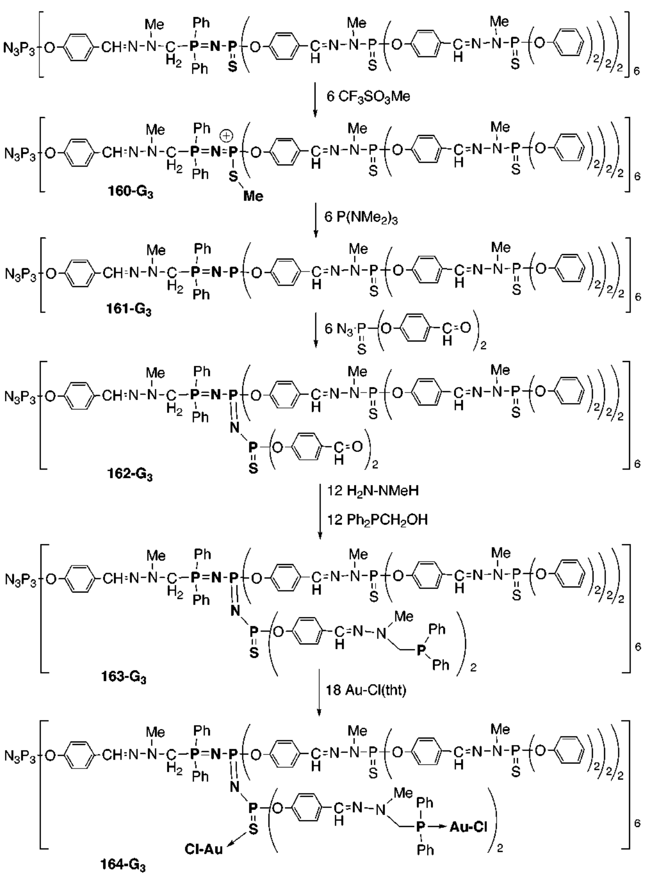
b. Incorporation of Gold. Regioselective gold complexation into the internal layers of dendritic and polydendritic macromolecules takes place not only on P=N−P=S groups but also on P=N−P=N−P=S fragments as well as on more classical CH_2PPh_2 moieties. Up to 90 AuCl units can be selectively grafted within the cascade structure of various dendrimers. Incorporation of these ligands in the internal layers of a number of dendritic or polydendritic structures is outlined in Schemes 74 and 75.[114]

c. Multidendritic Macromolecules. A way to build multidendritic macromolecules is that based on the use of internal functional groups of a dendrimer. For

Scheme 73



Scheme 74



this purpose it is necessary to be able to create very reactive functional groups in the internal layers either during the construction of the dendrimers or through regioselective postmodification of the macromolecular framework.

Two examples of the regioselective stepwise growth of six dendrimer units in the internal voids of a main dendrimer have been reported.[115] The central dendrimer **161-G$_3$** possessing six internal aminophosphite groups reacts with the azide $N_3P(S)(OC_6H_4\text{-}CHO)_2$ to give **167-G$_3$**: such a reaction allows incorporation of 12 aldehyde groups into the internal voids of a dendrimer. At this stage two different strategies can be used to start the construction of dendrimers within the cascade structure of **167-G$_3$** (Scheme 76).

In the first of these strategies 12 equiv of $H_2NN(CH_3)P(S)Cl_2$ are reacted with **167-G$_3$**; subsequent treatment of the resulting compound with the sodium salt $NaOC_6H_4CHO$ (24 equiv) leads to the grafting of six dendrimers of generation 2 into the cavities. Reiteration of this process permits the growth of these internal dendrimers to generations 3 and 4 (way a, Scheme 76).

The second strategy involves addition of methylhydrazine (12 equiv) to **167-G$_3$** and then the reaction of the resulting polyhydrazone first with the phosphane Ph_2PCH_2OH and then with $N_3P(S)(OC_6H_4\text{-}CHO)_2$. Such a branching pattern results in the grafting of six other dendrons of generation 2 within the internal cavities. Generations 3 and 4 of the six internal dendrimers can also be easily built up with this divergent method (way b, Scheme 76) (Figure 12).[115]

d. Reactivity of Internal Aminophosphite Groups. Internal $P{=}N{-}P<$ groups can be easily alkylated by methyl or allyl iodide leading to a new series of functionalized dendrimers including phosphonium salts at some precise internal layers. Other series of functionalized dendrimers are obtained by the Stauinger reaction of functionalized azides with the aminophosphite internal groups (isothiocyanate), and primary amine derivatives have been grafted regiospecifically in this way (Scheme 77).[116]

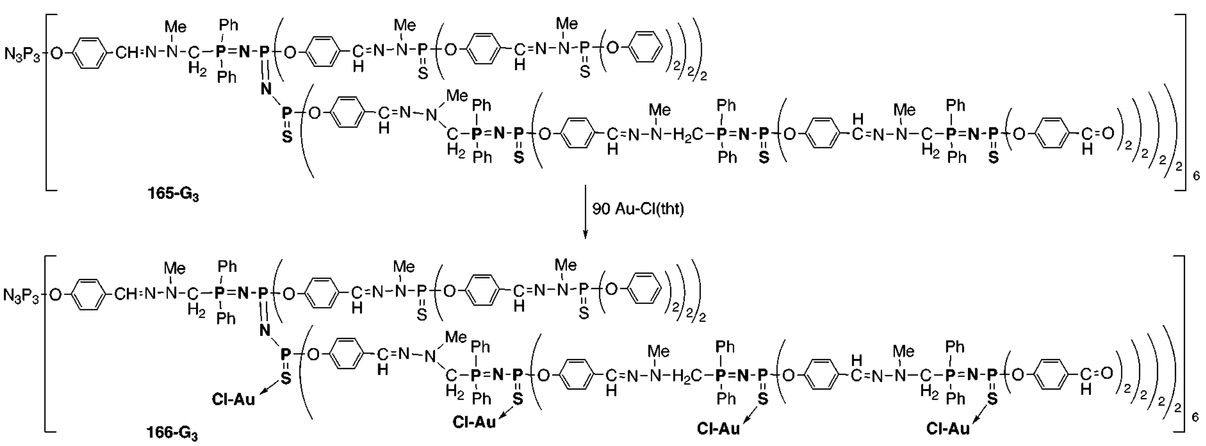
e. Reactivity of Internal Aldehyde Groups. Aldehyde groups incorporated within the cascade structure of dendrimers remain reactive (see above). Indeed treatment of a dendrimer possessing 12 internal aldehyde groups with 4′-aminobenzo-15-crown-5 (12 equiv) leads to the corresponding dendrimer bearing 12 crown ether units within the cascade structure (Figure 13).[116]

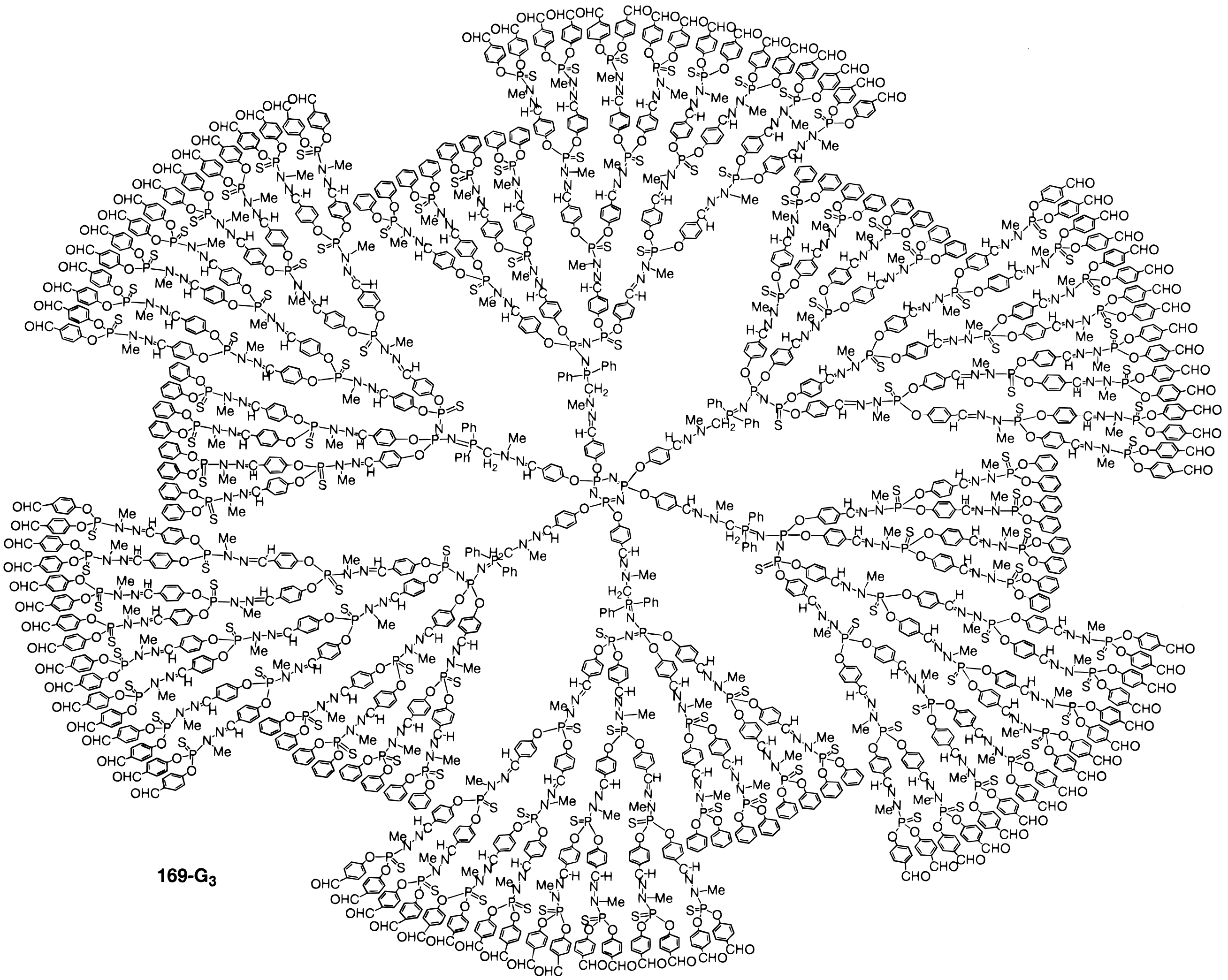
C. Characterization and Properties

1. Characterization

^{31}P NMR spectroscopy has been shown to be an extraordinary useful tool for following the growth of phosphorus-containing dendrimers and for controlling the progress of all reactions performed either in the internal layers or on the surface. This can be illustrated with two different examples: (i) the synthesis of dendrimers **85-G$_n$** (n = 1−4) (Figure

Scheme 75

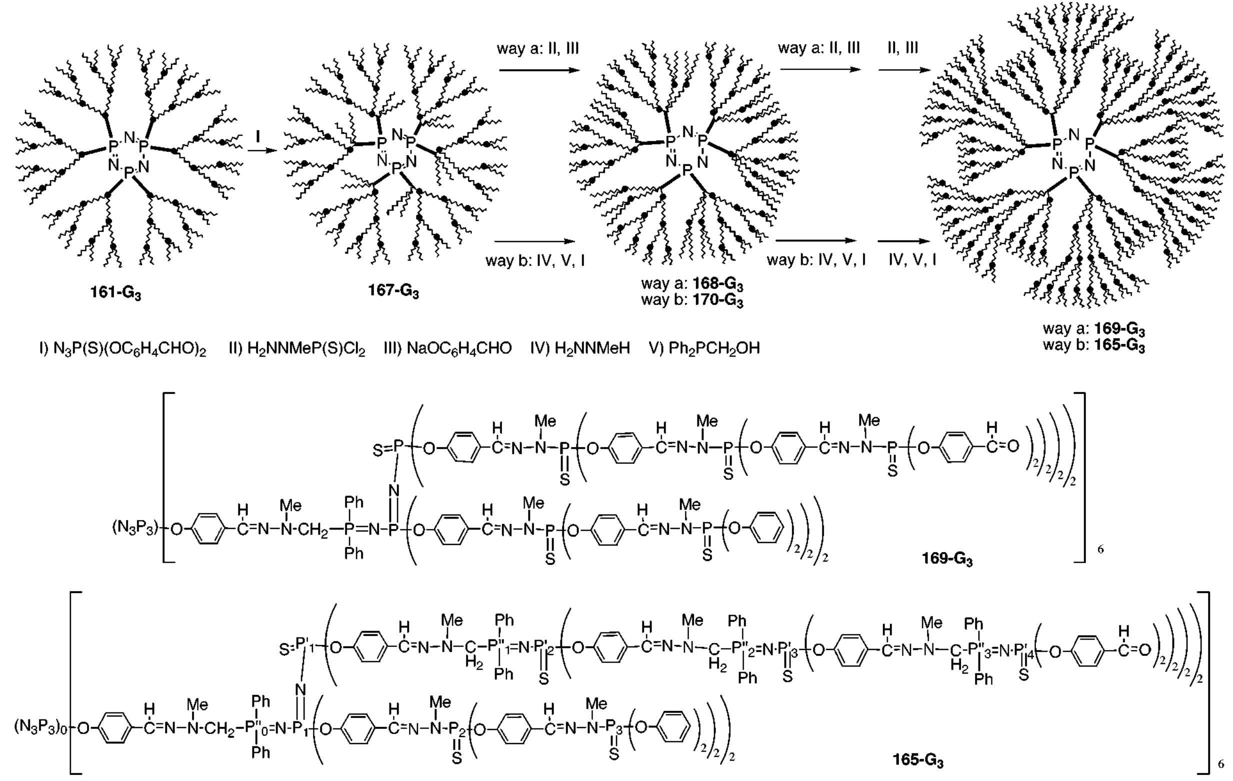




169-G$_3$

Figure 12. Representation of the polydendritic macromolecule **169-G$_3$**.

Scheme 76



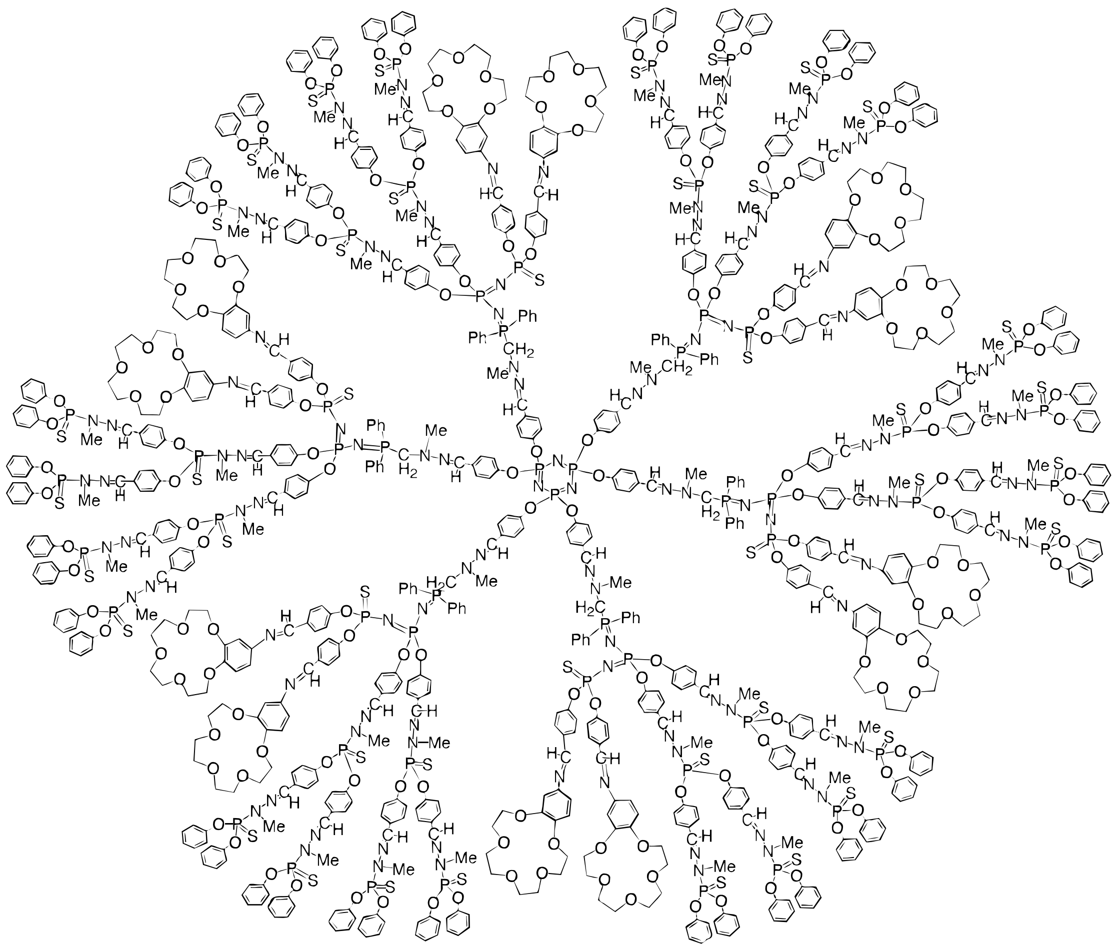
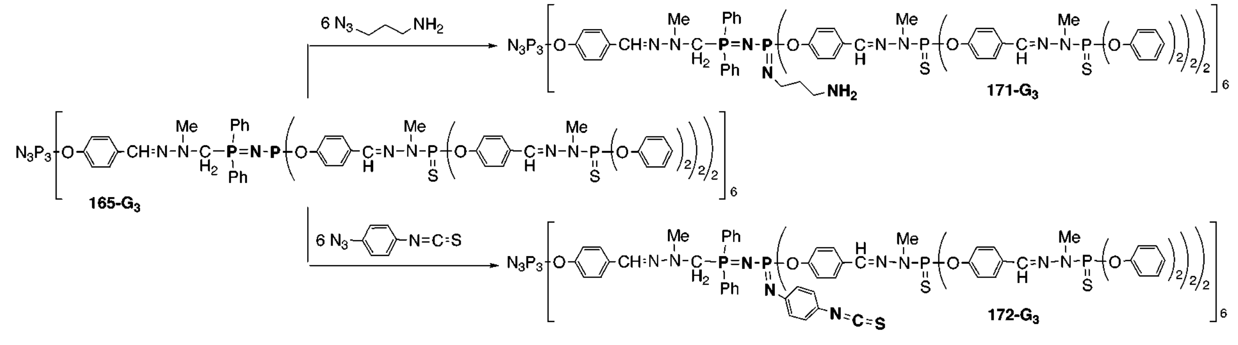


Figure 13. Dendrimer of generation 3 with 12 internal crown ether units.

Scheme 77



14)[84] and (ii) the construction of polydendritic systems (Figure 15).[115]

Indeed each generation of **85-G$_n$**, for example, gives a different chemical shift, and substitution reactions on the surface generally result in a shielding or deshielding effect (depending on the type of substitution) of the signal due to the phosphorus atoms of the upper generation *n* and a slight deshielding effect for the phosphorus atoms of generation $n - 1$. Remarkably up to generation 6 the signal of the phosphorus atom of the core can be detected and therefore can be used as an internal probe to follow the build up of dendrimers: lack of substitution on the surface at one or several of the terminal functional groups from generations 1–6 can thus be observed. Moreover, the possibility of incorporation of different phosphorus groups at each generation (P═S or P═O moieties) offers additional information since these groups show quite different chemical shifts.

However ^{31}P NMR spectroscopy is not able to evidence that perfect dendrimers are obtained above generations 5–6; the combination of methods used for polymer characterization is necessary to judge the perfection of the structures. As an example a whole range of species beside the dendrimer of generation 12, **85-G$_{12}$**, may be present with varying perfection even after careful purification. ^{1}H and ^{13}C NMR are obviously not of help for generations higher than 2. Mass spectrometry (FAB) allows to characterize dendrimers up to generation 3. MALDI-TOF should be the best tool to prove that preparation of these dendrimers has been achieved and to give information concerning the polydispersity. However, laser

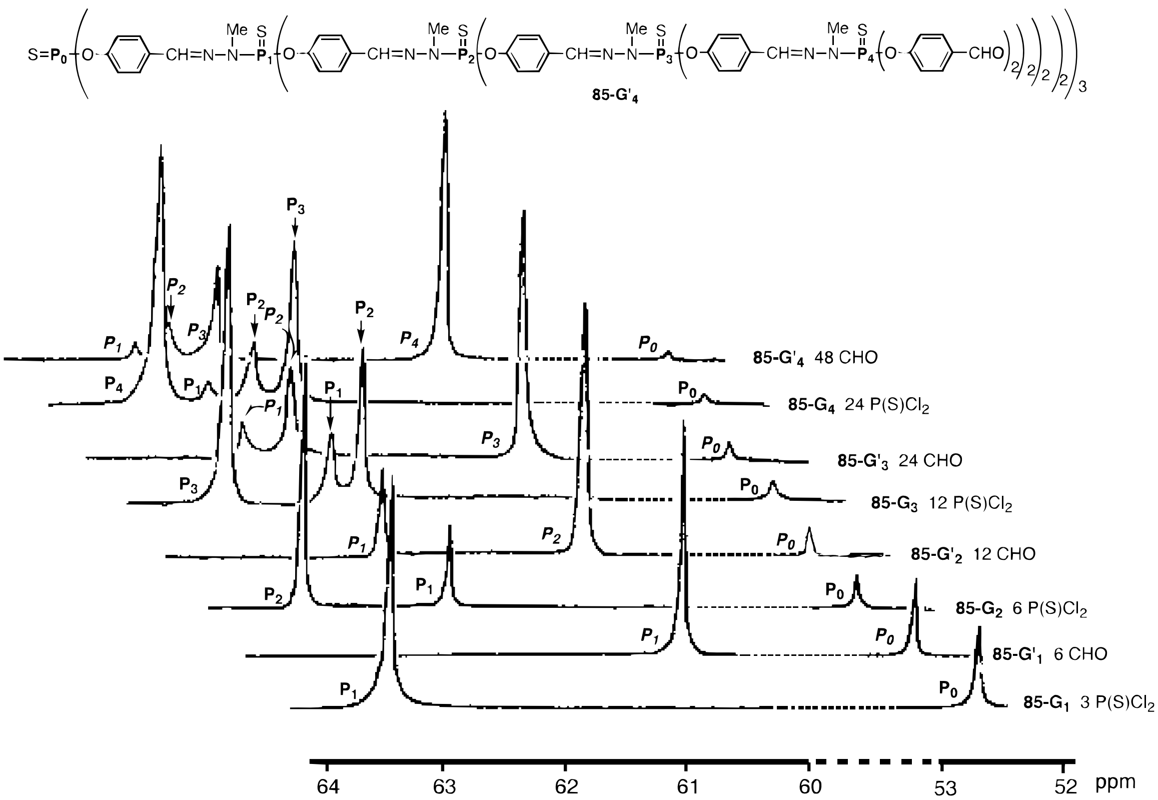


Figure 14. ^{31}P NMR spectra of dendrimers of generations 1–4, **85-G$_1$**–**85-G′$_4$**.

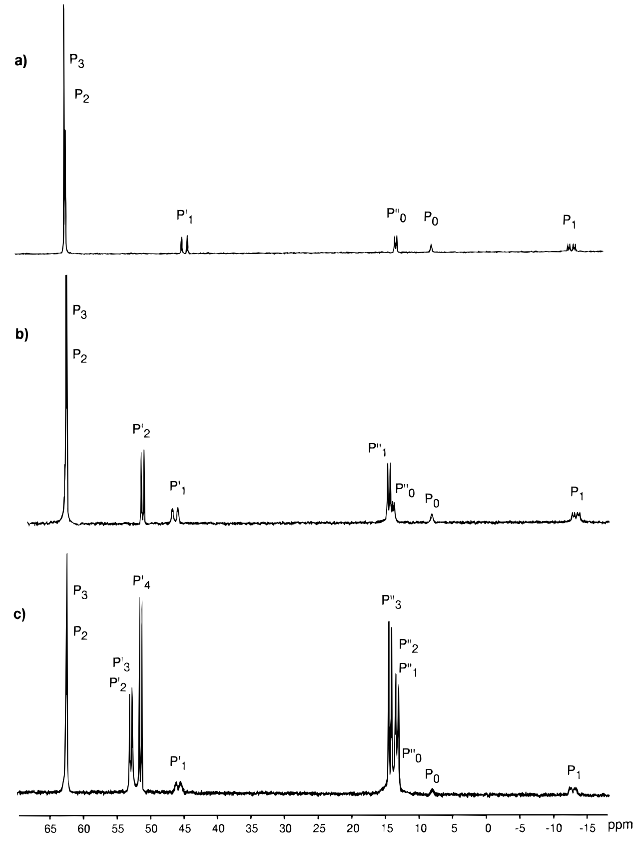


Figure 15. ^{31}P NMR spectra of the polydendritic macromolecules **167-G$_3$**, **170-G$_3$**, and **165-G$_3$** (see Scheme 85 for the numbering used): (a) compound **167-G$_3$** central dendrimer P_0, P''_0, P_1, P_2, P_3, internal dendron P'_1; (b) compound **170-G$_3$** central dendrimer P_0, P''_0, P_1, P_2, P_3, internal dendrimers P'_1 P''_1, P'_2; (c) compound **165-G$_3$** central dendrimer P_0, P''_0, P_1, P_2, P_3, internal dendrimers P'_1 P''_1, P'_2, P''_2, P'_3, P''_3, P'_4.

irradiation provoks cleavage of the hydrazono fragment, and suitable experimental conditions to avoid this breakdown have not yet been reported. Other methods of characterization include intrinsic viscosity, DSC-TGA, and glass transition temperature.[117]

Dendrimers containing phosphorus and nitrogen in the backbone are stable up to 250 °C (aldehyde chain ends), and thermal stability seems to be very dependent on the nature of functional groups linked on the surface.

2. Dipole Moments

Values of the dipole moment, μ in Debye (D), versus generation of both CHO- or P–Cl-terminated dendrimers increase exponentially from 8.43 (**85-G$_1$**) to 258 (**85-G$_{10}$**) D and from 8.27 (**85-G′$_1$**) to 328 (**85-G$_{11}$**) D (Figure 16).[96]

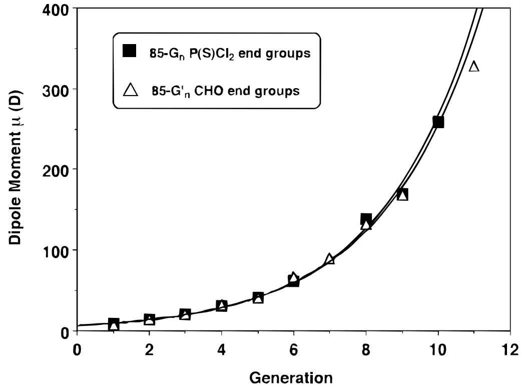


Figure 16. Plots of dipole moments versus generation for dendrimers **85-G$_1$**–**85-G$_{10}$** and **85-G′$_1$**–**85-G′$_{11}$**.

Dipole moment versus molecular weight does not increase in a linear fashion, as was previously observed for organic dendrimers.[118] A plot of the dipole moments as a function of the square root of molecular weights was found to be a straight line: this is in agreement with previous calculations on statistical mean dipole moments of polymers. The dipole moment ratio D_r ($D_r = \mu^2/N(\mu_0)^2$, where μ is the dipole moment of the dendrimer, N is the number of monomer units, and μ_0 is the dipole moment of the monomer unit) versus molecular weight is a constant ($D_r = 2.3$) (Figure 17). This unusually large value indicates considerable local correlation between neighboring dipoles. It is to be noted that the contribution of each polar unit, the P=S group, to the global dipole moment μ decreases exponentially from 2.1 (**85-G$_1$**) or 2.07 (**85-G′$_1$**) to 0.08 (**85-G$_{10}$**) or 0.05 (**85-G$_{11}$**) D (Figure 18).[96]

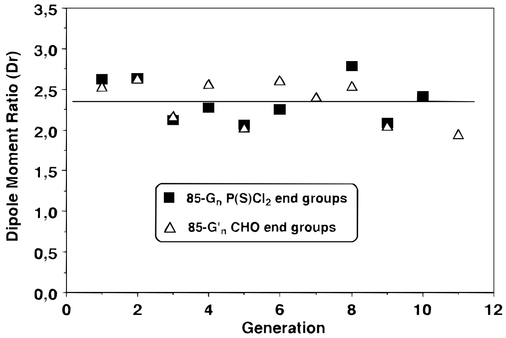


Figure 17. Dipole moment ratio versus generation $D_r = \mu^2/N(\mu_0)^2$ (N = number of monomer units, $\mu_0 = 3.03$ for **85-G′$_0$**).

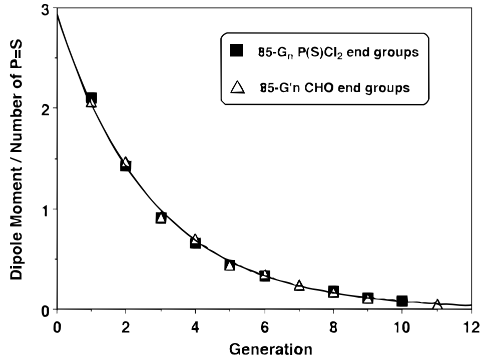


Figure 18. Dipole moment/number of P=S polar units versus generation for dendrimers **85-G$_1$**–**85-G$_{10}$** and **85-G′$_1$**–**85-G′$_{11}$**.

Cyclophosphazenic “dandelion” dendrimers reported by Fayet et al. also have significant dipole moments (see Scheme 45) with values up to 2702 D for generation 8! This is claimed to be due to a noncentrosymmetrical distribution of the lone pairs of the nitrogen atoms of their amino groups and functions.[119]

It is clear that there is a lack of knowledge and information concerning the physical characterization and physical properties of these dendrimers.

IV. Dendrimers Containing Other Heteroelements

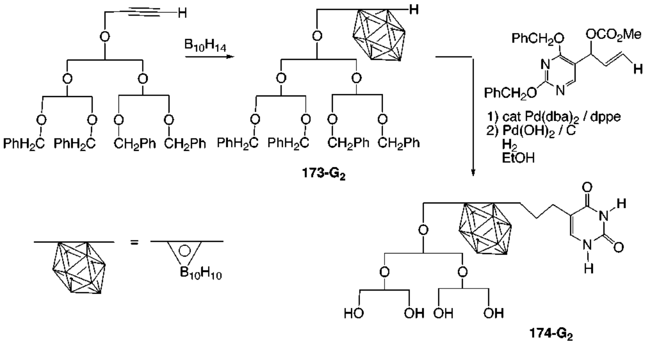
With the exception of silicon and phosphorus, very few heteroelements have been used to build dendrimers. In fact only three papers, one for bismuth and two for germanium, describe dendrimers with these heteroelements at the branching points.

Several other papers concern boron, but this element is always grafted after the synthesis of an organic dendrimer and is not a building block constituent of the dendrimer. Boron is generally used as the $B_{10}H_{10}$ cluster in view of potential biological applications. Indeed, the stable isotope ^{10}B can be used in cancer treatment by boron neutron capture therapy. This method is based on the nuclear reaction that occurs when ^{10}B is irradiated with low-energy neutrons [$^{10}B + n_{th} \rightarrow [^{11}B] \rightarrow {}^4He(\alpha) + {}^7Li + 2.39$ MeV]. The energy emitted can destroy the tumor if 10^9 ^{10}B atoms are delivered to each tumor cell.[120]

A. Boron-Containing Dendrimers

In most cases, the introduction of boron on the dendrimer takes advantage of the propensity of alkyne moieties to react with decaborane ($B_{10}H_{14}$) to afford 1,2-dicarba-*closo*-dodecaboranes. The first example, described by Nemeto et al.,[121] concerns reaction of decaborane with the triple bond located at the core of a polyol dendrimer which is soluble in water (Scheme 78). The coupling of this dendrimer **173-G$_2$** with a uracyl moiety via a route that includes a palladium-catalyzed carbon–carbon bond formation reaction affords a new species **174-G$_2$** that could have enhanced incorporation into cells.[122]

Scheme 78

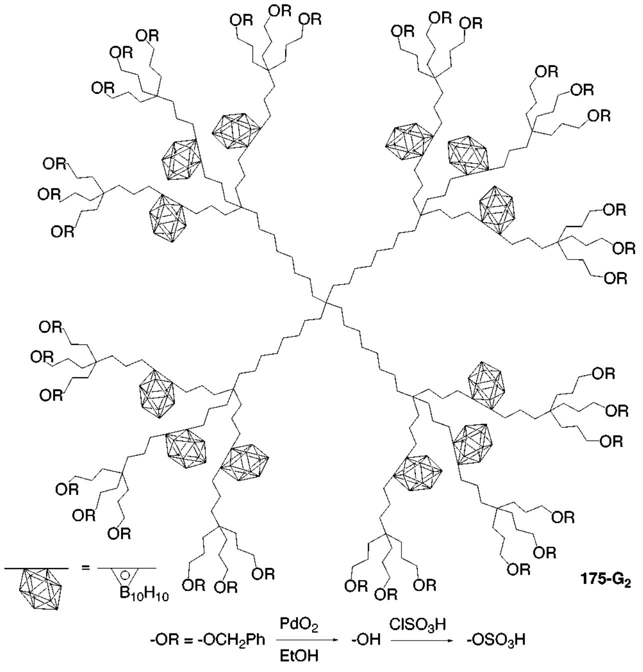


Four and 12 $B_{10}H_{10}$ clusters have been included within the first- and second-generation dendrimers, respectively, by site- and depth-specific reactions.[123] These boron superclusters **175-G$_2$** become water soluble by transformation of the ether end groups, first into alcohol functions and then into sulfate moieties (Scheme 79).

Boron clusters have been grafted also to the surface of dendrimers. For instance, $B_{10}H_{10}$ can be linked to a terpyridine group which forms a complex with ruthenium. The reaction of this complex with a tetra(terpyridine) core affords the first generation of the organometallic dendrimer **176-G$_1$** (Scheme 80).[124]

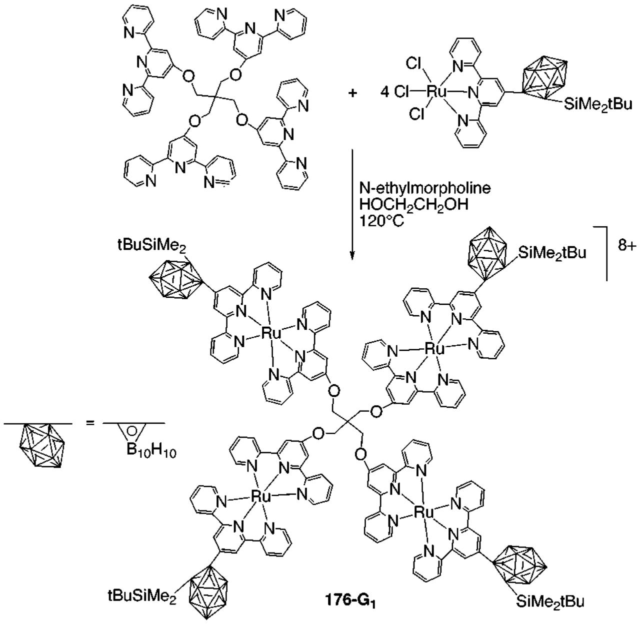
None of these decaborane-containing dendrimers could really be used for boron neutron capture therapy. Indeed, it is difficult to imagine how these dendrimers could deliver ^{10}B to the targeted tumor cells. For this purpose, boron-containing dendrimeric immunoconjugates have been prepared. Poly(amido)amine (PAMAM)[2] dendrimers from generation 0 to 4 (3 to 48 NH_2 end groups) are first reacted with the

Scheme 79



175-G$_2$

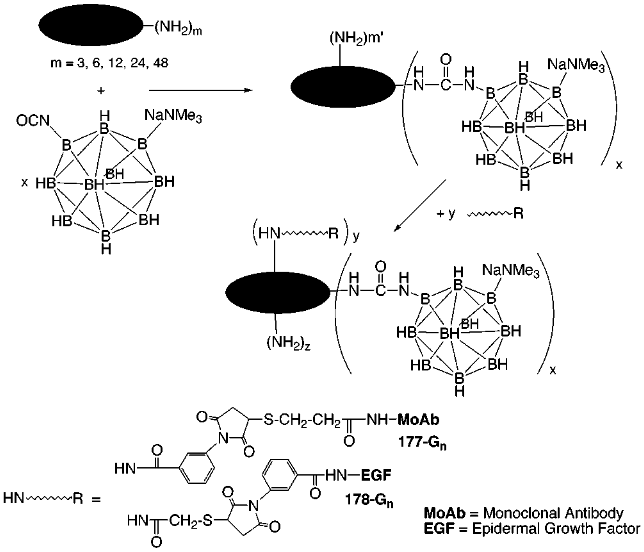
Scheme 80



176-G$_1$

isocyanato polyhedral borane NaMe$_3$NB$_{10}$H$_8$NCO (less than the stoichiometric quantity). The remaining NH$_2$ end groups are then reacted with either a monoclonal antibody[120] or an epidermal growth factor[125] derivative (Scheme 81). Pharmacokinetic studies of the immunoconjugates show that **177-G$_n$** retain a high level of immunoreactivity in vitro but do not have high in vivo tumor uptake and have a strong propensity to localize in the liver and spleen.[120] In vitro tests with the boronated dendrimer–epidermal growth factor bioconjugates **178-G$_n$** indicate that they are endocytosed, and this results in the accumulation of boron in lysosomes.[125]

Scheme 81



These compounds are inherently heterogeneous, but molecules with a better defined number of boron atoms are needed for protein labels in electron microscopy. For this purpose, the second generation of a polylysine dendrimer **179-G$_2$** has been designed to possess: (i) NH$_2$ end groups which are acylated with (*S*)-5-(2-methyl-1,2-dicarba-*closo*-dodecaborane-(12)-1-yl)-2-aminopentanoic acid, (ii) a reactive handle (thiol function of a cysteine residue) to graft the carborane-containing dendrimer to defined loci of targeting molecules, (iii) a fluorescent probe (ϵ-*N*-dansyllysine) to allow spectroscopic monitoring of the coupling to targeting proteins, and (iv) a poly(ethylene glycol) tail to enhance the solubility in water (Figure 19).[126]

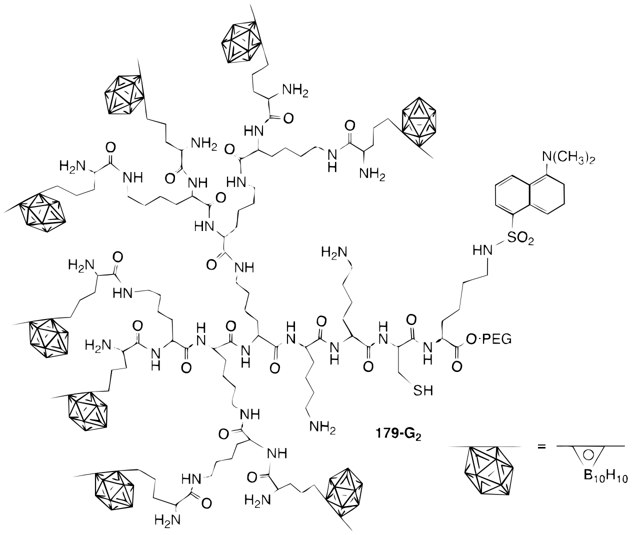
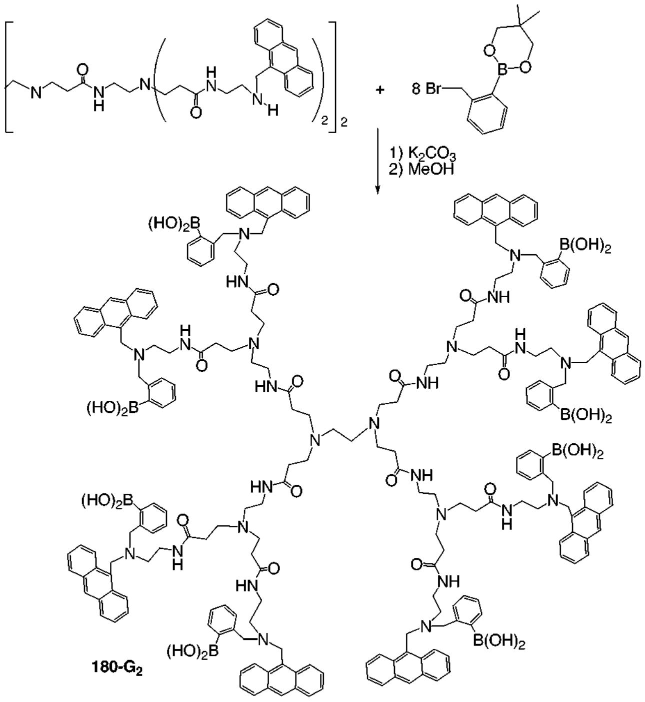


Figure 19. Dendrimer **179-G$_2$**. PEG = poly(ethylene glycol) ≈ 68 glycol units.

Another example of a boron derivative linked to the surface of dendrimers has been described.[127] The last step consists of coupling a protected boronic acid derivative to a PAMAM dendrimer[2] derivatized with anthracene (Scheme 82). The resulting dendritic boronic acid **180-G$_2$** forms stable complexes with various saccharides, particularly with D-galactose and D-fructose.[127]

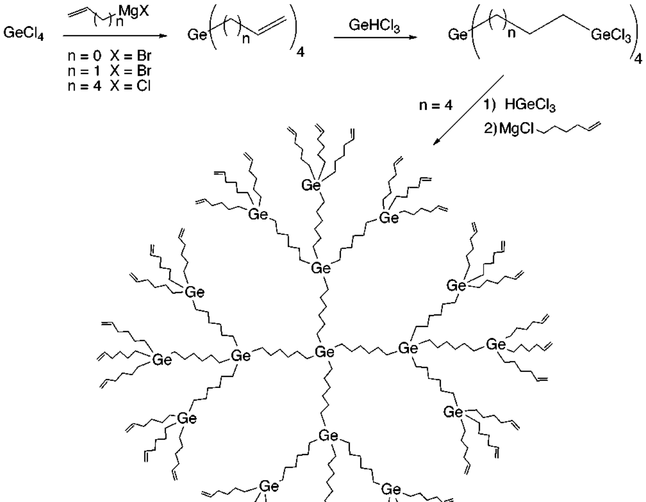
Scheme 82



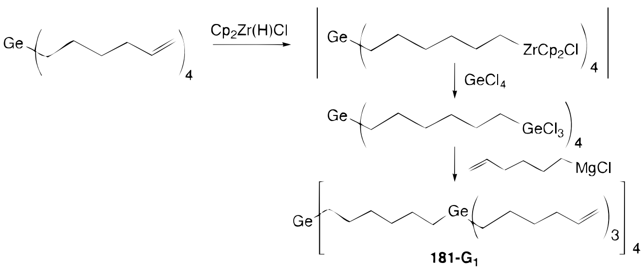
B. Germanium-Containing Dendrimers

The first dendrimers including germanium at the branching points have been described by Mazerolles and co-workers[128] who have used both divergent and convergent methods. The divergent method consists of successive alkenylation and hydrogermylation reactions starting from germanium tetrachloride. However, cleavage of germanium–carbon bonds occurs easily with the vinylic and allylic derivatives, forming byproducts that are difficult to remove. The use of ω-ethylenic chains allows one to overcome these problems and to obtain the second-generation dendrimer **181-G₂** (Scheme 83). Hydrozirconation of organogermanium polyalkenes, followed by transmetalation and alkenylation, allows one to obtain the first generation of the same dendrimer (Scheme 84).

Scheme 83



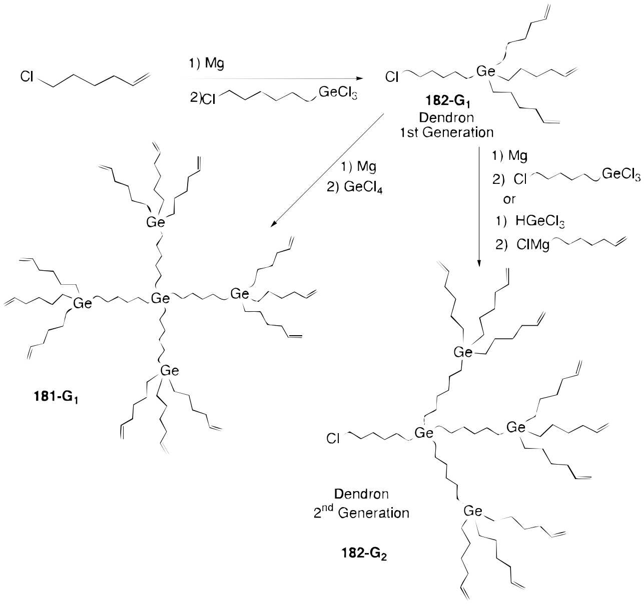
Scheme 84



However, this compound is contaminated with a series of byproducts; therefore, the other divergent method is more advisable.[128]

In the convergent method, the dendron possesses a chlorohexyl chain linked to the core (Scheme 85).

Scheme 85



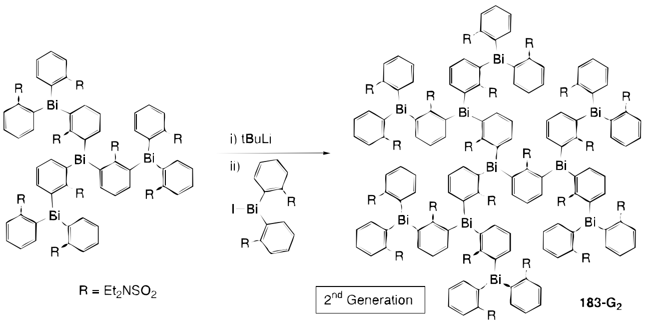
The reaction of the Grignard derivative of the first-generation dendron **182-G₁** with $GeCl_4$ leads to the dendrimer **181-G₁** already obtained by the convergent method. However, the Grignard derivative of the second-generation dendron **182-G₂** does not react cleanly with $GeCl_4$ because of steric constraints, to give access to the corresponding second-generation dendrimer **181-G₂**.[128]

A dendrimer with alternating germanium and silicon atoms at the branching points has also been obtained, as already shown in Scheme 17.[33]

C. Bismuth-Containing Dendrimer

The first and so far unique dendritic bismuthane **183-G₂** was synthesized up to the second generation by Suzuki and co-workers.[129] This compound was obtained in 20% yield by utilizing the direct ortho lithiation of arylbismuthanes bearing a sulfonamide function at the ortho position of the aromatic ring, followed by reaction with bis[2-(diethylaminosulfonyl)phenyl]bismuth iodide (Scheme 86).

Scheme 86



V. Conclusion

Despite the fact that only a few methods for the synthesis of dendrimers containing main group elements have been reported until now, it is clear that these dendrimers constitute a fascinating class of macromolecules. Incorporation of silicon or phosphorus at the core, at each generation, and on the surface dramatically increases the number of reactions which can be done with these special materials and as a consequence the number of possible applications.

The insertion of phosphorus groups allows one to follow rigorously the construction of the dendrimers up to the highest generation known to date: generation 12 (molecular weight higher than 3 000 000 Da).

The contribution of silicon and phosphorus in the area of dendrimer chemistry is of great interest for many reasons:

- Phosphorus at the core can be tri-, tetra-, or pentacoordinated, and therefore the core can be tri-, tetra-, or pentadirectional.
- A number of phosphorus or silicon cores can be used; they can be di-, tri, tetra-, hexa-, or octafunctionalized allowing the construction of dendrimers of various forms (bowl-shaped, “cauliflower”, “bow tie”, bolaform, etc.).
- Very reactive groups can be anchored at the surface, and these groups remain available for further reactions therefore giving the possibility of developing reactions in all fields of chemistry.
- Three types of bonds can be encountered at the branching points of these dendrimers, either Si−C, Si−O, and Si−Si bonds for silicon derivatives or P−O, P−N, and P−C bonds for the corresponding phosphorus compounds, allowing one to play with physical and chemical properties of these macromolecules.
- $P(X)Cl_2$ ($X = O, S$)-terminated units allow the selective grafting of various other functional groups and the synthesis of multiplurifunctionalized dendrimers, i.e., formation of macromolecules possessing a large number of sets of two, three, or four functionalities on the surface.
- Phosphino and diphosphino units on the surface are excellent ligands and permit the preparation of a number of metalladendrimers incorporating various metals such as iron, tungsten, gold, palladium, rhodium, ruthenium, or platinum. Preliminary experiments on the catalytic properties of these species are promising. Similarly nickel(II) complexes anchored to siloxane dendrimers are effective catalysts for the Kharasch addition of halogenoalkanes to olefinic C=C double bonds.
- The postmodification of the backbone of dendrimers can be easily performed allowing regiospecific grafting of charges, functional groups, or metals into the internal layers.
- Neutral but also polycationic or polyanionic dendrimers can be prepared.
- The facile functionalization of the cavities allows the development of a macromolecular chemistry within the cascade structure of dendrimers: unique polydendritic macromolecules can be isolated.
- A number of phosphorus-containing dendrimers exhibit high dipole moment values.

Although not so intensively studied, boron-containing dendrimers also appear to present interesting properties as, for example, for the treatment of cancer by boron neutron capture therapy.

As said in the Introduction, inorganic dendrimers attracted the interest of chemists in the early 1990s after the pionneering work on organic dendrimers. That is probably the reason why very few applications concerning these macromolecules are reported till now. Most of them concern catalysis, but it can be envisaged to use these inorganic macromolecules in different fields: gene therapy, multilayer components, imaging techniques, hybrid materials, coatings lubricants, adhesives, etc.

The next review will mention without any doubt some very interesting applications of these new classes of dendrimers. As for recent news and advances, dendrimers containing chiral ferrocenyldiphosphine ligands were used for applications in highly enantioselective hydrogenation reactions.[130]

VI. References

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