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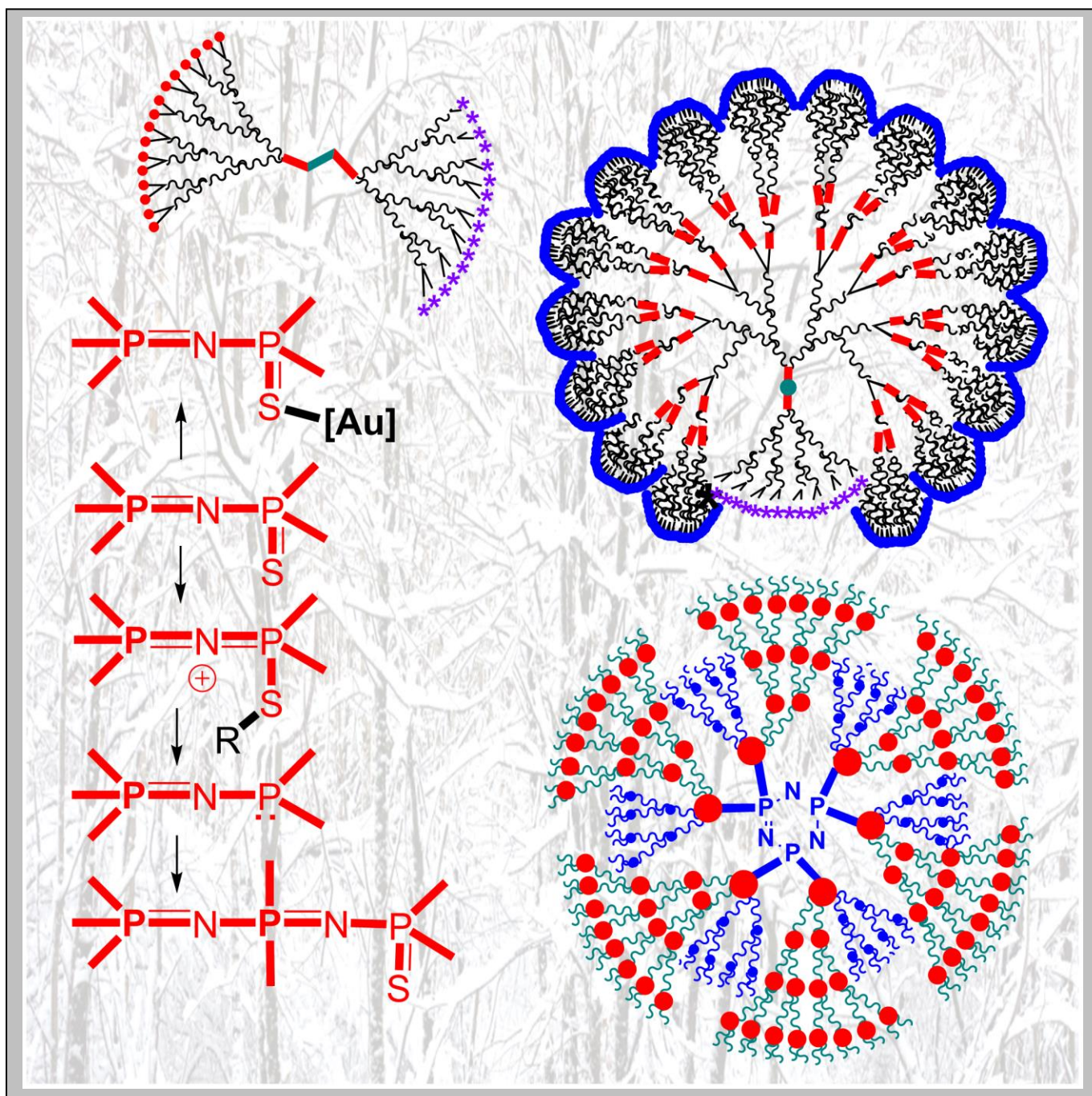
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# The Chemistry of P=N-P=X (X = S, O, NR) Linkages for the Synthesis of Dendritic Structures

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Dedication to Prof. Dr. Evamarie Hey-Hawkins on the occasion of her retirement

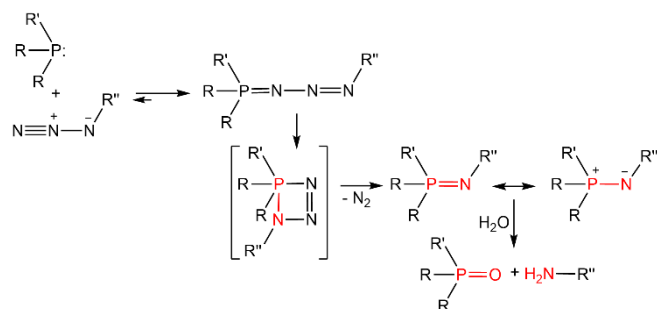


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**Abstract:** The Staudinger reaction between a phosphine and an azide, applied to phosphorus azides, has been used for the synthesis of a large variety of dendritic structures, incorporating P=N-P=X moieties (X = mainly S, but also O and N-R). Conjugation of the P=N bond with the P=X bond greatly stabilizes the P=N bond. Highly branched structures such as dendrons, dendrimers, Janus dendrimers, layered dendrimers, surface-block dendrimers, and diverse other dendritic structures incorporating such linkage have been elaborated. Accelerated methods of synthesis of dendrimers are also based on the Staudinger reaction. A versatile reactivity was observed exclusively on the sulfur atom of P=N-P=S linkages, such as alkylation or complexation. Alkylation on S induces a weakening of the strength of the P=S bond, which can be easily cleaved to generate phosphines able to react in Staudinger reactions inside the structure of dendrimers, thus affording highly sophisticated dendritic structures.

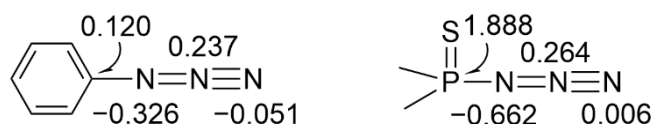
## 1. Introduction

The Staudinger reaction between a phosphine and an azide [1] creates readily a P=N bond, with N<sub>2</sub> as the only by-product (Scheme 1). This P=N bond is easily cleaved by water, affording primary amines together with phosphine oxide. Such method is considered as especially useful to get primary amines [2].



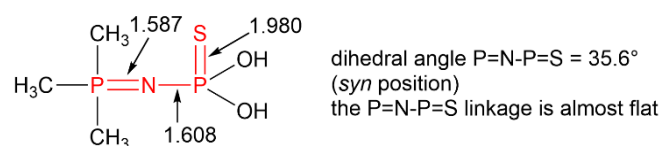
**Scheme 1.** The Staudinger reaction, its mechanism, and its use for synthesizing primary amines by hydrolysis of the P=N bond.

At first glance, this Staudinger reaction appears not convenient for the synthesis of dendrimers, as sensitive linkages could prevent the isolation of pure dendritic compounds. However, the use of an azide able to afford a conjugation and thus an electronic delocalization after the Staudinger reaction, could stabilize the P=N bond. Indeed, it was noted in the very first example of synthesis of a P=N-P=O linkage that the P=N bond was rather stable to hydrolysis [3]. Quantum-chemical density functional theory (DFT) studies have demonstrated that an azide linked to a P=S function behaves differently from an organic azide. In particular, the charge distribution is very different, with a higher electronegativity of nitrogen linked to phosphorus compared to nitrogen linked to carbon (Figure 1) [4].



**Figure 1.** Comparison of the calculated partial charges of the atoms between an organic azide and a phosphorus azide.

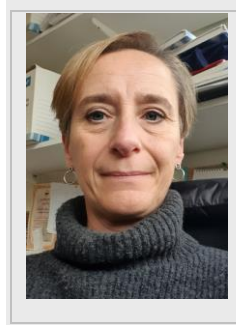
It is thus expected that after the Staudinger reaction, the P=N-P=S linkage should be very different from the P=N-Ar linkage. Indeed, calculations on a high level of theory (B3LYP/6-311G(d,p)), applied to a small model compound ((CH<sub>3</sub>)<sub>3</sub>P=N-P(S)(OH)<sub>2</sub>), demonstrated an electronic delocalization all along the P=N-P=S linkage. The calculated P=N (1.587 Å) and N-P (1.608 Å) bond lengths are almost identical, and both shorter than the expected value for a N-P single bond (1.77 Å). The P=N-P=S linkage is stabilized by strong donations of nitrogen and sulfur lone pairs, and is by far more stable than “normal” P=N bonds [5].



**Figure 2.** Calculated bond lengths of a P=N-P=S linkage. Values in Å.

The synthesis of small compounds possessing such P=N-P=S or in a few cases P=N-P=O linkage has been carried out with a large number of phosphines and thiophosphoryl or phosphoryl azides (Scheme 2). The crystal structure of some compounds, in particular based on ferrocene derivatives, could be recorded. The bond lengths measured for the P=N-P=S linkage corroborated the calculated lengths. Data were also recorded for the P=N-P=O linkage, for which the P=N-P bond lengths were found similar, confirming for both linkages an electronic delocalization affording an enhanced stability (Scheme 2) [6].

Valérie Maraval obtained her PhD in 2000 (supervision J.-P. Majoral). After a Post-Doc with B. Meunier and the Aventis company, she was recruited in 2005 as a CNRS Research Engineer at the Laboratoire de Chimie de Coordination (Toulouse). She worked during 17 years with R. Chauvin, mainly on acetylenic chemistry for physics and biology. She completed her Habilitation in 2014. In 2022, she joined the group of A.-M. Caminade, where her research projects concern organic and organo-phosphorus chemistry.

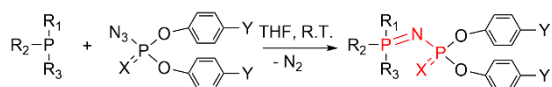


## REVIEW

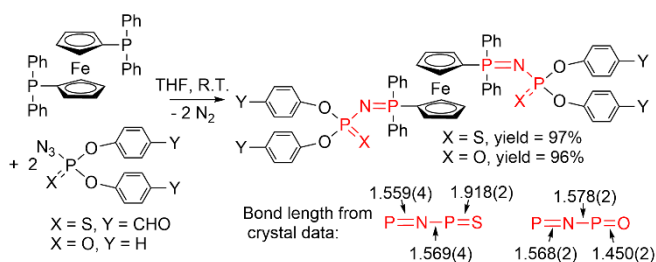
Régis Laurent received his PhD in 1994 in Toulouse (France, supervision J. Dubac, A. Laporterie). After a post-Doc. in Saarbrücken (Germany, M. Veith), and Toulouse (L. Gorrichon), he got in 1996 a CNRS position in the Laboratoire de Chimie de Coordination (Toulouse) in the group of J.-P. Majoral then A.-M. Caminade. His research interest is in synthesis, characterization, and applications of phosphorus dendrimers. He is deputy director of the Institut de Chimie de Toulouse.



Anne-Marie Caminade is Director of Research Exceptional Class at the CNRS, and Deputy Director of the Laboratoire de Chimie de Coordination (LCC) in Toulouse. She is co-author of about 510 publications and 18 patents (+16 WO extensions). Her  $h_{\text{index}}$  is 77. She recently received Prizes from the French (SCF) and German (GDCh) Chemical Societies. She is Member of the Academia Europaea and of the European Academy of Sciences.



R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	X	Y	Yield
Ph	Ph	Ph	S	CHO	97%
<i>p</i> ClC <sub>6</sub> H <sub>4</sub>	<i>p</i> ClC <sub>6</sub> H <sub>4</sub>	<i>p</i> ClC <sub>6</sub> H <sub>4</sub>	S	CHO	95%
CH <sub>2</sub> CH <sub>2</sub> CN	CH <sub>2</sub> CH <sub>2</sub> CN	CH <sub>2</sub> CH <sub>2</sub> CN	S	CHO	94%
<i>t</i> Bu	CC-Ph	CC-Ph	S	CHO	70%
Ph			S	H	90%
Me	Ph	Ph	S	H	88%
Ph	Ph	Ph	O	H	97%
Me	Ph	Ph	O	H	96%



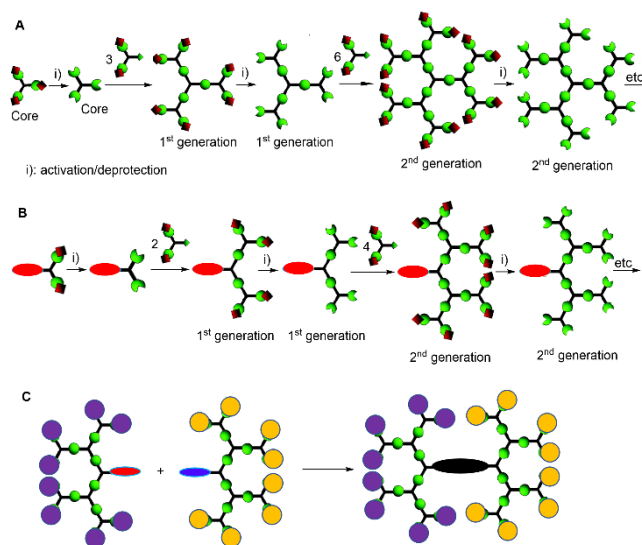
**Scheme 2.** Synthesis of small compounds incorporating P=N-P=S or P=N-P=O linkages. Bond lengths for such linkages were obtained from X-ray diffraction data in the case of the ferrocene derivatives. Values in Å.

These data confirmed the stabilization of the P=N bonds, and thus the possibility to use the Staudinger reaction for the synthesis of dendritic structures. Indeed, the fact that the Staudinger reaction is quantitative, and the only by-product is N<sub>2</sub> make this process very clean and suitable in particular for obtaining sophisticated dendritic architectures.

The presence of phosphorus atoms inside the structure of dendrimers can be a very important asset, thanks to <sup>31</sup>P NMR, which is very sensitive to changes around phosphorus atoms. In the case of P=N-P=X linkages, two doublets are observed in <sup>31</sup>P NMR. For X = S, typical chemical shifts are at ca 50 ppm for P=S and ca 14 ppm for P=N, with a <sup>2</sup>J<sub>PP</sub> coupling constant of ca 30 Hz. For X = O, typical chemical shifts are at ca -7 ppm for the P=O, also with a <sup>2</sup>J<sub>PP</sub> coupling constant of ca 30 Hz [6]. However, it was found in this work that P=N-P=X linkages with X = S were more stable over time than when X = O. That is the reason why almost all the work concerning dendrimers was carried out with X = S.

The two main types of known dendritic architectures are dendrimers [7], and dendrons [8]. Dendrimers are most generally synthesized step-by-step by a divergent process from a multivalent core, to which branched monomers are sequentially and radially attached (Scheme 3, part A). Dendrons are built by either a convergent or a divergent process, but in both cases, there is one function linked to the core which is different from all the others (Scheme 3, part B). For both dendrimers and dendrons, a new generation is created each time the number of terminal functions is multiplied. The nature of the terminal functions at a given generation can be easily modified, especially in the case of divergent processes, to afford the desired properties to the dendritic structures. Dendrons have their own properties, but they can also be used as building blocks for the preparation of more sophisticated architectures, such as Janus dendrimers, which possess two different faces [9] (Scheme 3, part C).

It must be emphasized that quantitative reactions are needed at each step of the synthesis of dendrimers, to ensure the modification of all the terminal functions. Indeed, it is not possible to purify a dendrimer in which a few functions are missing from the fully substituted one, as their physicochemical properties are too similar to permit a separation by chromatography. The yields given in many of the following schemes are the isolated yields, obtained after the removal of the small excess of reagents (2 to 5% in most cases), carried out either by washings with diethylether, or by Size Exclusion Chromatography.



**Scheme 3.** A) Step-by-step divergent synthesis of dendrimers. B) Step-by-step divergent synthesis of dendrons. C) Janus dendrimer obtained by the association of two dendrons.

## REVIEW

In this review, we will present first the synthesis of dendrons having a single P=N-P=X linkage (X = essentially S) at the core, then the use of some of these dendrons for the synthesis of sophisticated dendritic structures, such as Janus dendrimers. The next parts will present dendrimers having a single layer of P=N-P=S linkages, and the reactivity of this linkage. Dendrimers having several layers of such linkages (a few, one among two, or at all layers) will then be presented. These layered dendrimers were generally synthesized with the aim of accelerating the synthetic process. P=N-P=N-P=N-P=N linkages were also obtained, using an azide linked to the cyclotriphosphazene. The reactivity of the P=N-P=S linkage was also studied. It was in particular used to form selectively P=N-P=S→AuCl complexes, and to generate P=N-P: moieties, which can be applied in another Staudinger reaction to give access to P=N-P=N-P=S units. All reactions shown in this review were carried out in the 0.1-1 g scale.

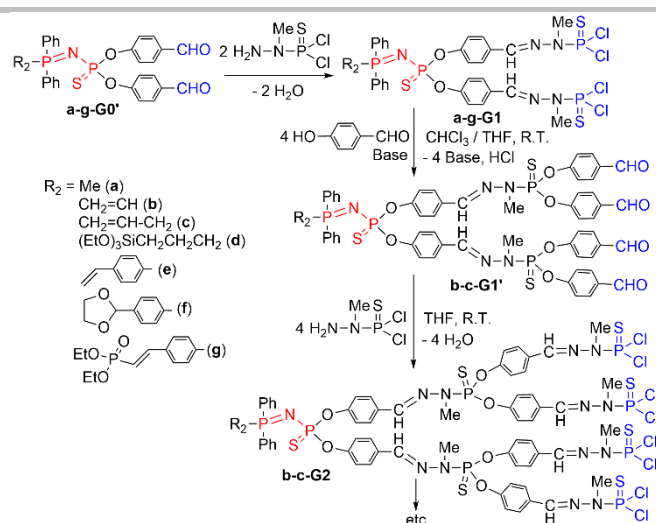
### 2. A single P=N-P=S linkage at the core of dendrons

The main types of dendrons possessing a P=N-P=S linkage at the core synthesized in the early times can be found in reference [10]. Thus, only the most salient examples and recent results will be displayed here.

#### 2.1. Synthesis of dendrons

The synthesis of dendrons bearing a single P=N-P=S group at the core is carried out as shown in Scheme 2 for small compounds. The presence of two aldehyde functions in some of these compounds enables the growing of the dendritic structure by the repetition of two steps. The condensation reaction with the branched monomer H<sub>2</sub>NNMeP(S)Cl<sub>2</sub>, obtained by reaction of P(S)Cl<sub>3</sub> with methylhydrazine at low temperature, that was used for the synthesis of phosphorhydrazone dendrimers [11] is first carried out. The second step of the synthetic process is the reaction of the P(S)Cl<sub>2</sub> functions with hydroxybenzaldehyde in basic conditions (Scheme 4). The first point to be verified with this robust synthetic process concerned the stability of the P=N-P=S linkage in these conditions, and thus its compatibility. <sup>31</sup>P NMR in particular showed the stability of these P=N-P=S linkages, all along the synthetic process.

Different types of diphenyl phosphines were used, as shown in Scheme 4. The synthesis was carried out only up to the first generation for R<sub>2</sub> = Me [12] (case a), R<sub>2</sub> = (EtO)<sub>3</sub>Si-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub> [13] (case d), CH<sub>2</sub>=CH-*p*-C<sub>6</sub>H<sub>4</sub> [14] (case e), [-CH<sub>2</sub>O-]<sub>2</sub>CH-*p*-C<sub>6</sub>H<sub>4</sub> [12] (case f), and (EtO)<sub>2</sub>P(O)CH=CH-*p*-C<sub>6</sub>H<sub>4</sub> [15] (case g). On the contrary, larger dendrons, up to generation 3, were obtained in the cases b (R<sub>2</sub> = vinyl) [16, 17] and c (R<sub>2</sub> = allyl) [14]. The thermal stability of the family of dendrons having a vinyl core (compounds b-Gn) was compared to that of the corresponding dendrimers built from a trifunctional core. The thermal behavior was almost identical for generation 3, whereas a dramatic difference was observed for generation 2. The percentage of mass retained at high temperature (70% at 1000°C) in the case of the dendron was by far higher than in the case of the dendrimer (50% at 1000°C), presumably due to a polymerization of the vinyl group at the core of the second generation dendron. Such process was not observed with generation 3, in which the vinyl core is presumably too buried inside the structure to be polymerized [18].

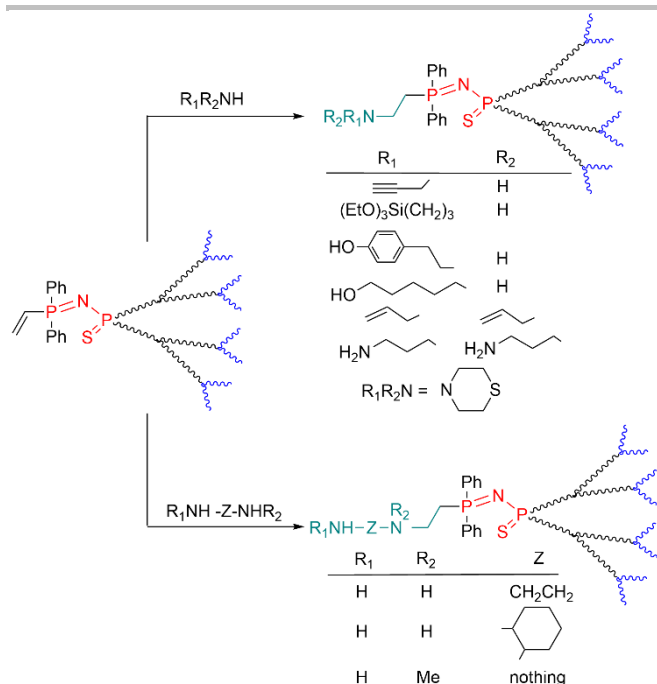


**Scheme 4.** First steps of the synthesis of dendrons having a P=N-P=S linkage at the core.

#### 2.2. Reactivity at the core of dendrons

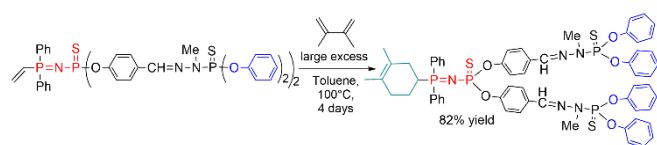
The presence of a vinyl group linked to the P=N-P=S linkage enabled to study a versatile reactivity at the core of the dendrons. Indeed, DFT calculations carried out with dendrons **1b-G0'** [19], **1b-G1** [20], **1b-G1'** [21] revealed that the most reactive part of the dendron is the =CH<sub>2</sub> side of the vinyl group, which is in particular preferred for nucleophilic attack. It was shown that the P=N-P=S linkage induces an electron-withdrawing effect on the attached vinyl group, and thus enhances its reactivity [22].

Diverse types of primary and secondary amines have been tested for nucleophilic attacks on the vinyl group, i.e. Michael-type additions (Scheme 5). The reactions were carried out up to generation 3 in several cases. Of course, such type of reactions with primary amines cannot be carried out with aldehyde or P(S)Cl<sub>2</sub> terminal functions, on which primary amines react readily. The primary amines used were propargylamine [17], 5-aminopentanol [23], and 3-aminopropyltriethoxysilane [13]. The case of tyramine is interesting, as only the amino group reacted, not the phenol [17], and the same behavior was observed with 5-aminopentanol, in which only the amine reacted [23]. The secondary amines were diallylamine [17], and thiomorpholine [17]. Interestingly, in the case of N-(3-aminopropyl)-1,3-propanediamine, which possesses two primary amines and one secondary amine, only the secondary amine reacted, affording two free primary amines. Indeed, <sup>1</sup>H and <sup>13</sup>C NMR spectra indicated that the grafted triamine remained symmetrical. The two NH<sub>2</sub> functions are eventually suitable for further reactions [24]. Several diamines were also used, in large excess in general to avoid the reaction with two dendrons. Ethylenediamine [17], *trans*-1,2-diaminocyclohexane [17] and methylhydrazine [17], were in particular reacted. Most of these core-functionalized compounds were used later on for grafting either to materials or to other dendritic structures. In all cases of Michael additions, the completion of the reaction was monitored by <sup>1</sup>H NMR, which displays the disappearance of the signal corresponding to the CH<sub>2</sub> part of the vinyl group, characterized by two doublets of doublets at ca 6.1 and 6.4 ppm, and also by <sup>31</sup>P NMR. Yields in isolated compounds are generally comprised between 90 and 98%.



**Scheme 5.** Michael-type addition of amines on a vinyl group linked to a P=N-P=S linkage at the core of dendrons.

Another type of reaction was carried out at the core of these dendrons. A Diels-Alder cycloaddition was attempted, using a large excess of 2,3-dimethylbutadiene on the vinyl group linked to the P=N-P=S linkage. This reaction necessitated heating at 100°C for 4 days in toluene to go to completion [25]. Scheme 6 displays this reaction, in which the dendron reagent is represented in a linear way, with parentheses after each branching point, and the resulting product is shown with its full chemical structure. Such linear drawing will be used in most of the following schemes.

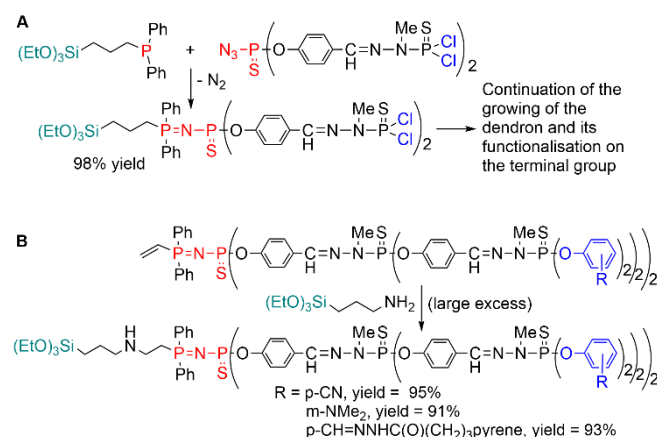


**Scheme 6.** Diels-Alder cycloaddition at the vinyl core of a small dendron.

### 2.3. Modification of materials with dendrons

The presence of a suitable function at the core of the dendrons for the grafting to materials concerned mainly a triethoxysilyl group usable for the grafting to silica. The first example implied two types of dendrons, in which the (EtO)<sub>3</sub>Si(CH<sub>2</sub>)<sub>3</sub> group is either present till the beginning of the synthetic process (Scheme 7A), or introduced in the last step by the addition of the 3-aminopropyltriethoxysilyl group on the vinyl group (Scheme 7B). This second way was found more suitable than the first one, because a partial hydrolysis of the triethoxysilyl group was observed in some cases during the multiple steps of the growing of the dendron issued from way A. Dendrons of different generations (from 0 to 3), with different terminal functions, and different internal structures were synthesized. The co-hydrolysis and polycondensation of these dendrons with a defined and

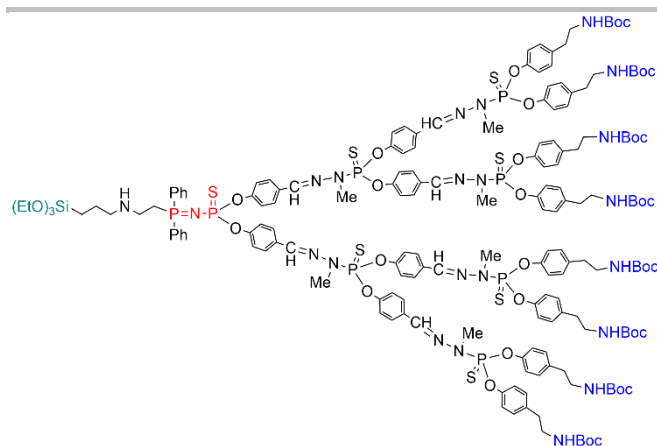
varying quantity of tetraethoxysilane (TEOS) was carried out via sol-gel protocol. In all cases, dendron-silica xerogels were obtained. The texture of the xerogel depended in part on the length and the chemical nature of the linker between the Si(OEt)<sub>3</sub> and PPh<sub>2</sub> groups. Solid state <sup>31</sup>P MAS NMR of these xerogels proved that the dendrons were not damaged during the process, whereas <sup>29</sup>Si MAS NMR confirmed that the dendrons were covalently attached to the silica. It was shown in some cases by N<sub>2</sub> adsorption-desorption isotherms that some materials were mesoporous with a narrow pore size distribution. The BET surface areas varied from 10 to 590 m<sup>2</sup>/g, depending on the size of the dendron, the length of the linker, and the quantity of TEOS added [13].



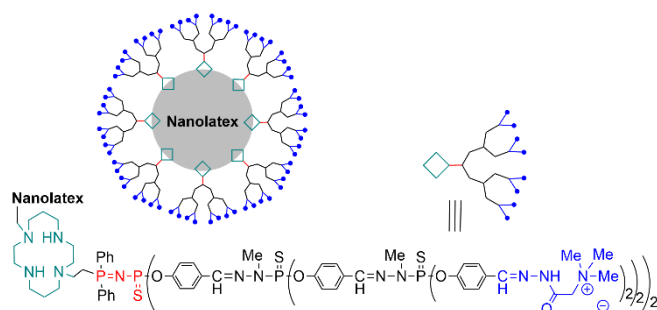
**Scheme 7.** Two ways for the functionalization of the core of dendrons with a triethoxysilyl group. A) at the very beginning of the synthesis of the dendron. B) in the last step of the synthesis of the dendron.

After this pioneering work, a series of dendritic structures incorporating one or several triethoxysilyl groups, together with several Boc-protected amines at the surface was synthesized. Some of these dendritic structures were dendrons, obtained as shown in Scheme 7B [26]. All these dendritic structures were grafted to different types of mesoporous silica. Deprotection of the Boc-protected tyramine surface groups was carried out after the grafting to silica. The free amines of the material obtained after deprotection were used for the trapping of carbon dioxide. The second generation dendron was found the most efficient among the various dendritic structures tested. Its structure, before the grafting and deprotection, is shown in Figure 3 [27].

Another example in the field of materials concerned the grafting of dendrons to nanolatex polystyrene particles functionalized on the surface with cyclam derivatives. Several generations of dendrons having a vinyl-P=N-P=S linkage at the core and ammonium terminal functions of type Girard T were reacted with the remaining available NH functions of cyclam (Figure 4). The number of dendrons per nanoparticles depended on the generation of the dendrons, ca 300 for generation 0, ca 150 for generation 1, and ca 90 for generation 2. The cationic dendrons provided a remarkable improvement of the colloidal stability, preventing aggregation of the nanoparticles. Besides, the colloidal suspension in water gave rigid stable translucent hydrogels upon standing at room temperature for 1 week. About 105 000, 185 000 and 345 000 water molecules were estimated to be involved in the gelation process by one grafted dendron of generation 0, 1 and 2 respectively [28].



**Figure 3.** Chemical structure of a dendron before its grafting to silica and then its use for trapping  $\text{CO}_2$  after deprotection of the tyramine terminal functions.



**Figure 4.** Schematic representation of second generation dendrons grafted to a polystyrene nanoparticle pre-functionalized with cyclam.

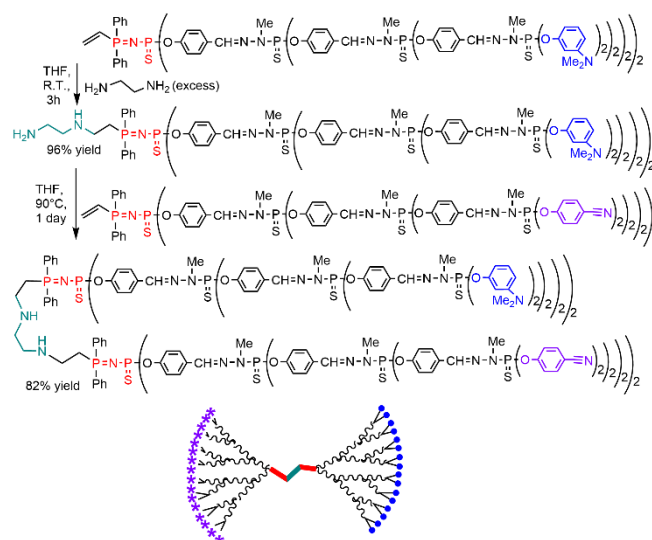
### 3. Dendritic architectures elaborated from dendrons

The possibility to react diamines at the core of vinyl dendrons enables the grafting of a second dendron, affording Janus dendrimers (two different types of terminal functions located in two different areas of the molecule). The grafting of the second dendron takes a longer time than for the first one, and in some cases requires harder conditions. The grafting to other types of dendritic architectures, in particular to dendrimers was also carried out.

#### 3.1. Janus dendrimers obtained by Michael-type additions

The first example of a Janus dendrimer based on phosphorus dendrons was obtained in two steps from two different dendrons having a vinyl group at the core. A large excess of ethylene diamine was first reacted to the vinyl core of a third generation dendron functionalized with 16 terminal functions of type 3-dimethylaminophenol. The second step was the reaction of the  $\text{NH}_2$  group at the core of the first dendron with the vinyl group at the core of another third generation dendron functionalized with 16 terminal functions of type 4-cyanophenol, to afford a Janus dendrimer (Scheme 8). The same process was also applied to the corresponding generation zero dendrons. Interestingly, no large difference in the conditions used was necessary depending on the generation of the dendrons. Indeed, the excess of the second

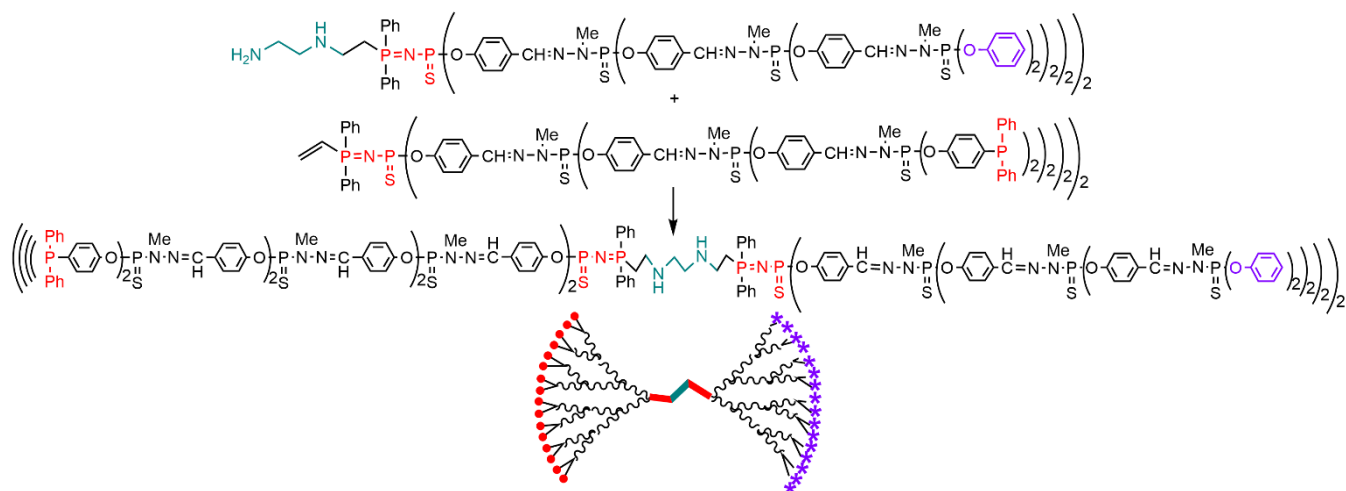
dendron was 170% for generation zero, whereas it was 100% for generation 3. The reaction conditions were 1 day at  $90^\circ\text{C}$  for both generations. However, the isolated yields were much better with generation 3 (82%) than with generation 0 (53%). Such large difference in the isolated yield can be explained by the different method of purification used: normal phase silica column chromatography with generation 0, Size Exclusion Chromatography with generation 3 [16].



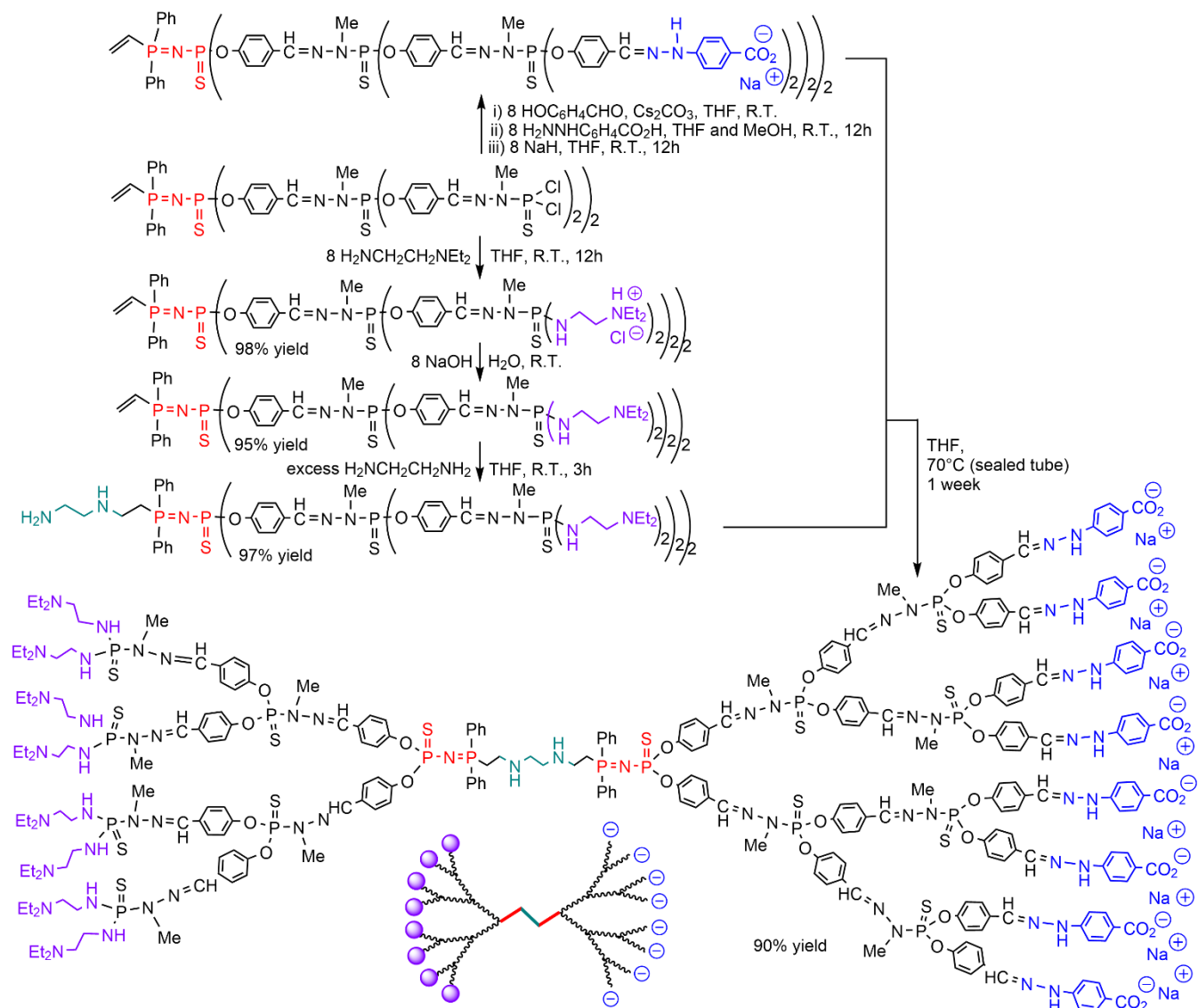
**Scheme 8.** First example of synthesis of a Janus dendrimer composed of two phosphorus dendrons associated by their core via an ethylene diamine linker.

The same linker (ethylenediamine) was also used to react first on the vinyl core of a third generation dendron having phenyl terminal functions. The resulting dendron was used to react with the vinyl core of a dendron having 16 triphenylphosphine functions on its surface (Scheme 9). This compound was not isolated, but its phosphines were suitable for further reactions, as will be shown later (section 3.2., Scheme 13) [17].

The example shown in Scheme 9 displays a Janus dendrimer bearing reactive functions on one side. The next step to expand the potential uses of Janus dendrimers consisted in having a different potentially reactive function on each side. A second generation dendron bearing 4  $\text{P}(\text{S})\text{Cl}_2$  terminal functions was used as precursor of a dendron bearing 8 carboxylate terminal functions, but also of a dendron bearing 8 tertiary amine terminal functions (Scheme 10). The vinyl core of the latter was reacted with an excess of ethylenediamine, and the resulting dendron was added to the vinyl core of the dendron bearing carboxylate terminal functions, to afford the difunctional Janus dendrimer shown in Scheme 10. The same process was applied to different dendrons having the same types of terminal functions (tertiary amines or carboxylates) but of different generations. Some examples are schematized in Figure 5A, associating for instance a second generation with a first generation, or a third generation with a first or second generation. The synthesis of the Janus dendrimers was carried out in relatively hard conditions, that are heating at  $70^\circ\text{C}$  in a sealed flask for one week. However, the isolated yields were rather good, between 86 and 93% [29].



**Scheme 9.** Another example of use of ethylene diamine as linker between two different dendrons, one of them bearing 16 phosphines as terminal functions.

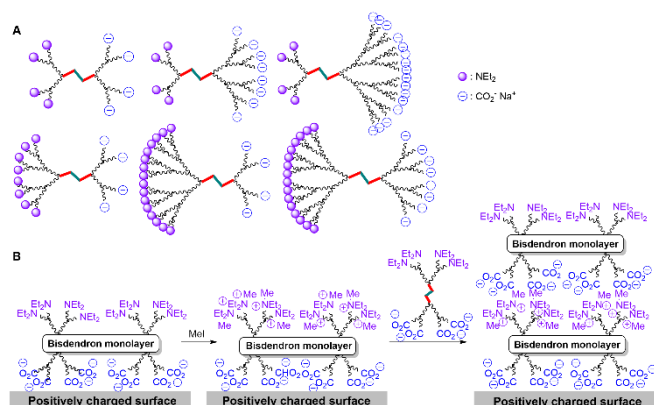


**Scheme 10.** Synthesis of a second-generation Janus dendrimer having negatively charged carboxylates on one side and tertiary amines on the other side, which could be quaternized.



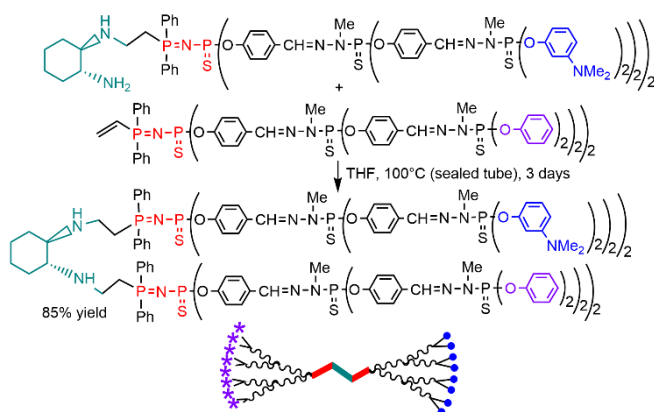
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The Janus dendrimer of second generation shown in Scheme 10, (as well as the corresponding first generation), was then used to interact with positively charged surfaces obtained by the modification of quartz or silicon dioxide with 3-aminopropyl(diethoxy)methylsilane). A single layer of Janus dendrimers was thus deposited (Figure 5B). Addition of MeI induced the quaternization of the tertiary amines, affording again a positively charged surface. The reaction was carried out by dipping the substrate in a solution of MeI in THF at 40°C for 12h. A second layer of Janus dendrimers bearing carboxylates on one side was then deposited, and the process was repeated up to 4 layers (Figure 5B). Uniform films were obtained at each step, as demonstrated by spectroscopic and microscopic studies [30].



**Figure 5.** A) Schematized structure of Janus dendrimers composed of different generation dendrons. B) Step-by-step modification of a positively charged surface.

Another example of Janus dendrimer was obtained by using *trans*-1,2-diaminocyclohexane instead of ethylene diamine as linker. The first step was the reaction of a large excess of *trans*-1,2-diaminocyclohexane on the vinyl core of a second generation dendron having 8 terminal functions of type 3-dimethylaminophenol. The second step was the reaction of this core-modified dendron with the vinyl core of a second generation dendron functionalized with 8 phenol groups on the surface. Such reaction was also carried out in a sealed tube, at 100°C, to afford another type of Janus dendrimer (Scheme 11) [17].

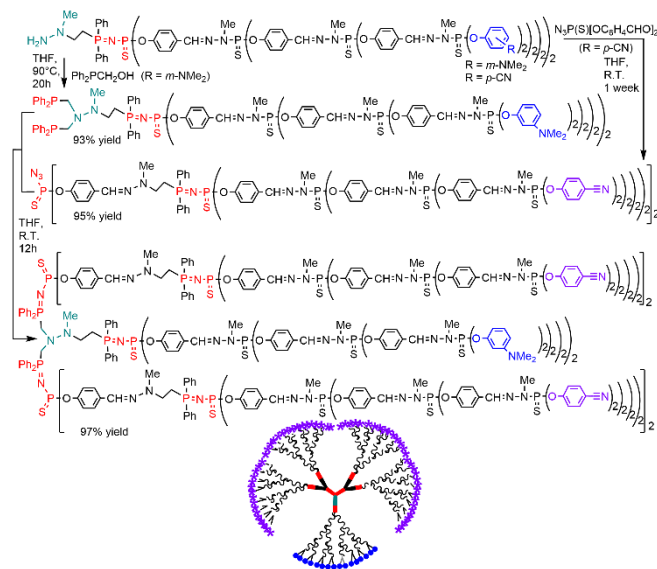


**Scheme 11.** Janus dendrimer obtained by the association of two second generation dendrons on a *trans*-1,2-diaminocyclohexane linker.

### 3.2. Janus dendrimers obtained by Staudinger reactions

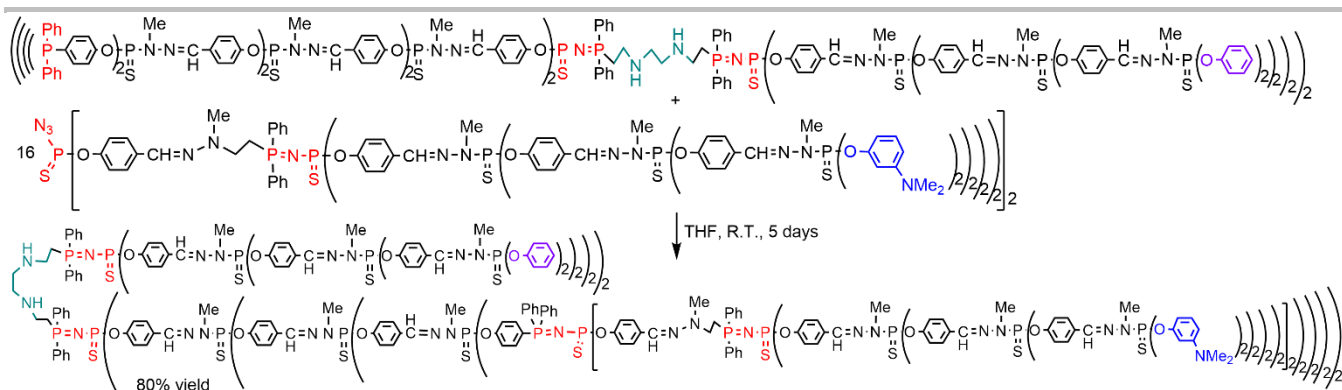
The presence of amines at the core of dendrons after the Michael-type addition of diamines or hydrazines on the vinyl group at the core enabled in a further step the grafting of phosphines or azides, suitable for Staudinger reactions. The grafting of methylhydrazine was thus performed at the core of a third generation dendron bearing 16 R groups, being either 3-dimethylaminophenol or 4-cyanophenol. This core functionalization enabled the reaction with Ph<sub>2</sub>PCH<sub>2</sub>OH, generated by reaction of neat Ph<sub>2</sub>PH with paraformaldehyde (CH<sub>2</sub>O)<sub>n</sub>, in a pressure Schlenk tube for 2h at 120°C. Two phosphines were grafted, on the dendron with R = 3-dimethylaminophenol on the surface, and the reaction with the azido dialdehyde N<sub>3</sub>P(S)(OC<sub>6</sub>H<sub>4</sub>CHO)<sub>2</sub> for grafting an azide was carried out on the dendron with R = cyanophenol on the surface (Scheme 12). The Staudinger reaction of the diphosphine dendron with two equivalents of the azido dendron afforded a Janus dendrimer bearing 64 cyano groups and 16 dimethylamino terminal groups, corresponding to a generation 5 on one side, and a generation 3 on the other side, as well as 7 P=N=P=S linkages inside the structure (Scheme 12). Despite the large size of these third generation dendrons, the Staudinger reaction occurred at room temperature for 12h, and the corresponding Janus dendrimer was isolated in 97% yield [16].

A related structure was obtained from the Janus dendrimer shown in Scheme 9, bearing 16 phosphino groups on one side, by reaction with 16 equiv. of a dendron possessing an azide at the core. The Staudinger reaction afforded a Janus dendrimer bearing on one side 16 phenyl groups, and on the other side 512 dimethylamino groups, and 50 P=N=P=S linkages inside the branches. Such structure corresponds to a generation 3 dendrimer on one side and a generation 8 on the other side (Scheme 13). The Staudinger reaction was also carried out at room temperature, but needed a longer time (5 days) to go to completion. The excess of dendron having an azide core used in the reaction was removed by Size Exclusion Chromatography purification. The full structure is schematized in Figure 6 [17].

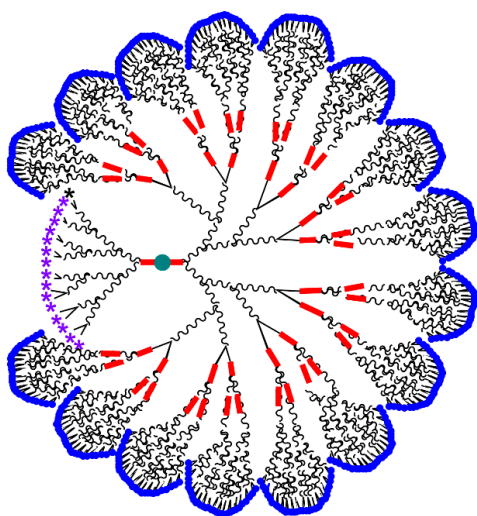


**Scheme 12.** Modifications at the core of third generation dendrons, to graft either phosphines or azide functional groups. The following Staudinger reaction afforded a Janus dendrimer of generation 3 on one side, and generation 5 on the other side.

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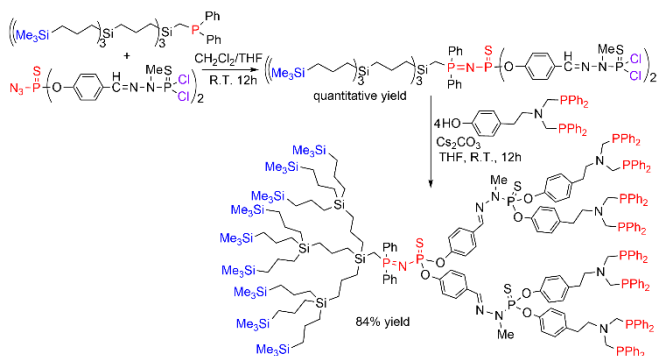


**Scheme 13.** Staudinger reaction affording a Janus dendrimer of generation 3 on one side, and generation 8 on the other side.



**Figure 6.** Schematized full structure of the Janus dendrimer shown in Scheme 13.

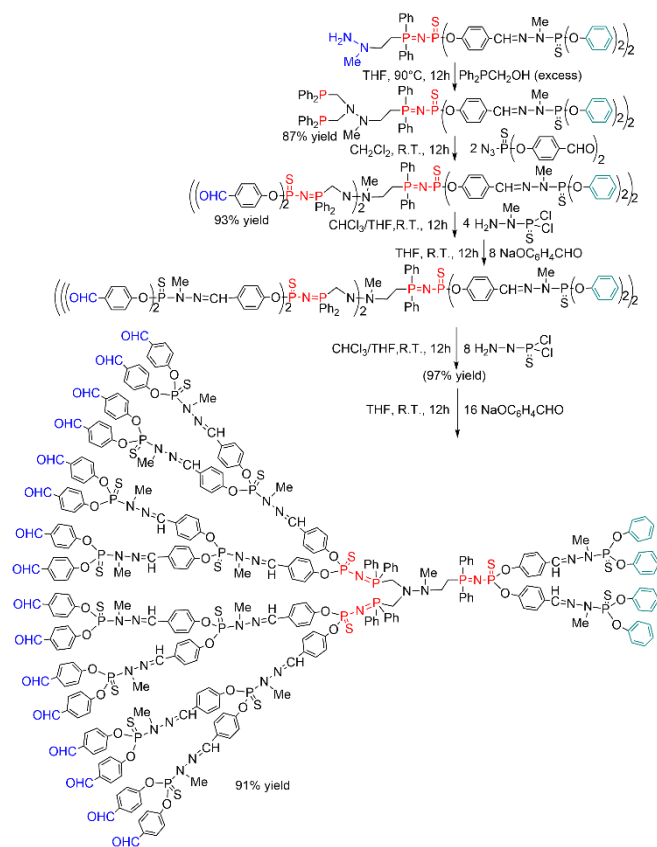
All the above-mentioned Janus dendrimers were composed of halves based on phosphorus dendrons. The following example is based on a carborasilane dendron having a phosphine at the core, and a small phosphorus dendron having an azide at the core and two  $P(S)Cl_2$  terminal functions. A single Staudinger reaction afforded quantitatively the Janus dendrimer bearing two  $P(S)Cl_2$  terminal functions, which were then reacted with different phenols bearing one or two phosphines. An example with a diphosphine is shown in Scheme 14 [31].



**Scheme 14.** Synthesis of a Janus dendrimer based on a carborasilane dendron, and a phosphorus dendron, and further functionalization with diphosphines.

### 3.3. Janus dendrimers obtained by growing branches from the core of a dendron

Another way to get Janus dendrimers from dendrons consisted in growing the second dendritic wedge from the core of a dendron. Such process was applied to a small dendron having a methylhydrazine at the core, on which two  $Ph_2PCH_2OH$  phosphines were reacted. Further Staudinger reactions with  $N_3-P(S)(OC_6H_4CHO)_2$  provided aldehydes on which the growing of the branches was carried out, as shown in Scheme 15. Janus dendrimers were isolated in very good yield at each step. The final compound in this series was composed of a generation 1 on one side and a generation 3 on the other side [12].



**Scheme 15.** Step-by-step synthesis of a dendron from the core of another dendron to produce Janus dendrimers.

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### 3.4. Dendrons for the functionalization of different molecular architectures

Besides the synthesis of Janus dendrimers, dendrons bearing one or several P=N-P=S linkages have been grafted on the surface of different molecular architectures, in particular on the surface of dendrimers, but not only. The use of dendrons permits to multiply rapidly in a single step the number of terminal functions of dendrimers. The 24 phosphine groups on the surface of a third-generation dendrimer were involved in Staudinger reactions with 24 equiv. of a dendron having an azide at the core and 32 nitriles on the surface, thus affording directly in one step an eight-generation dendrimer, functionalized with 768 nitrile end groups (Scheme 16). The reaction occurred smoothly at room temperature, and need 40h to go to completion. This dendrimer possesses two layers of P=N-P=S linkages, and was purified by Size Exclusion Chromatography. The full structure is schematized in Figure 7 [16].

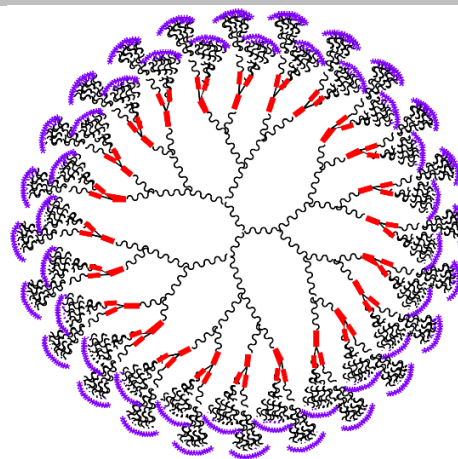
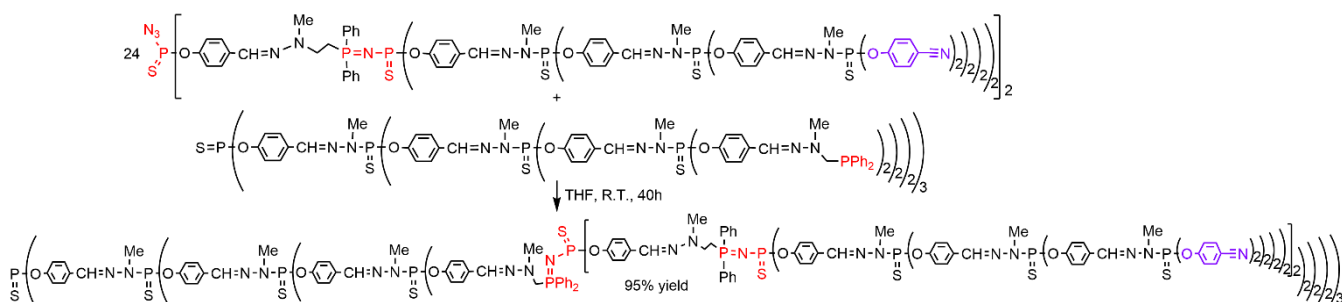
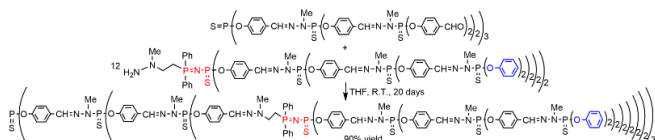


Figure 7. Schematized full structure of the dendrimer shown in Scheme 16.



Scheme 16. Straightforward synthesis of a generation 8 dendrimer in one step, from a generation 3 dendrimer.

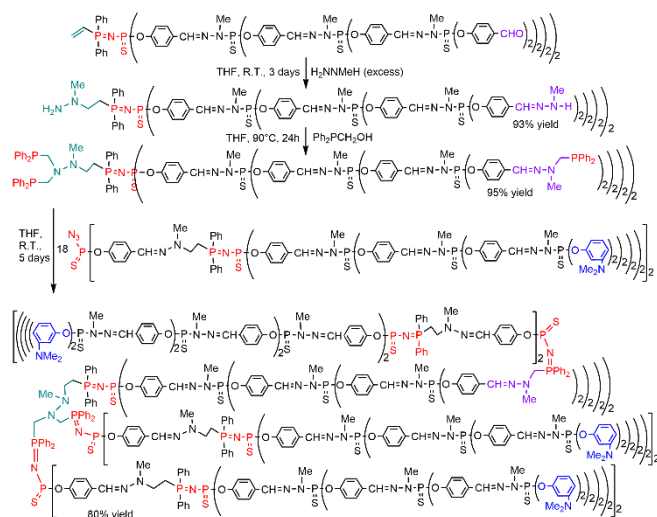
Another way to increase in one step the number of generations consisted in the condensation of a third generation dendron functionalized with methyl hydrazine at the core onto the surface of a second-generation dendrimer bearing 12 aldehyde terminal functions. The condensation reaction was very slow, and needed 20 days to go to completion. The reaction was monitored by the disappearance of the signal corresponding to the aldehydes, by both  $^1\text{H}$  NMR and IR spectra. A generation 6 dendrimer was obtained directly in this way from a generation 2 (Scheme 17) [17]. The condensation reaction used here appeared to be much slower than the Staudinger reaction previously used to prepare the larger dendrimer shown in Figure 7 and Scheme 16, thus evidencing the interest of P=N-P=S linkages to build large dendritic architectures.



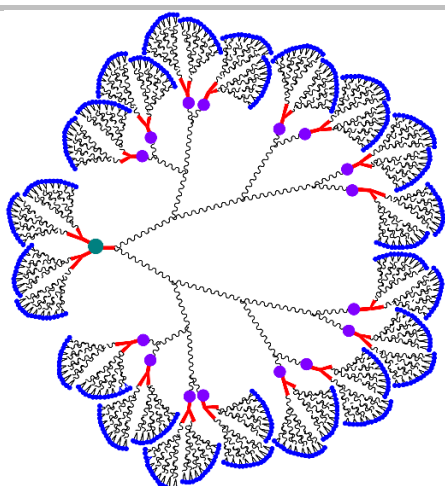
Scheme 17. From generation 2 to generation 6 dendrimer in a single step.

A special third generation dendron, functionalized with two phosphines at the core and 16 phosphines on the surface, was reacted with 18 equiv. of another dendron functionalized with an azide at the core and 32 dimethylamino groups on the surface.

The Staudinger reaction occurred both on the core and on the surface of the first dendron, offering a non-symmetrical dendritic structure, a kind of layered segment-block dendrimer having on one side two fourth generation dendrons and on the other side one eighth generation layered dendron linked to a  $(\text{PCH}_2)_2\text{-NNMeCH}_2\text{CH}_2\text{P}$  trifunctional core (Scheme 18 and Figure 8). This very complex structure was isolated in 80% yield after 5 days of reaction at room temperature [16].

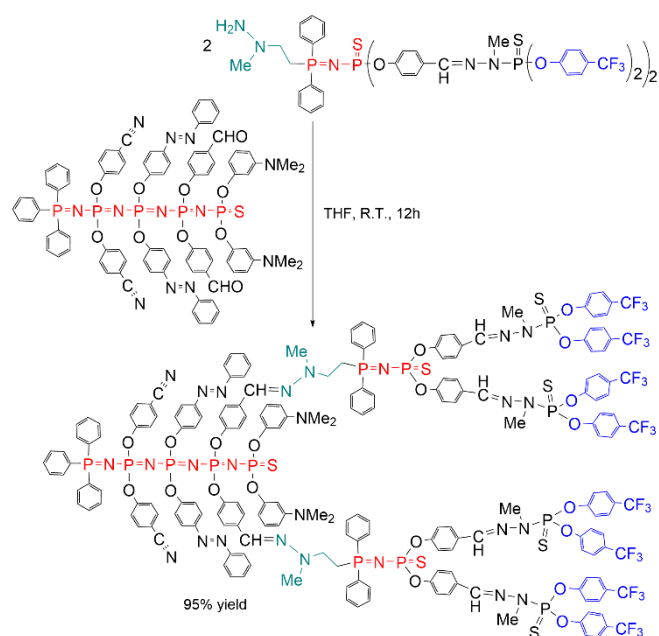


Scheme 18. Straightforward synthesis of a non-symmetrical dendritic structure.



**Figure 8.** Schematized full structure of the layered segment-block dendrimer shown in Scheme 18.

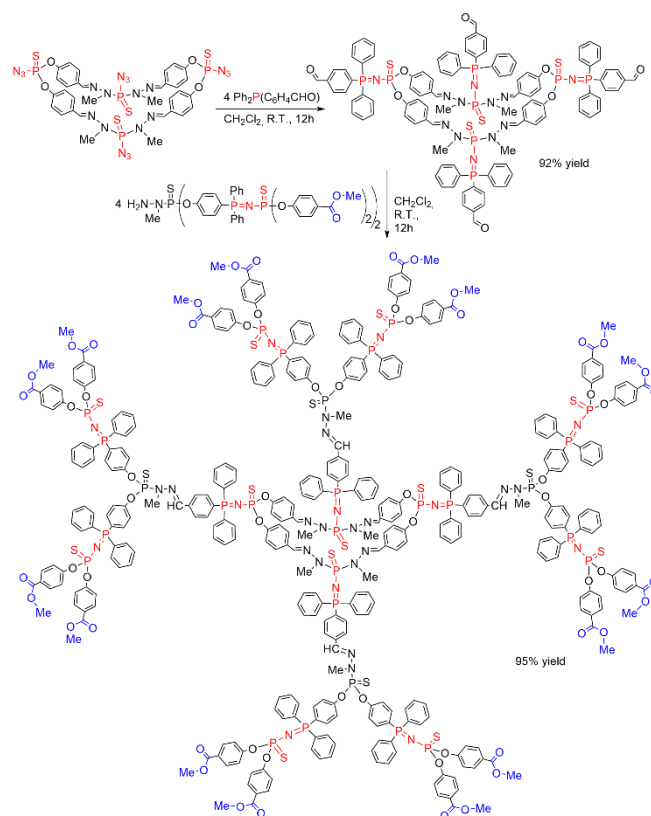
Besides dendrimers, the condensation reaction was applied to a very special core, consisting in a succession of P=N- linkages grown step-by-step by a series of Staudinger reactions [32]. Each phosphorus was bearing different functional groups. One of the phosphorus was functionalized with two aldehydes, which were reacted with a second generation dendron having a methylhydrazine at the core, affording a special type of dendritic structure built from an oligophosphazene core (Scheme 19). The condensation reaction was carried out for 12h at room temperature [33].



**Scheme 19.** Synthesis of a dendritic structure on an oligophosphazene core.

Another type of core consisted in a phosphorus macrocycle, bearing 4 azide functions [34], on which a phosphine derivative of benzaldehyde was reacted to afford 4 aldehyde functions. The condensation reaction with a small dendron functionalized by methylhydrazine at the core afforded a dendritic structure with a macrocycle as core (Scheme 20). Interestingly, the presence of

such bulky dendritic substituents on the macrocycle allowed for the first time the amplification of topological differences in the macrocycle. Indeed, the existence of diastereoisomers at the level of the 4 phosphorus atoms included in the macrocyclic ring, which was expected, but never demonstrated previously, was revealed by the presence of several signals in the  $^{31}\text{P}$  NMR spectrum [35].



**Scheme 20.** Synthesis of a dendritic structure based on a tetraphosphorus macrocycle.

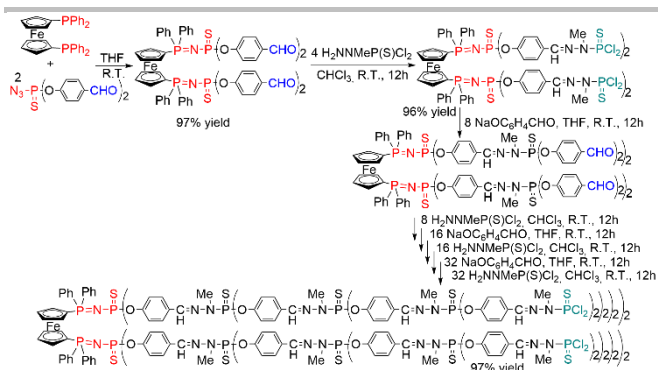
## 4. Dendrimers having one or a few layers of P=N-P=S linkages and their reactivity

Different types of phosphorhydrazone dendrimers incorporating one (or two) layer of P=N-P=S linkages in their branches have been synthesized. In many cases, these dendrimers were prepared to study the special and specific reactivity of such linkages.

### 4.1. Synthesis of dendrimers

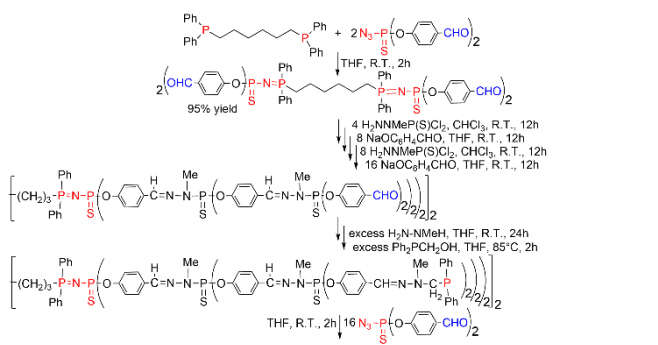
A series of dendrimers built from a 1-1'-bis(diphenyl)phosphine ferrocene core was synthesized up to the fourth generation, using the "classical" method of synthesis of phosphorus dendrimers [11], as shown in Scheme 21. The two P=N-P=S groups directly linked to the ferrocene act as electron withdrawing substituents, which dramatically modify the electrochemical properties of the ferrocene. Indeed, the electrochemical reaction is followed by a degradation of the P=N-P=S linkages, which destroys the compounds [36].

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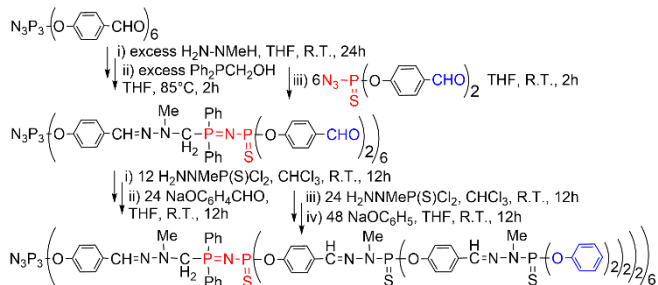
**Scheme 21.** Synthesis of dendrimers built from a ferrocene core.

Another type of diphosphine used as core for the synthesis of dendrimers is the 1,6-bis(diphenylphosphino) hexane. It was reacted with the same phosphoryl azide as in Scheme 21, and the growing of the dendrimer was carried out accordingly. After a few steps, an excess of methylhydrazine was reacted with the aldehyde terminal functions, then  $\text{Ph}_2\text{PCH}_2\text{OH}$  was grafted. The same azide was again used in the Staudinger reaction affording a new layer of  $\text{P}=\text{N}-\text{P}=\text{S}$  linkages. Such sequence of reactions was carried out at different levels. Scheme 22 displays one example of such types of dendrimers having  $\text{P}=\text{N}-\text{P}=\text{S}$  linkages at discrete and chosen layers [37].



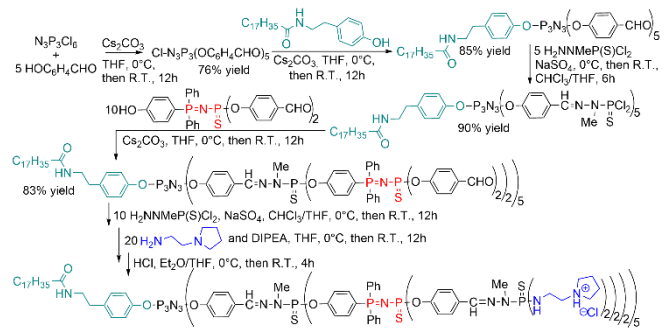
**Scheme 22.** Synthesis of dendrimers with  $\text{P}=\text{N}-\text{P}=\text{S}$  linkages at discrete layers.

The same type of process was used on the 6 aldehyde terminal functions of a dendrimer built from the cyclotriphosphazene core, as shown in Scheme 23. The synthesis was carried out to the third generation [38].

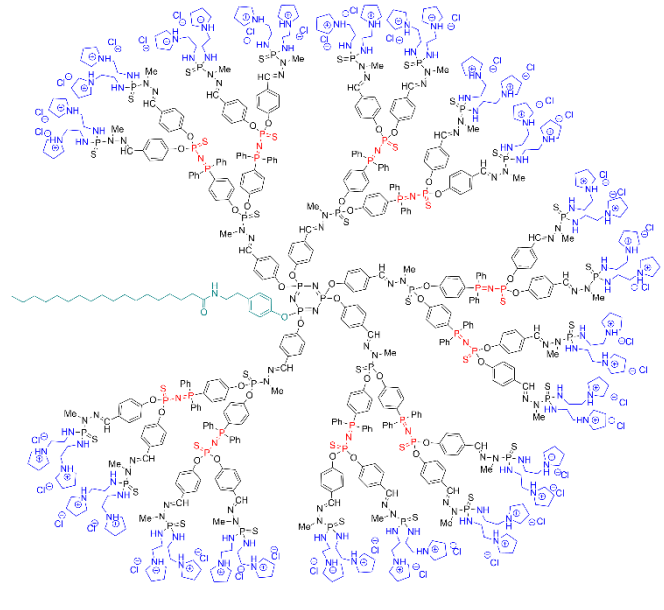


**Scheme 23.** Synthesis of a 3<sup>rd</sup> generation dendrimer with one layer of  $\text{P}=\text{N}-\text{P}=\text{S}$ .

A very recent result concerns the synthesis of a dendron bearing one long alkyl chain linked to the cyclotriphosphazene core. Ten  $\text{P}=\text{N}-\text{P}=\text{S}$  linkages were introduced by reacting a phenol dialdehyde on the  $\text{P}(\text{S})\text{Cl}_2$  terminal functions at the level of the first generation. The diphenylphosphino groups associated with such linkages increased the hydrophobicity of the internal structure of the dendron. The final step of the synthesis was the reaction of 1-(2-aminoethyl)-pyrrolidine at room temperature in the presence of *N,N*-diisopropylethylamine (DIPEA) as a base, followed by protonation with  $\text{HCl}$  (Scheme 24). This dendron is amphiphilic, due to the presence of the  $\text{C}_{17}$  chain at the core and of 40 ammoniums on the surface (Figure 9), and it self-associates in water to form micelles with a mean diameter of 26.3 nm. Such micelles of dendrons possess good intrinsic anticancer activity. Furthermore, they are able to encapsulate large quantities (42.4%) of the anticancer drug doxorubicin (DOX). The dendron and DOX act collectively to take down breast cancer cells *in vitro*, and also *in vivo* on a xenografted tumor model in BALB/c nude mice. An enhanced cancer cell apoptosis was observed, together with a significantly abolished toxicity compared to the free DOX drug [39].



**Scheme 24.** Synthesis of an amphiphilic dendron bearing an alkyl chain at the core, 10  $\text{Ph}_2\text{P}=\text{N}-\text{P}=\text{S}$  linkages inside the structure, and 40 ammoniums on the surface.



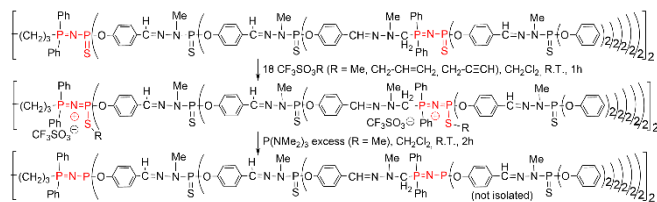
**Figure 9.** Full structure of an amphiphilic dendron, forming micelles in water, and suitable for encapsulating the anti-cancer drug doxorubicin.

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## 4.2. Reactivity of P=N-P=S linkages inside dendrimers

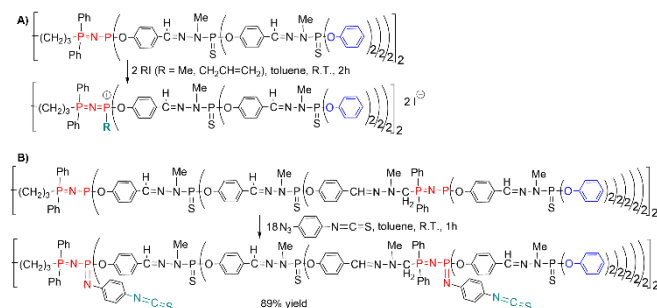
Interestingly, the P=N-P=S linkage can be written in a mesomeric form P<sup>+</sup>-N=P-S<sup>-</sup>, with a negative charge on sulfur. Indeed, DFT calculations afforded as Hirshfeld atomic charges (in a.u.) -0.23 on the S atom and +0.42 on the P atom linked to S. Such values are much lower for the other P=S groups (not included in a P=N-P=S linkage) with -0.17 on S and +0.31 on P [20]. Such difference should induce a different reactivity of the P=S groups, depending if they are included or not in a P=N-P=S linkage.

The specific alkylation of the sulfur in P=N-P=S linkages was carried out first with methyl trifluoromethane sulfonate (methyl triflate). Alkylation occurred exclusively on the P=S groups included in P=N-P=S linkages, not on the other P=S groups of the dendrimers. Such reaction was carried out with different dendrimers, one example in which the P=N-P=S linkages are present both at the level of the core and inside the branches is shown in Scheme 25. The alkylation induced large changes in <sup>31</sup>P NMR spectra, since the two doublets attributed to the P=N-P=S neutral fragments are replaced by two other doublets for the [P=N=P(SMe)]<sup>+</sup> cationic moieties [40]. Such alkylation was also carried out with other triflates such as allyl triflate and propargyl triflate, with the same specificity [41]. Alkylation of the sulfur atom induces a weakening of the strength of the Phosphorus Sulfur bond, which can be cleaved with P(NMe<sub>2</sub>)<sub>3</sub> [42]. Such reaction was in particular carried out in the case of alkylation by a methyl group, and affords tricoordinated phosphorus atoms inside the structure of dendrimers (Scheme 25) [37].



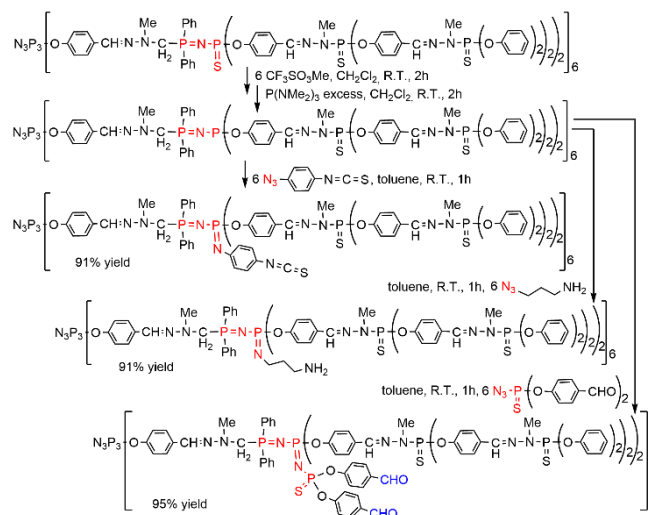
**Scheme 25.** Specific reactivity of alkyl triflates on the sulfur group of P=N-P=S linkages, followed by a desulfurization reaction.

The presence of tricoordinated phosphorus atoms inside the dendritic structure offers many possibilities for further reactions. It was for instance possible to alkylate this phosphorus atom with methyl or allyl iodide as illustrated with one example in Scheme 26A [37]. Another possibility concerns the use of an azide, for instance 4-azidophenylisothiocyanate, which affords P=N-P=N linkages, as shown in Scheme 26B [37].



**Scheme 26.** Reactivity of tricoordinated phosphorus atoms inside the structure of dendrimers. A) Alkylation reactions. B) Staudinger reaction with an azide.

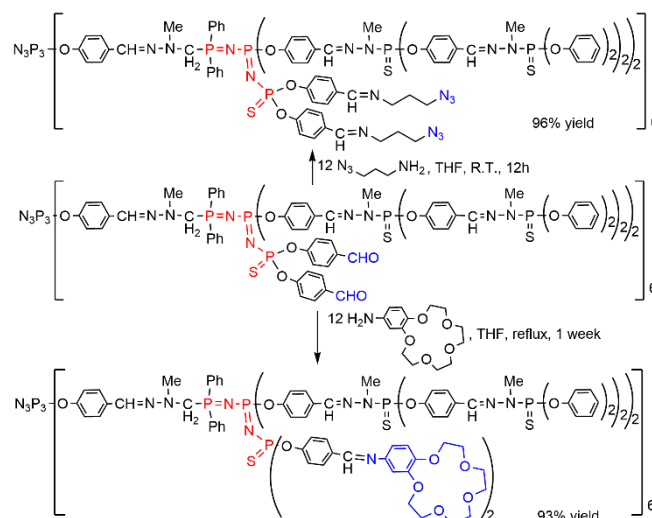
The same sequence of reactions, i.e. alkylation, desulfurization, and Staudinger reactions with azides was also carried out with the dendrimers built from the cyclotriphosphazene core. These reactions were in particular carried out with functionalized azides such as 4-azidophenylisothiocyanate, 1-amino-3-azidopropane, and N<sub>3</sub>P(S)(OC<sub>6</sub>H<sub>4</sub>CHO)<sub>2</sub>, as shown in Scheme 27 [37]. Reaction with this phosphorus azide created P=N-P=N-P=S linkages, and introduced internal aldehyde functions. All these Staudinger reactions inside the structure of dendrimers occurred in 1h at room temperature.



**Scheme 27.** Staudinger reactions for the internal functionalization of dendrimers.

## 4.3. Further reactivity inside dendrimers

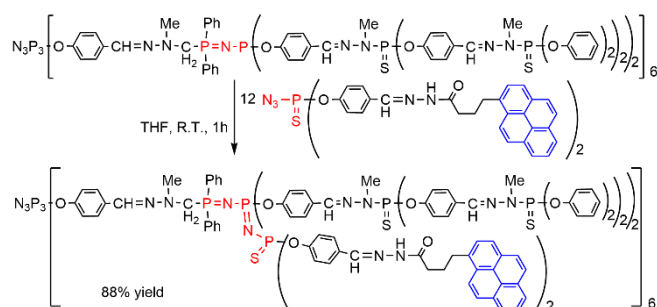
The presence of aldehydes inside the structure of dendrimers was particularly useful for further reactions. A review has gathered the early examples of such reactivity [43]. Condensation reactions, using different amines such as 1-amino-3-azidopropane, and 4'-aminobenzo-15-crown-5 were the first internal reactions carried out (Scheme 28) [37].



**Scheme 28.** Reactivity of aldehydes inside a dendrimer for grafting new functions.

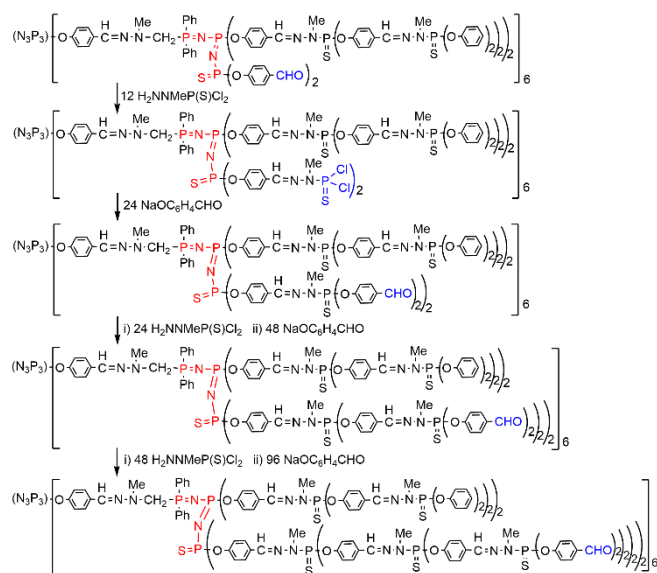
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Another example of internal reactivity concerned the condensation with 1-pyrenebutyric hydrazide, which afforded a fluorescent dendrimer (Scheme 29). Interestingly, the ratio of the intensity of pyrene-pyrene excimer and pyrene monomer emissions ( $I_E/I_M$ ), decreased with increasing solvent viscosity. Such finding indicated that i) the interior of dendrimers contained many solvent molecules, and ii) movements of the internal pyrene groups were not hindered by interactions with branches of the dendrimers, only by interactions with viscous solvents [44].



**Scheme 29.** Grafting a fluorescent pyrene derivative inside a dendrimer, for studying their movement.

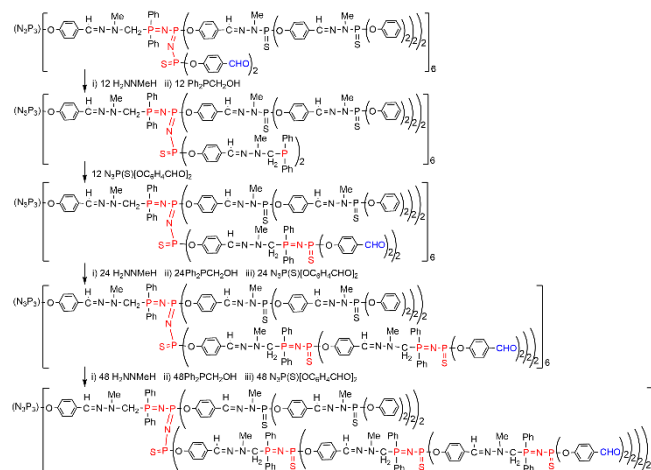
The internal aldehyde functions are also suitable for continuing the synthesis of new branches inside the dendritic structure, by the method used for the synthesis of classical phosphorhydrazone dendrimers, i.e. by reacting first the phosphorhydrazone  $H_2NNMeP(S)Cl_2$ , then the sodium salt of hydroxybenzaldehyde [11] (Scheme 30). The growing of the internal branches was continued until they became larger than the initial branches, as shown in Figure 10 [38].



**Scheme 30.** Synthesis of new phosphorhydrazone branches inside a dendrimer, by the repetition of two steps.

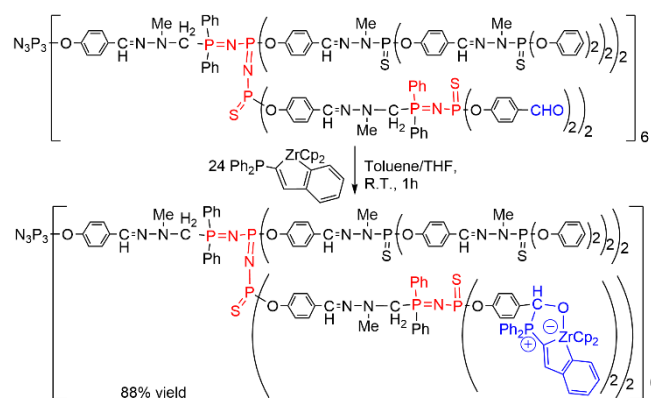
Another way for growing new branches inside the main dendrimer consisted in the repetition of three steps, instead of two in the previous case. These three steps begin with the condensation of methylhydrazine, followed by the condensation with  $Ph_2PCH_2OH$ , and finally the Staudinger reaction with the azide

$N_3P(S)(OC_6H_4CHO)_2$ , which affords new  $P=N-P=S$  linkages. The possibility to continue the growing from the aldehydes was demonstrated by the repetition of the same three steps. Such process was carried out 3 times to afford the dendritic structure having two different types of branches, as shown in Scheme 31 [38].



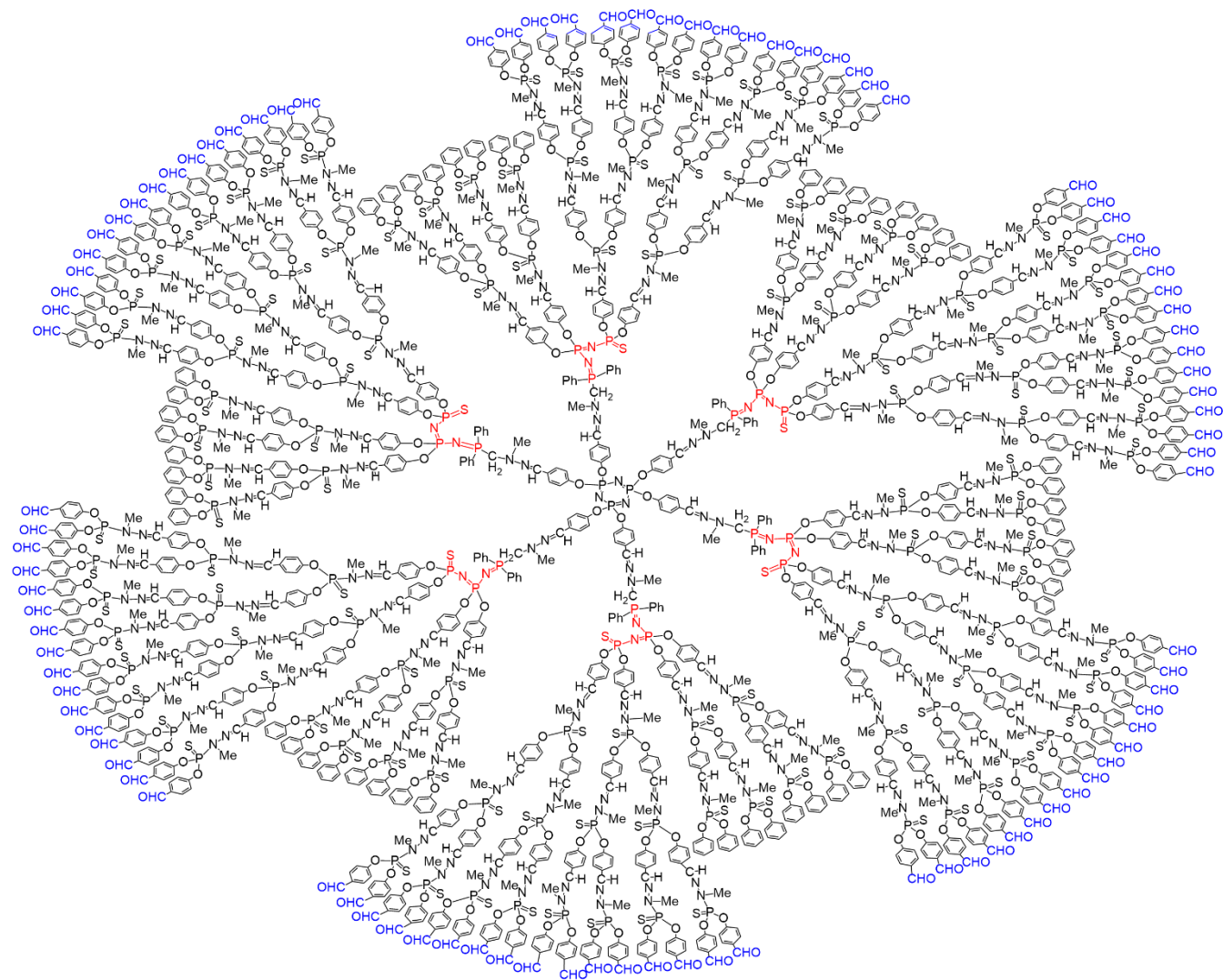
**Scheme 31.** Synthesis of new branches having  $P=N-P=S$  linkages at each generation inside a main dendrimer, by repetition of a three-step process.

An original reactivity was observed on the internal aldehydes using 2-diphenylphosphino-1-zirconaindene. A formal [3+2] cycloaddition reaction led rapidly (1h at room temperature) to stable zwitterionic zirconocene complexes inside the dendrimer, as shown in Scheme 32. It should be noted that such type of reaction also occurred on the aldehyde terminal functions of classical phosphorhydrazone dendrimers [45].

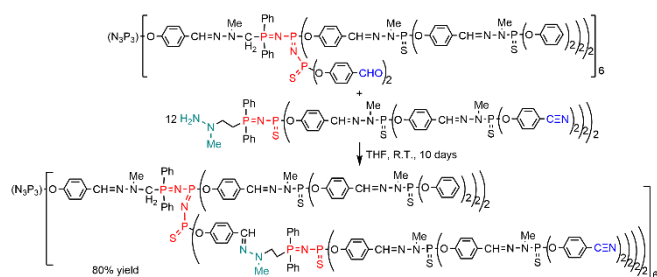


**Scheme 32.** Formal [3+2] cycloaddition reactions of 2-diphenylphosphino-1-zirconaindene on aldehyde internal functions producing a poly-zwitterionic dendritic structure.

A third way to incorporate new branches inside a main dendrimer consisted in the condensation of the internal aldehydes with a dendron functionalized with methylhydrazine at the core. The reaction occurred lengthily with the second generation dendron, which required 10 days at room temperature to go to completion, but the inside branches were obtained in a single step in that case (Scheme 33) [17].



**Figure 10.** Full structure of a dendrimer having new branches grown from inside its structure, as shown in Scheme 30.

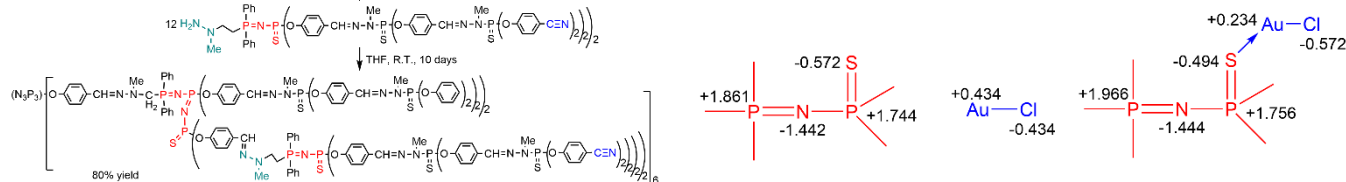


**Scheme 33.** Grafting dendrons by condensation reactions inside a dendrimer.

#### 4.4. Complexation of P=N-P=S linkages

In view of the reactivity of the sulfur atom in P=N-P=S linkages, it was attempted to study the complexation properties of such linkage, in particular with gold. Indeed, DFT calculations, and in particular the partial charges of the atoms determined by natural population analysis demonstrated that the complexation on sulfur modifies the charges on only two atoms, that are the S atom as expected, with a decrease of its negative charge, and surprisingly not the P atom linked to S, but the other P atom, with an increase

of its positive charge, illustrating again the electronic delocalization all along the P=N-P=S linkage (Figure 11) [46].

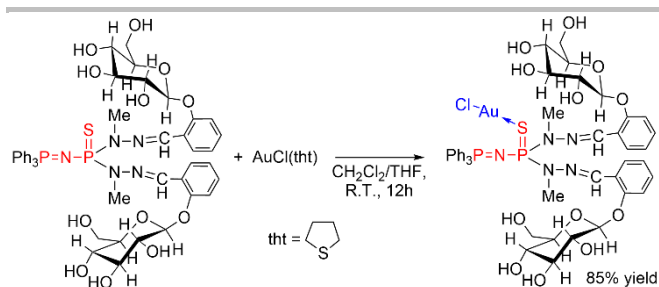


**Figure 11.** Calculated charge distribution (in e) in P=N-P=S linkages before and after complexation with gold.

To illustrate this possibility of complexation, a very small compound bearing one P=N-P=S linkage and 2 helicin derivatives was reacted with AuCl(tht) (tht = tetrahydrothiophene). The reaction occurred only on the P=S group, as shown in Scheme 34, demonstrating the compatibility of this reaction with the presence of alcohols [47]. The generation zero of the ferrocene dendrimers shown in Scheme 21 was also used to complex AuCl. A copper complex was also obtained, using CuSO<sub>3</sub>CF<sub>3</sub> [36].

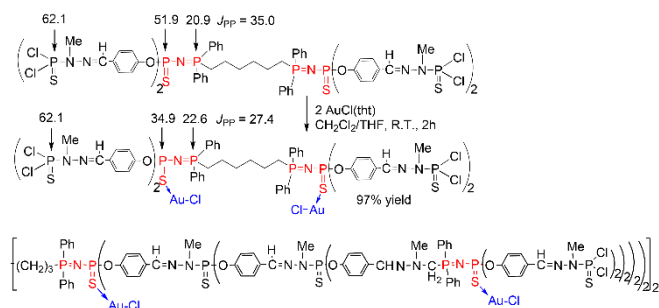


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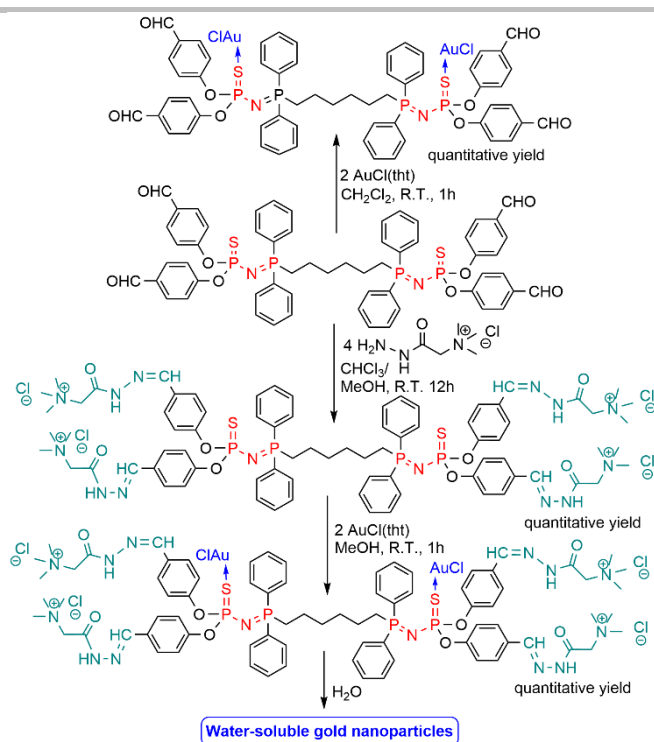
**Scheme 34.** Gold complexation on the sulfur atom in a derivative containing helicin moieties.

The family of dendrimers built from 1,6-bis(diphenylphosphino) hexane, as shown in Scheme 22, was used for demonstrating the specificity of the complexation of gold on the P=S groups included in P=N-P=S linkage, and not on the other P=S groups.  $^{31}\text{P}$  NMR was especially useful to demonstrate this specificity, as the chemical shifts of the two doublets corresponding to the P=N-P=S linkages, as well as their coupling constant, were dramatically modified by the complexation (Scheme 35). On the contrary the chemical shift of the other P=S groups was not modified. The crystal structure of the first generation dendrimer complexing gold was obtained, and confirmed that the complexation occurred only on the P=S functions included in P=N-P=S linkages. The complexation was carried out with other dendrimers of this family, an example of a large dendrimer complexing gold at two internal layers is also shown in Scheme 35 [48].



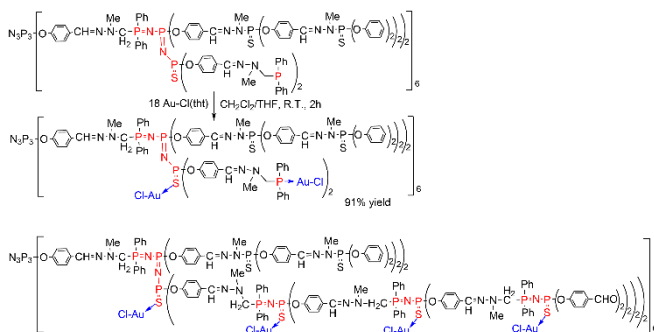
**Scheme 35.** Some examples of complexation with gold exclusively on P=N-P=S linkages.  $^{31}\text{P}$  NMR chemical shifts (in ppm) and coupling constant (in Hz) before and after complexation.

A recent example of complexation of a member of this family concerned a small compound functionalized with 4 Girard T reagents, suitable for inducing solubility both in methanol and in water. Complexation of P=S groups with gold was carried out in methanol, and occurred as expected (Scheme 36), affording a colourless solution. However, when solubilizing this complex in water, a deep red colloidal suspension was instantaneously obtained. Such color was indicative of the presence of gold nanoparticles. Their presence was confirmed by a shoulder in the UV-Vis. spectrum at about 545 nm, and by Transmission Electron Microscopy (TEM) images. These nanoparticles have a variety of slightly different shapes, but all issued from triangles. The dendrimer acts both as a mild reducing agent, and as a nanoreactor for the self-assembly of gold atoms, for stabilizing the gold nanoparticles, and finally inducing their solubility in water by forming colloidal suspensions [49].



**Scheme 36.** Synthesis of gold nanoparticles by simply adding water to a small dendrimer complex.

The complexation properties of the family of dendritic structures shown in Scheme 31 were also studied. The smallest compound of this family possesses both P=N-P=N-P=S linkages and internal phosphines. It was previously shown that phosphines on the surface of dendrimers readily reacted with AuCl(tht) [50], thus complexation of the internal phosphines was expected, whereas the behavior of the P=N-P=N-P=S linkages was an open question. In fact, such linkages were complexed on the sulfur atom, as for the P=N-P=S linkages, as shown in Scheme 37. The same complexation behavior was observed on the branches grown inside the main dendrimer (compound shown in Scheme 31 before complexation and in Scheme 37 after), and was demonstrated in particular by  $^{31}\text{P}$  NMR [48].

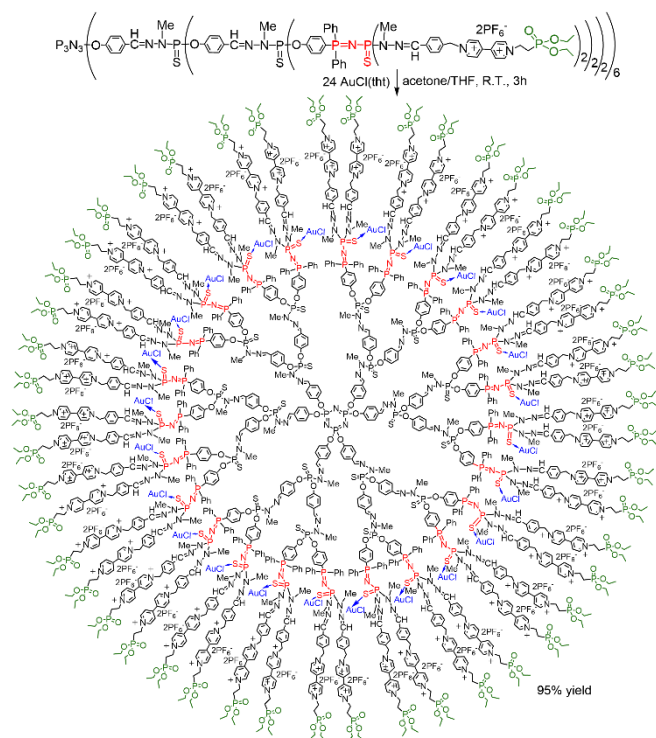


**Scheme 37.** Specific complexation of gold on phosphines, P=N-P=S and P=N-P=N-P=S linkages.

An onion peel (layered) dendrimer was synthesized to have phosphorus atoms with different types of environments at almost each layer. The most internal layer was a cyclotriphosphazene used as core, then two layers of P=S groups, one layer of P=N-

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P=S linkages, one layer of viologens having  $\text{PF}_6^-$  as counter-ion, and finally a layer of phosphonates on the surface. Despite the presence of many different types of phosphorus moieties, the complexation of gold occurred only on the P=S groups included in P=N-P=S linkages, as shown in Scheme 38 [51].



**Scheme 38.** Onion peel (layered) dendrimer having different types of phosphorus moieties in its structure. Only the P=N-P=S linkages were able to complex gold.

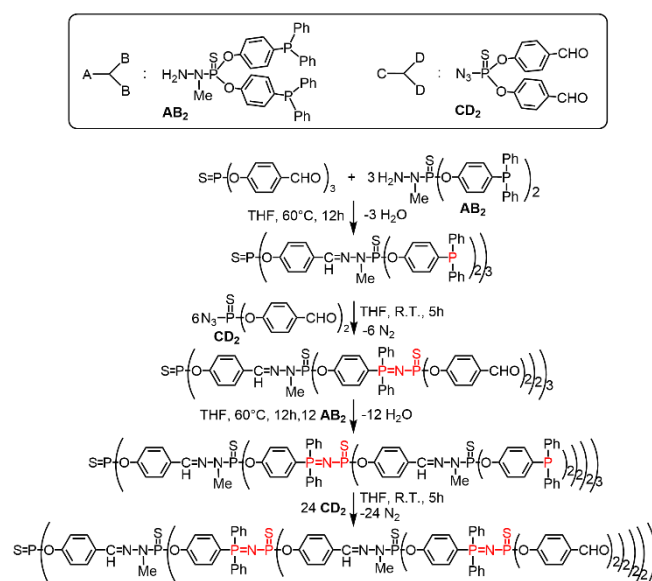
### 5. Accelerated syntheses of dendrimers built with P=N-P=S linkages at several layers

The synthesis of dendrimers is always a lengthy process, thus methods to accelerate it are always searched. The use of two types of branched monomers having orthogonal functions for a specific reactivity, instead of a single branched monomer in classical methods of synthesis, should improve the synthetic process. The main difficulty is to find the suitable functions, and the scaffold to hold them [52]. The condensation reaction between hydrazines and aldehydes on one side and the Staudinger reaction between phosphines and azides on the other side, are both quantitative reactions, generating benign by-products ( $\text{H}_2\text{O}$  and  $\text{N}_2$ , respectively), and producing stable functions.

#### 5.1. P=N-P=S every two layers inside the structure of dendrimers

The design of  $\text{AB}_2$  and  $\text{CD}_2$  branched monomers necessitates to find functions in which A reacts with D (not with B and C), and B reacts with C (not with A and D). Suitable functional groups that fulfill these requirements are A = methylhydrazine, B = triphenylphosphine, C = azide, and D = benzaldehyde derivatives. These functions were grafted to P=S groups, as shown in the

insert on Scheme 39. Starting from a trialdehyde core, the repetition of the condensation reaction with  $\text{AB}_2$ , followed by the Staudinger reaction with  $\text{CD}_2$  produced a 4<sup>th</sup> generation of a layered dendrimer in only four steps, instead of at least 8 in classical methods of synthesis (Scheme 39). Interestingly, a one-pot experiment was also carried out to obtain directly the fourth generation dendrimer starting from the core. A strict control of the stoichiometry, and a sequential addition of the reagents was needed, but in these conditions, the  $^{31}\text{P}$  NMR characteristics of this compound was very similar to that of the dendrimer obtained in a stepwise process with a purification at each step [53].

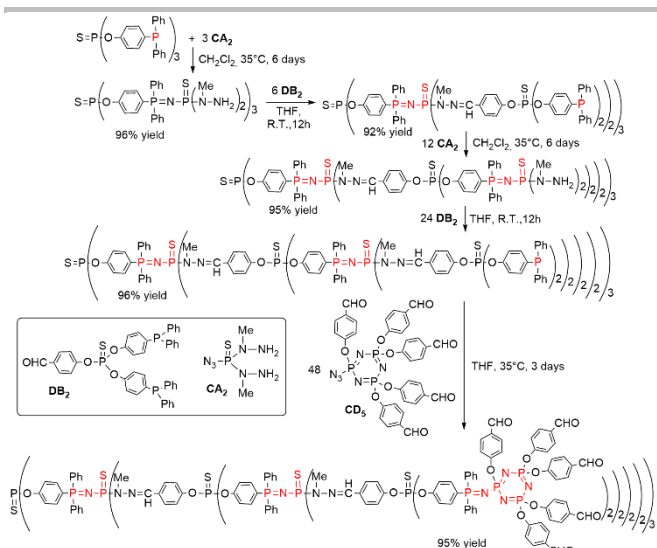


**Scheme 39.** Four-step synthesis of a 4<sup>th</sup> generation dendrimer using the branched monomers  $\text{AB}_2$  and  $\text{CD}_2$ .

Another way to organize the A, B, C, and D functions consists in synthesizing  $\text{DB}_2$  and  $\text{CA}_2$  branched monomers (insert in Scheme 40), instead of  $\text{AB}_2$  and  $\text{CD}_2$ . In that case, the synthetic scheme started from a triphosphine as core, then the growing was carried out by using successively and repetitively the  $\text{CA}_2$  and  $\text{DB}_2$  monomers [54]. In the last step, a  $\text{CD}_5$  monomer was used, instead of the  $\text{CA}_2$  monomer. This  $\text{CD}_5$  monomer is built from the cyclotriphosphazene core, in which one function (an azide) is different from the five others (benzaldehydes). This easy difunctionalization is a very interesting property of  $\text{N}_3\text{P}_3\text{Cl}_6$  [55]. Reaction of the  $\text{CD}_5$  monomer afforded an original P=N-P=N-P=N-P=N-P=N- cyclic linkage, as shown in Scheme 40 [54].

Another use of the  $\text{CA}_2$  monomer concerned its association with the phosphinoaldehyde  $\text{OHC-C}_6\text{H}_4\text{-PPh}_2$ , which is a linear  $\text{DB}$  monomer (Scheme 41) [56]. Such method is not an accelerated method of synthesis, but it provides  $\text{NH}_2$  terminal functions every two steps, as for the most classical dendrimers, that are PAMAM [57] and PPI [58] dendrimers. The possibility of condensation reactions with functionalized benzaldehydes was then tested, essentially with the second generation dendrimer, which afforded dendrimers decorated with carboxylic acid, boronic acid, or glucose (helicin) derivatives (Scheme 41) [56]. The same type of condensation reaction was carried out with the fourth generation dendrimer, for the grafting of an azobenzene derivative, in view of studying its photo-chemical properties (isomerisation) under light irradiation (Scheme 41) [59].

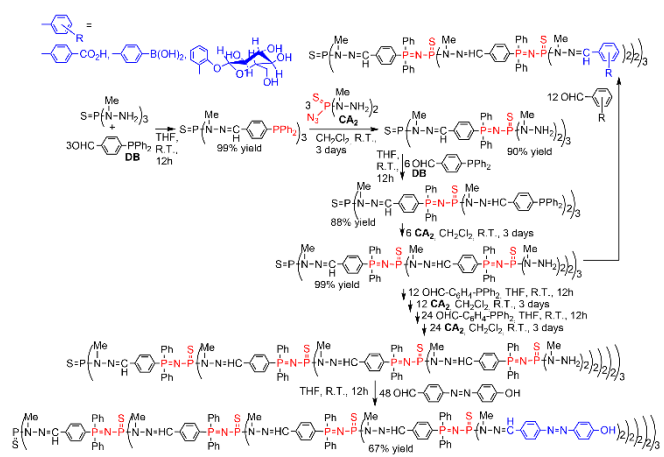
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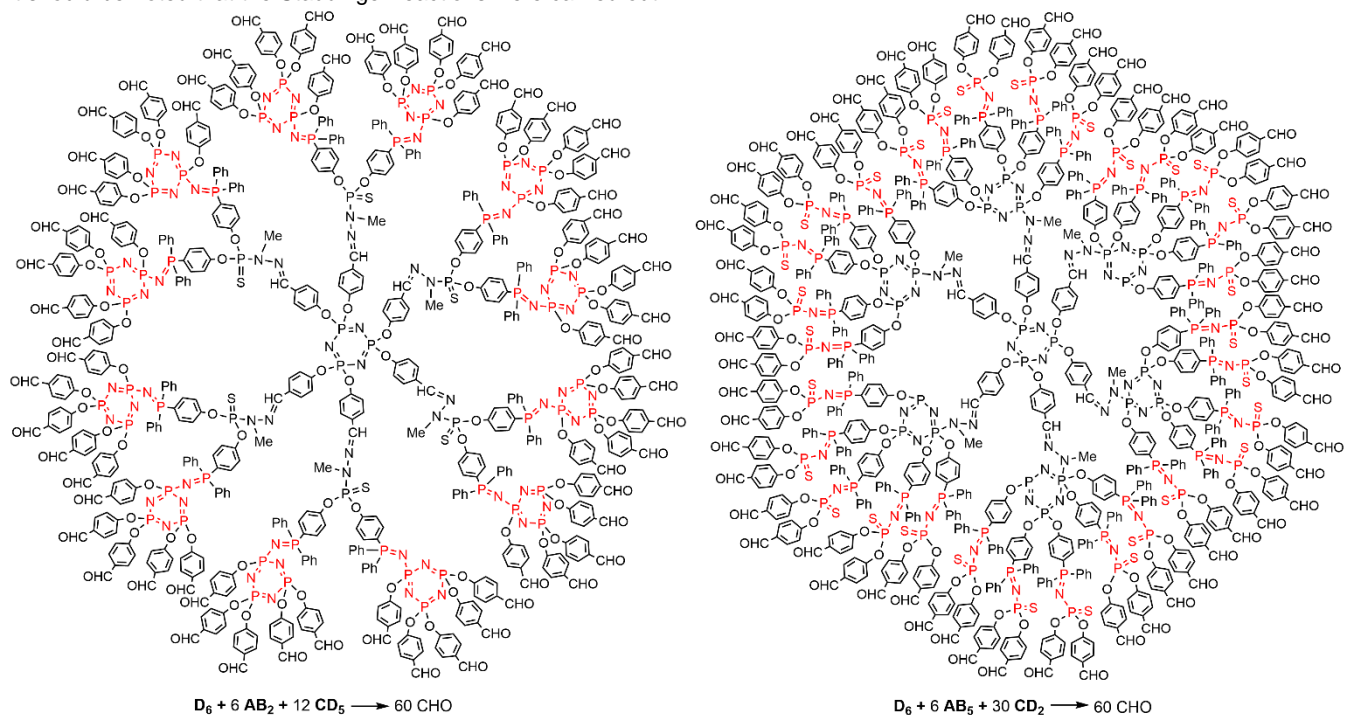
**Scheme 40.** Synthesis of a layered dendrimer using the branched monomers **DB<sub>2</sub>** and **CA<sub>2</sub>**. The highly branched monomer **CD<sub>5</sub>** was finally used to decorate the surface.

Another monomer built on the cyclotriphosphazene was the **AB<sub>5</sub>** monomer. The use of the **AB<sub>2</sub>** and **CD<sub>5</sub>** monomers on one side, and the use of the **AB<sub>5</sub>** and **CD<sub>2</sub>** monomers on the other side generated two families of dendrimers, starting in both cases from the hexa-aldehyde built from the cyclotriphosphazene core (Scheme 42, structure of the branched monomers in the insert). The use of the highly branched monomers permits to multiply rapidly the number of terminal functions. The synthesis was carried out up to the fourth generation, which bears in both cases 600 aldehyde terminal functions, obtained in only four steps [60]. It should be noted that the Staudinger reactions were carried out

at 45°C for two days, and that the condensation reactions were carried out at 100°C in a sealed tube, illustrating the steric hindrance encountered in such structures. The full structure of both second generation dendrimers, having both 60 aldehyde terminal functions and synthesized in only two steps, are shown in Figure 12. It can be seen that, despite their similarities, their internal structures are very different. This can be of importance for their properties, as the internal structure of dendrimers cannot be considered as an innocent scaffold [61].

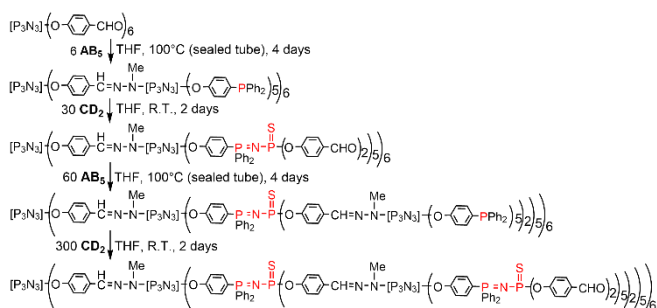
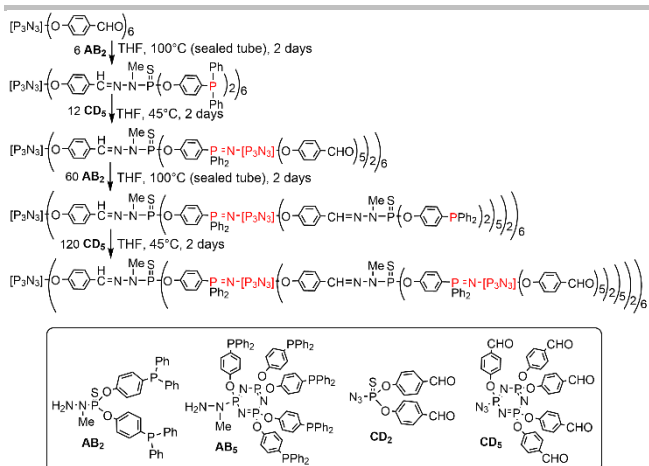


**Scheme 41.** Another example of the use of the **CA<sub>2</sub>** monomer in a two-step process with a **DB** monomer. Reactivity of the amine terminal functions with diversely functionalized benzaldehydes, carried out on the second and fourth generations.



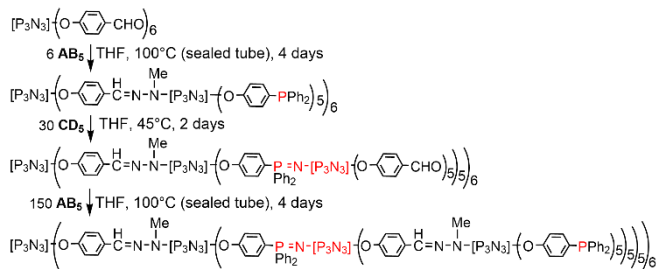
**Figure 12.** Full structure of the 2<sup>nd</sup> generation dendrimers shown in Scheme 42, built in only two steps from different branched monomers.

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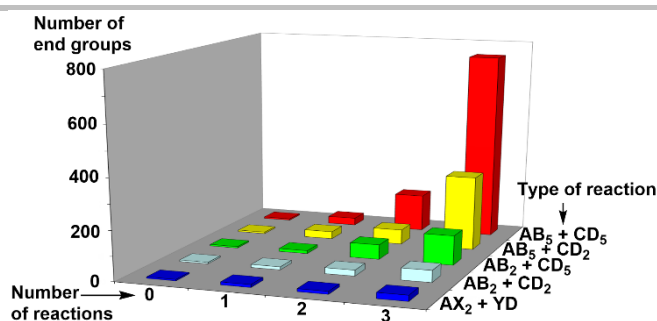


**Scheme 42.** Two accelerated methods of synthesis of dendrimers, using  $AB_2$  with  $CD_5$  (upper part) or  $AB_5$  with  $CD_2$  (lower part) branched monomers.

The next step to multiply more rapidly the number of terminal functions consisted in using both highly branched monomers  $AB_5$  and  $CD_5$ . Starting from the hexa-aldehyde core, the first reaction afforded 30 phosphines, the second 150 aldehydes, and the third one 750 phosphines (Scheme 43). Due to steric hindrance in such family of dendrimers, the reactions are carried out for longer times (several days) and in harder conditions ( $100^\circ C$  in a sealed tube) than for the other dendrimers. Within this family, the next reaction could theoretically provide 3750 aldehydes, but the dendrimer surface obtained at the third step was already too crowded to permit all the phosphines to react. Figure 13 displays the variation of the number of terminal functions after 3 steps, depending on the monomer used to build the dendrimer [60]. It should be emphasized that the number of terminal functions in the classical  $AX_2 + YD$  method is 12, whereas it is 750 with the  $AB_5 + CD_5$  method, after 3 synthetic steps, starting in all cases from the hexafunctional core  $P_3N_3(OC_6H_4CHO)_6$ .



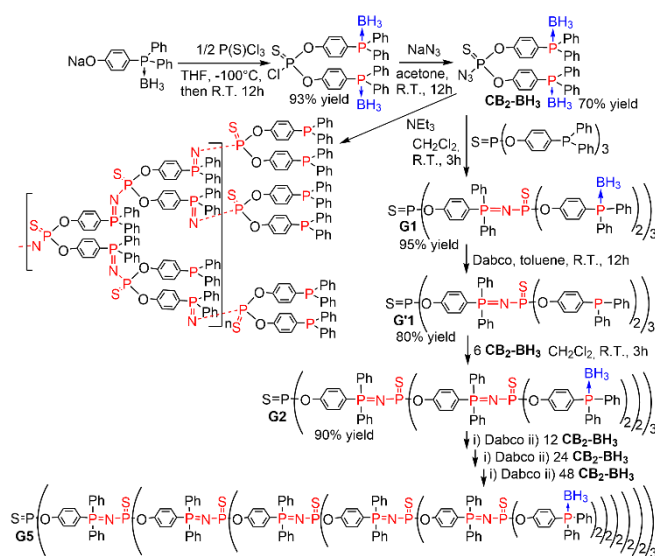
**Scheme 43.** Dendrimer functionalized with 750 phosphines in 3 steps.



**Figure 13.** Number of terminal functions after 3 reactions, depending on the monomer used.

## 5.2. P=N-P=S at all layers inside the structure of dendrimers

Another rapid method of synthesis of dendrimers was based on a single branched monomer of type  $CB_2$ . However, phosphines and azides react readily, as we have shown all along this review, thus the phosphines (**B**) have to be protected. Protection was carried out using  $BH_3$ , affording  $CB_2-BH_3$  (Scheme 44). This compound was the precursor of both hyperbranched polymers, obtained in one step from the deprotected phosphine  $CB_2$ , and dendrimers. For the latter, the first reaction was the Staudinger reaction between  $CB_2-BH_3$  and a triphosphine, followed by the deprotection of the terminal phosphines with Dabco, which were reacted again with  $CB_2-BH_3$ , and so on (Scheme 44) [62]. This family of dendrimers was characterized by Size Exclusion Chromatography, using an apparatus equipped with a multi-angle laser-light scattering (MALLS) detector.

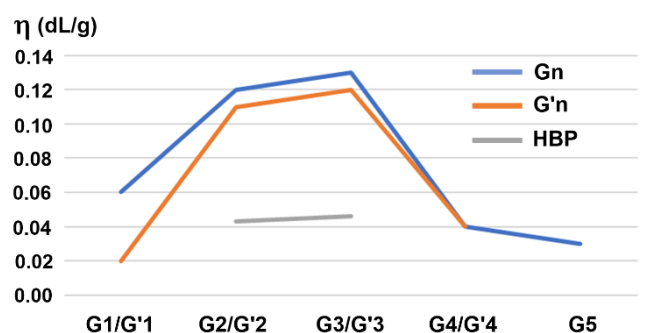


**Scheme 44.** Synthesis of hyperbranched polymers and dendrimers constituted of the same branched monomer.

Despite being composed of the same elemental unit, hyperbranched polymers and dendrimers have very different properties. The polydispersity index (PDI) was 1.014 for the highest generation dendrimer, whereas it was 1.32 for the hyperbranched polymer of a lower molecular weight. However, the largest difference between both families concerns the intrinsic viscosity  $[\eta]$ , which is not a measure of viscosity, but can be

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viewed as an indicator of the hydrodynamic volume. The intrinsic viscosity can be written as the ratio of the hydrodynamic volume ( $V_h$ ) to the molar mass ( $M$ ). In the case of dendrimers, the molar mass increases as  $(2^{g+1}-1)$ , whereas the hydrodynamic volume is supposed to expand in  $(g+1)^3$ , with  $g$  being the generation number in both cases. Thus, the  $[\eta]$  should pass through a maximum at a given generation, between 2 and 4. Figure 14 displays the variation of  $[\eta]$  for the different generations of the dendrimer shown in Scheme 44, **G<sub>n</sub>** corresponding to dendrimers with protected phosphines, **G'<sub>n</sub>** to dendrimers with free phosphines, and **HBP** corresponding to hyperbranched polymers having molar masses analogous to second and third generations dendrimers. The expected maximum is indeed observed for generation 3 with both types of terminal functions [62]. These data confirmed that hyperbranched polymers cannot be considered as the true analogs of dendrimers.



**Figure 14.** Intrinsic viscosity  $[\eta]$  of hyperbranched polymers (**HBP**), and of dendrimers shown in Scheme 44 (**G<sub>n</sub>** protected phosphines, **G'<sub>n</sub>** free phosphines).

## 6. Conclusion

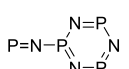
The old Staudinger reaction (1919) is nowadays a versatile and highly valuable tool for the synthesis of highly sophisticated dendritic structures, and also for accelerated methods of synthesis of dendrimers. No other type of reaction used so far for the synthesis of any type of dendrimers has demonstrated the possibility to generate a so large palette of dendritic structures. The fact that such reaction generates only  $N_2$  as by-product and is quantitative even in mild conditions (generally room temperature) is particularly helpful for the synthesis of such dendritic structures. The versatility of such reaction also enabled the one-step synthesis of hyperbranched polymers, and the comparison of their properties with those of pure dendrimers.

The characterization of dendrimers is always a difficult task, but phosphorus-containing dendrimers are essentially characterized with  $^{31}P$  NMR, which is a very precious tool at each step of the reaction process for assessing the completion of the reactions [63]. The presence of  $P=N-P=S$  linkages in combination with other  $P=S$  linkages affords in particular very complex, but very informative spectra [38].

When applied to thiophosphoryl azides, the  $P=N-P=S$  linkages generated in such Staudinger reactions are stable for years, but they display a specific reactivity on sulfur, for the complexation, especially of gold, and for the alkylation, which enables the desulfurization and further reactions on the phosphines generated

in this way. The very original possibility to grow new branches inside the structure of dendrimers was demonstrated for the first time, thanks to this reactivity. The different types of  $P=N-P=X$  linkages described in this review are summarized in the Table 1. They are all formed by Staudinger reaction, followed in some cases by a complexation, an alkylation or a desulfurization reaction that proceeded selectively and quantitatively on the  $P=N-P=X$  linkages, thus showing the interest of using this kind of moieties to build dendritic structures.

**Table 1.** Summary of the different types of  $P=N-P=X$  linkages found in the structure of phosphorus dendrimers.

$P=N-P=X$	Location (Schemes)
$P=N-P=S$	At the core (2,4-11,14,21) At the core and in the branches (12,13,15,16,18,20,22) In the branches (17,23,24,31-33,39-42,44)
$P=N-P=O$	At the core (2)
$P=N-P^+-S-Me$	At the core and in the branches (25)
$P=N-P:$	At the core and in the branches (25)
$P=N-P^+-R$	At the core and in the branches (26)
$P=N-P=S \rightarrow AuCl$	At the core (36) At the core and in the branches (35) In the branches (37)
$P=N-P=N-R$	At the core and in the branches (26) In the branches (27)
$P=N-P=N-P=S$	In the branches (27-33)
$P=N-P=N-P=S \rightarrow AuCl$	In the branches (37)
$P=N-P=N-P=N-P=N-P=S$	At the core (19)
	In the branches (40,42,43)

Even if such Staudinger reactions were carried out essentially for synthetic purposes, a few other uses have been recently discovered, such as the grafting of dendrons to silica for trapping  $CO_2$ , the spontaneous generation of gold nanoparticles, or an increased hydrophobicity, for favoring the formation of micelles of dendrons suitable for encapsulating and delivering the anti-cancer drug doxorubicin.

Besides, it should be emphasized that monomeric  $P=N-P=X$  linkages have been proposed as fungicides [64] and patented as insecticides [65], agrochemical fungicides [66], for reducing nitrogen loss and ammoniac pollution [67], as flame-resistant for

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textiles [68] and as flame-retardant for thermoplastic polymers sequential [69].

Thus, the field is largely opened to find new uses of structures incorporating P=N-P=S linkages, in particular in the field of materials. However, in view of the complexation properties, catalysis appears as one of the fields that could be explored, as recent papers have shown the interest of Au-Cl complexes [70]. Biology is also a field to be developed, as different metal complexes are of current use as anti-cancer drugs [71].

## Acknowledgements

Thanks are due to the CNRS for financial support, and to the GDR Phosphore.

**Keywords:** azide • dendrimer • dendron • phosphine • phosphorhydrazone

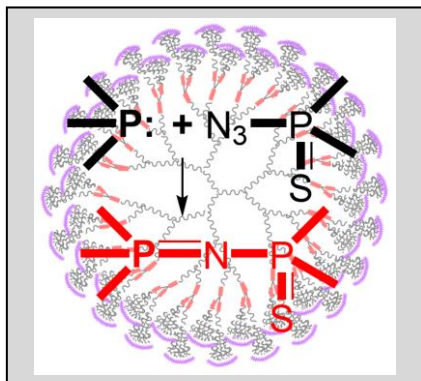
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## Entry for the Table of Contents



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The Staudinger reaction between phosphines and thiophosphoryl azides affords stable P=N-P=S linkages, which were used for synthesizing sophisticated dendritic structures, and also for accelerated methods of synthesis of dendrimers. Specific reactivity of such linkage occurs on sulfur with alkyl triflates, which weakens the strength of the P=S bond and can be easily cleaved. Complexation of gold was also observed.

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