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PEG-cored phosphorus dendrimers: Synthesis and functionalization

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Dedicated to Professor Claudio Pettinari on the occasion of his 58th birthday

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ABSTRACT

Dendrimers are macromolecular hyperbranched nano-structures, which properties are mainly driven by the type of their terminal functions. This paper reports the synthesis of dendritic structures built from difunctional polyethylene glycols (PEGs) used as core. Three different PEG lengths have been used: PEG_{300} (ca 6 CH_2CH_2-O units), PEG_{1000} (ca 22 CH_2CH_2-O units), and PEG_{2000} (ca 45 CH_2CH_2-O units). The first level of branching units is based on a dialdehyde of a dipiperazine triazine derivative. The second and third level of branching units are constituted of phosphorhydrazone linkages. The growing of the dendritic branches was found extremely slow with both PEG_{1000} and PEG_{2000} used as core, and was stopped early, whereas this problem was not observed with PEG_{300} used as core. These PEG-cored dendritic structures were finally functionalized on the surface with two types of nitrogen ligands.

Introduction

Dendrimers are monodispersed macromolecular hyperbranched structures, consisting of three basic architectural components, namely a core, an interior of monomer shells (named generations) consisting of repeating branch-cell units, and terminal functional groups which constitute the outer shell or periphery [1,2]. Most properties of dendrimers are governed by the nature of the terminal functional groups, even if the internal structure can play a key role, in particular for biology/nanomedicine [3]. The solubility in water of dendrimers is of utmost importance when considering their biological properties. In many cases, water-solubility is attained when having either positive [4] or negative charges on the surface. The most classical dendrimers such as PAMAM (polyamidoamine) [5] and PPI (polypropyleneimine) dendrimers [6,7] have nitrogen atoms as branching points, which can be easily protonated to increase the solubility in water. Besides charged entities, in the internal structure or on the surface, polyethylene glycol (PEG) is widely used as a neutral polymer, soluble in a large variety of solvents, including in water. A large number of dendrimers have been functionalized on their surface with PEGs of variable length, either on all the terminal functions [8], or on some of the terminal functions (stochastic grafting) [9]. Another way to increase the solubility of dendrimers in water, based on using a PEG polymer as core, with a dendritic wedge (dendron) grown on each side, has been developed. A non-exhaustive list of references concerning hybrid PEG-cored dendrimers comprises PAMAM dendrons [10–13], 1,3,5-triazine dendrons [14], L-Lysine dendrons [15–17], ether dendrons [18,19], ester dendrons [20,21], small citric acid dendrons [22], and special dendrons synthesized through orthogonal amine/epoxy and thiol-yne chemistries [23], but there is no example to date of PEG-cored phosphorus dendrimers.

However, phosphorus dendrimers [24], and especially phosphorhydrazone dendrimers have outstanding properties for catalysis [25], materials [26], and above all for nanomedicine [27,28]. The synthesis of such dendrimers has been already carried out starting from different cores, in particular $P(S)Cl_3$ [29], $N_3P_3Cl_6$ [30,31], which can be specifically functionalized [32], but also an octaaldehyde phthalocyanine [33,34], or a fluorescent linker [35]. This paper will present our results concerning the synthesis of the first PEG-cored phosphorhydrazone dendrimers, and representative examples of their surface functionalization with nitrogen ligands. Indeed, such type of ligands is able to complex diverse metals, and was recently found suitable for catalyzing

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Heck and Sonogashira couplings when complexing $PdCl_2$ on the periphery of phosphorhydrazone dendrimers [36]. The same family of dendrimers functionalized with nitrogen ligands also displays original anti-cancer properties when complexing $CuCl_2$ [37], or $[AuCl_2^+][AuCl_4^-]$ [38], but not $FeCl_2$ [39]. However, none of these complexes is soluble in water, which precludes real practical use in nanomedicine. We report here our efforts to try to increase the solubility in water of dendritic nitrogen ligands by introducing a PEG of variable length at the core.

Results and discussions

Synthesis of PEG-cored phosphorhydrazone dendrimers

Dihydroxy polyethylene glycols (PEGs) with different molar masses were chosen as core (**1a**, **1b**, and **1c**, Scheme 1). Small, medium, and large PEGs, with MW = 300, 1000, and 2000 g mol^{-1} (in average, 6, 22 and 45 O-CH_2-CH_2- units, respectively) were selected. As the classical synthesis of phosphorus dendrimers necessitates at one step the presence of aldehydes [29], we choose a di-(piperazinoaldehyde) (compound **2**) built from 2,4,6-trichloro-1,3,5-triazine, which was previously used as precursor of a building block suitable for the synthesis of original dendrimers. The presence of such structure (compound **2**) induces special color features, as the dendritic structures in which it is incorporated are either yellow or orange/red, depending on the synthetic step considered, and on the environment [40].

The reaction was carried out with 2 equiv. of the dialdehyde **2**, and one equiv. of the dihydroxy-PEGs **1a-c**, with KOH as base in refluxing dichloromethane, to afford generation zero dendrimers **3a-G'$_0$**, **3b-G'$_0$** and **3c-G'$_0$** (Scheme 1). The reaction was monitored by $^{13}C\{^1H\}$ NMR, showing the disappearance of the signals at 61 and 72.5 ppm corresponding to the carbon atoms in the α and β position of the PEG hydroxyl group, in favour of the appearance of signals at 66.9 and 69.2 ppm. Concurrently, ^1H NMR spectra of the three compounds **3a-G'$_0$**, **3b-G'$_0$** and **3c-G'$_0$** showed signals related to the aldehyde functions at ca 9.82 ppm, aromatic protons at ca 6.95 and 7.80 ppm and the signals for the piperazine protons at ca 3.48 and 4.00 ppm. The PEG chain displayed a broad signal between 3.4 and 3.8 ppm, whatever the chain length was. The $^{13}C\{^1H\}$ NMR showed the presence of two signals for the carbon atoms of the 1,3,5-triazine ring, one at 170.75 ppm for the carbon atom bearing the oxygen atom and the other at 165.6 ppm for the carbon atoms bearing the piperazine cycles. Compounds, **3a-G'$_0$**, **3b-G'$_0$** and **3c-G'$_0$** were isolated in 79%, 65% and 87% yield, respectively. Deceptively, dendrimer **3a-G'$_0$** with a PEG_{300} as core is not soluble in water, but dendrimers **3b-G'$_0$** and **3c-G'$_0$** with PEG_{1000} and PEG_{2000} as core, respectively, are water-soluble.

As in the "classical" synthesis of phosphorus dendrimers [29], the next step involved the condensation of the phosphorhydrazide **4** on the aldehyde functions of compounds **3a-c-G'$_0$**, in chloroform. The reaction was monitored with $^{31}P\{^1H\}$ NMR, by the appearance of a singlet at ca 63 ppm, and with ^1H NMR, by the disappearance of the aldehyde proton signal. The synthesis of the first generation dendrimer **3a-G$_1$** was performed at room temperature for 24 h, whereas the synthesis of the first generation dendrimers **3b-G$_1$** and **3c-G$_1$** required heating at 40° C for three weeks (Scheme 2). After completion of the reaction and purification, these first generation dendrimers were isolated in 56%, 68% and 71% yield, respectively.

These differences, i.e. the increase in temperature but also time to perform the reaction, could be explained by the fact that increasing the size of PEGs can create different geometries (Fig. 1), as already proposed [14]. It is obvious that the terminal functions should be more easily accessible for the PEG_{300} core than for the PEG_{2000} core, which could hide the functional groups.

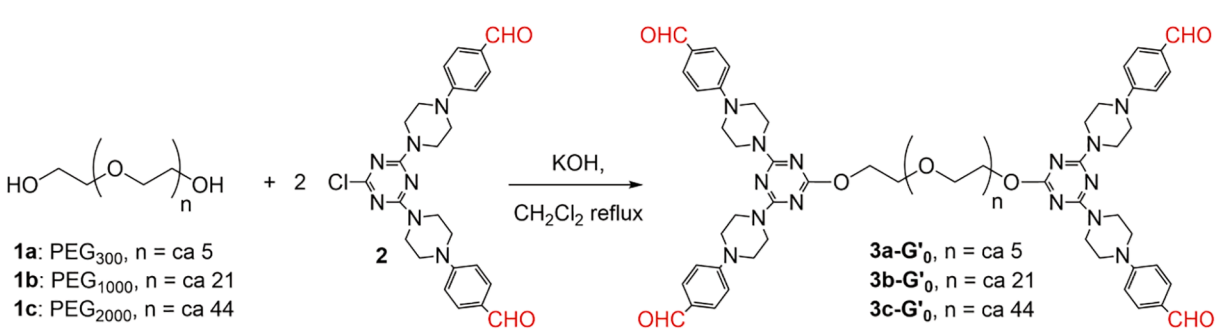
In view of the very long reaction times needed for the synthesis of dendrimers **3b-G$_1$** and **3c-G$_1$**, only **3a-G$_1$** was used for the preparation of higher generation dendrimers. The chlorine atoms of **3a-G$_1$** were substituted with 8 equiv. of 4-hydroxybenzaldehyde **5**, in the presence of cesium carbonate, at room temperature in THF, to afford dendrimer **3a-G'$_1$**, functionalized with 8 aldehydes (Scheme 3). The reaction was monitored by $^{31}P\{^1H\}$ NMR, which showed that the signal corresponding to the phosphorus atoms in the $P(S)Cl_2$ group at 63.12 ppm disappeared in favor of a more shielded signal at 60.85 ppm. Furthermore, the signal for aldehyde protons was clearly observable in ^1H NMR at 9.95 ppm. Dendrimer **3a-G'$_1$** was obtained as yellow-orange solid with 65% yield.

The 2nd generation dendrimer **3a-G$_2$** was obtained by condensation reaction of the phosphorhydrazide **4** on the aldehyde functions of **3a-G'$_1$**, as was done previously for the synthesis of **3a-G$_1$** from **3a-G'$_0$** (Scheme 4). The reaction was followed by ^1H NMR, via the disappearance of the aldehyde signal. Dendrimer **3a-G$_2$** is characterized in particular by the presence of two singlets in $^{31}P\{^1H\}$ NMR, at 62.04 ppm, corresponding to the internal layer of phosphorus atoms, and at 63.03 ppm corresponding to the terminal $P(S)Cl_2$ functions. Dendrimer **3a-G$_2$** was obtained as a red solid in 86% yield.

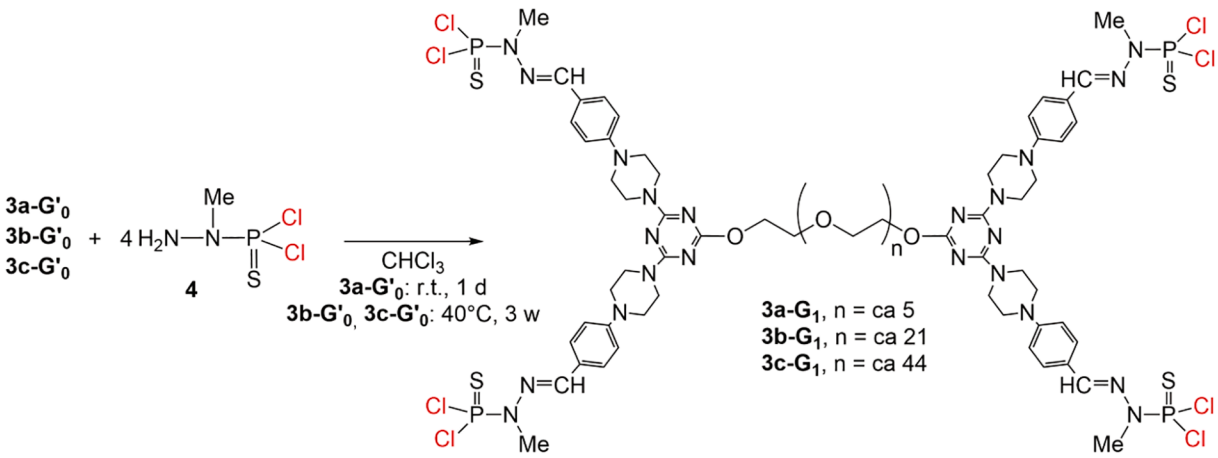
The synthesis of the second generation dendrimer bearing aldehyde terminal functions, **3a-G'$_2$** was carried out by substituting the chlorine atoms of **3a-G$_2$** by 16 equiv. of 4-hydroxybenzaldehyde **5** in the presence of cesium carbonate (Scheme 5), as done previously for the synthesis of **3a-G'$_1$** from **3a-G$_1$**. The reaction was followed by $^{31}P\{^1H\}$ NMR spectroscopy, which displayed a shielding of the signal of the phosphorus atoms at the periphery of the dendritic structure, from 63.03 ppm for **3a-G$_2$** ($P(S)Cl_2$) to 60.55 ppm for **3a-G'$_2$** ($P(S)(OAr)_2$). The obtained compound **3a-G'$_2$** was isolated as red solid in 62% yield. In view of the facility of the reactions carried out at each step, higher generations could be obtained, but we decided to stop the growing of this hybrid dendrimer/polymer at this step.

Functionalization of the surface of PEG-cored dendrimers with N,N-ligands

We have already shown the usefulness of diverse types of nitrogen ligands for catalysis and for biology [41], as indicated in the introduction. In a first attempt, we have functionalized the PEG-cored dendrimers bearing aldehyde terminal functions with 2-hydrazinopyridine, **6**. The condensation reactions were first carried out with the generation



Scheme 1. Synthesis of generation zero of PEG-cored dendrimers.



Scheme 2. Synthesis of 1st generation PEG-dendrimers.

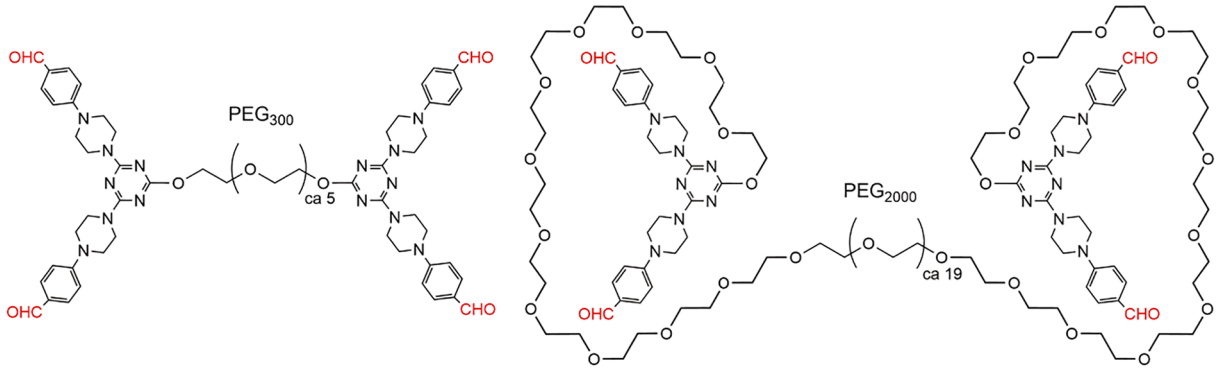
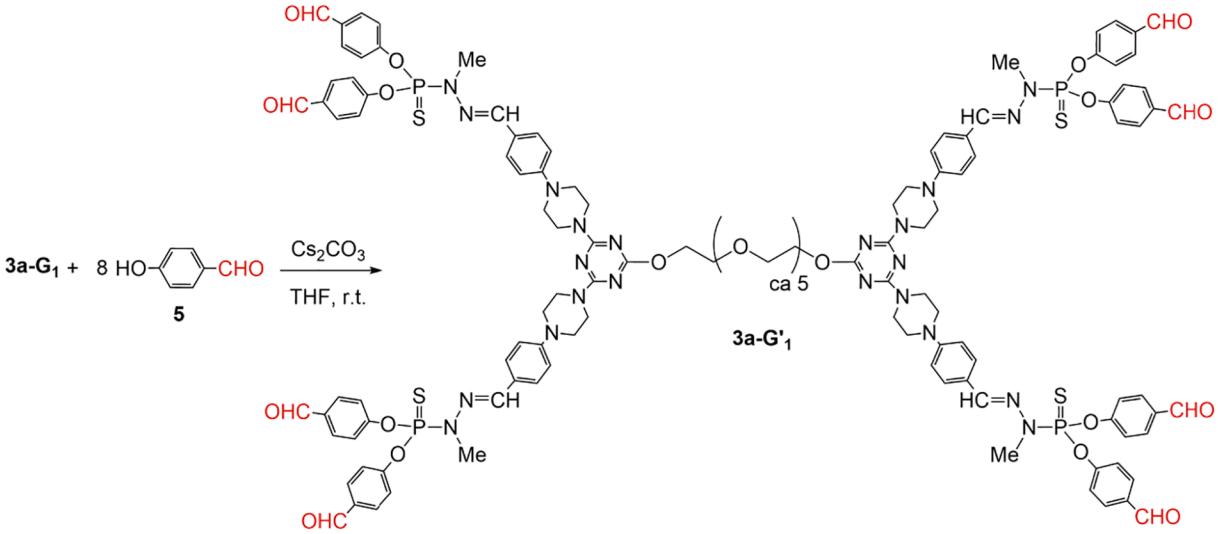
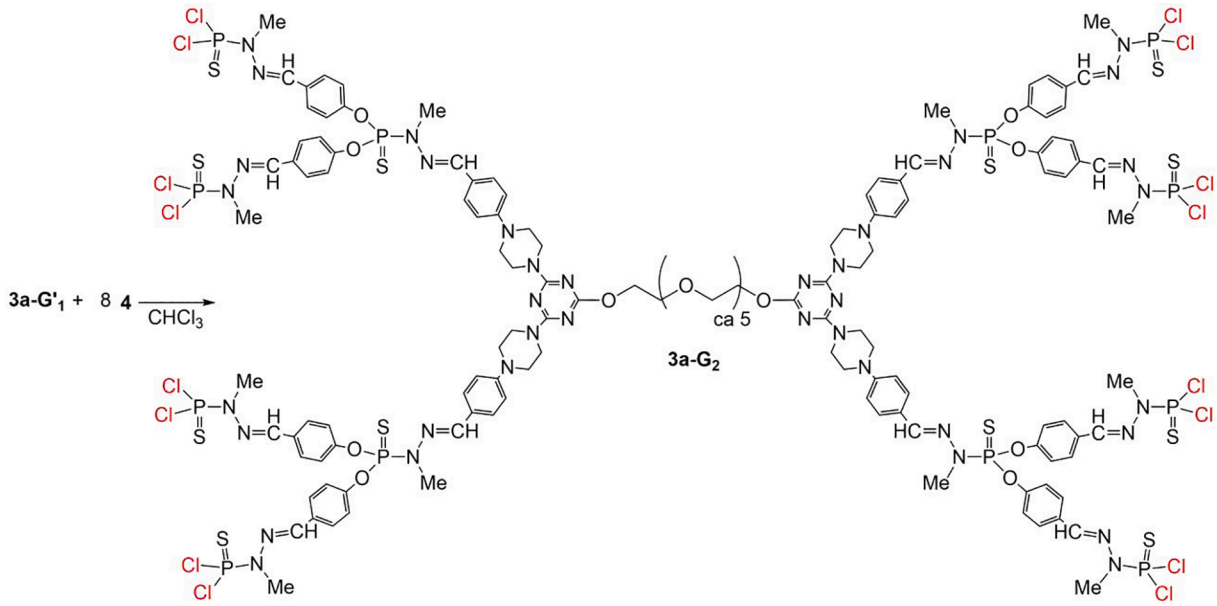


Fig. 1. Possible different geometries of PEG chains, depending on their length, and showing a possible shielding of the functional groups by the long PEG chain.

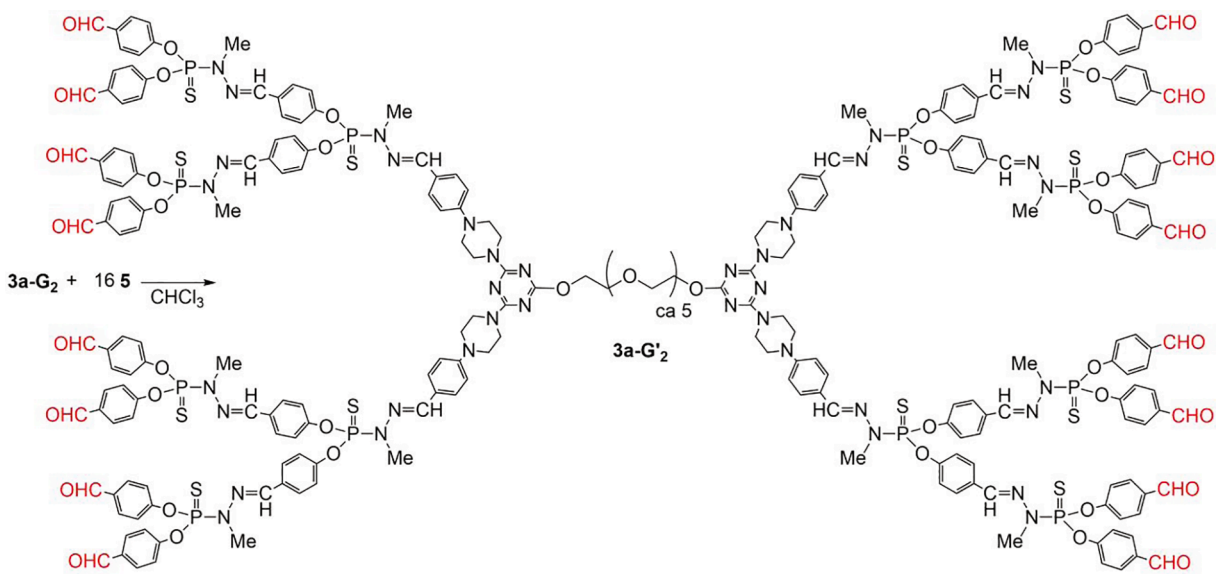


Scheme 3. Synthesis of dendrimer **3a-G'$_1$**.

zero dendrimers **3a-c-G'$_0$**, by heating in THF, to afford compounds **7a-c-G'$_0$** (Scheme 6). Under these conditions, the condensation was relatively fast (2 days) with dendrimer **3a-G'$_0$**, but very slow with dendrimers **3b-G'$_0$** which needed 9 days at 40 °C and above all with dendrimer **3c-G'$_0$**, which needed 9 days at 40 °C, followed by 10 days at reflux, to go to completion. Such behavior is reminiscent to what we have observed for the condensation of the same dendrimers with the phosphorhydrazide **4**, and is certainly due here also to the shielding of the active functions by the long PEG chain. The reaction was monitored with ^{1}H NMR by the disappearance of the characteristic signals of aldehyde functions at 9.82 ppm. Compounds **7a-c-G'$_0$** were characterized with ^{13}C {^{1}H} NMR by a signal at 126.2 ppm, characteristic of the carbon atom of the CH = N bond formed and a signal at 7.74 ppm in ^{1}H NMR for the corresponding proton. Compounds **7a-G'$_0$**, **7b-G'$_0$**, and **7c-G'$_0$** were isolated in 75%,



Scheme 4. Synthesis of the second generation dendrimer **3a-G$_2$**.



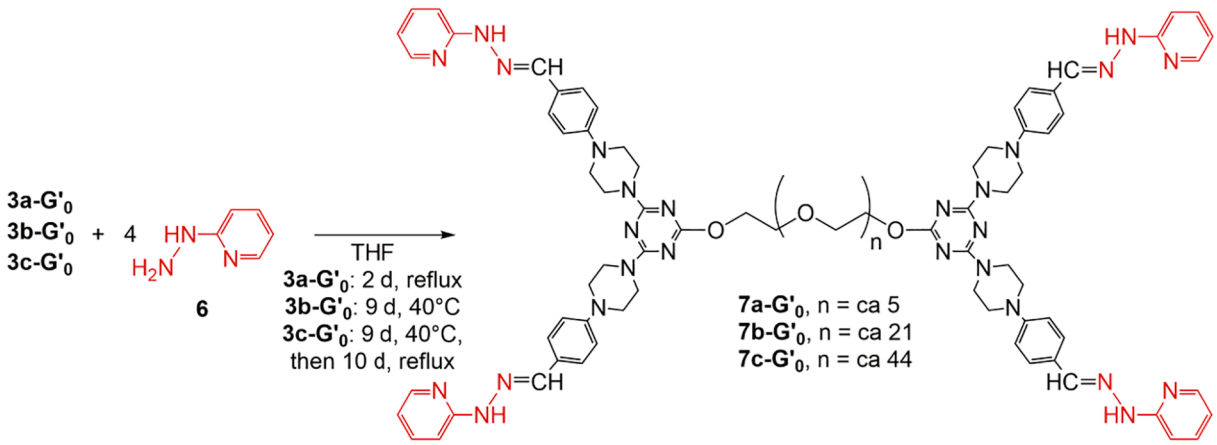
Scheme 5. Synthesis of dendrimer **3a-G'$_2$**.

98%, and 99% yield, respectively.

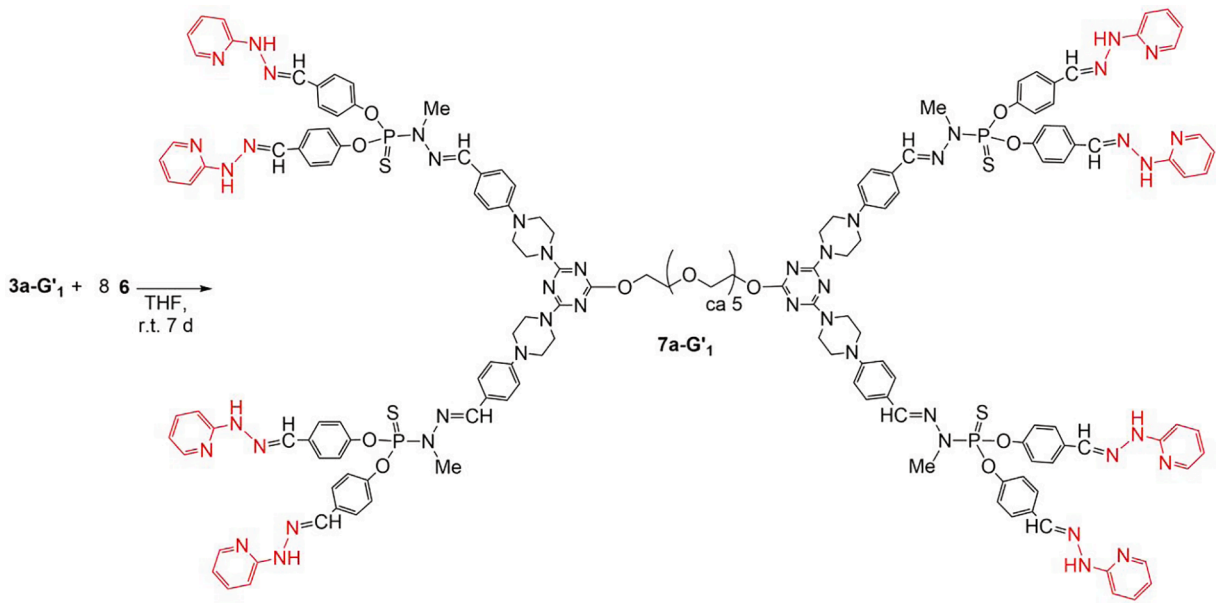
The condensation reaction of 2-hydrazinopyridine with the 1st generation dendrimer **3a-G'$_1$** was also carried out at room temperature, but it needed 7 days to afford **7a-G'$_1$** (Scheme 7). The reaction was monitored by $^{31}P\{^1H\}$ NMR spectroscopy, which showed a slight signal shielding, from 60.85 ppm to 60.25 ppm. The ^1H NMR spectrum displayed both the disappearance of the signal corresponding to the aldehyde functions, and the appearance of the signal of the CH = N at 7.92 ppm. Dendrimer **7a-G'$_1$** was isolated as a red powder in 93 % yield.

The second type of reaction used for grafting nitrogen ligands on the PEG-cored dendrimers was carried out with the phenol **8**, synthesized by condensation reaction, between tyramine and di-2-pyridyl ketone, as recently published [36]. Such phenol is suitable for the grafting to P(S)Cl_2 terminal functions of the dendrimers. The reaction was performed with dendrimer **3a-G$_1$**, in THF, in the presence of cesium carbonate, at room temperature, to afford dendrimer **9a-G$_1$** in 65% yield (Scheme 8). The reaction was monitored by $^{31}P\{^1H\}$ NMR, which showed the shielding of the signal from 62.56 ppm to 60.45 ppm in $CDCl_3$.

Complexation of copper has been attempted with some of the dendrimers bearing the iminopyridine N,N-ligands as terminal functions. Dendrimers **7a-G'$_0$** and **7a-G'$_1$** were dissolved in DMF, then an excess of a solution of $CuCl_2$ was gradually added (8.78 equiv. for **7a-G'$_0$**, for maximum 8 equiv. needed; 17.37 equiv. for **7a-G'$_1$**, for maximum 12 equiv. needed), considering that both the pyridine imine, and the piperazine could complex copper. Afterwards, this excess of copper was removed by washing with methanol until a colorless washing solution was obtained. The copper species were obtained as dark brown powders in good yields, 91 and 92% yield, respectively. They are slightly soluble in DMF and DMSO, but not in water or in other organic solvents. Their NMR spectra could not be recorded, as these species are both very poorly soluble as indicated, and paramagnetic, due to the presence of copper (II). Thus, these species have neither been characterized, nor been tested in biology.



Scheme 6. Condensation reaction of 2-hydrazinopyridine with the PEG-cored dendrimers of generation zero.



Scheme 7. Condensation reaction of 2-hydrazinopyridine with the first generation dendrimer **3a-G'$_1$**.

Conclusion

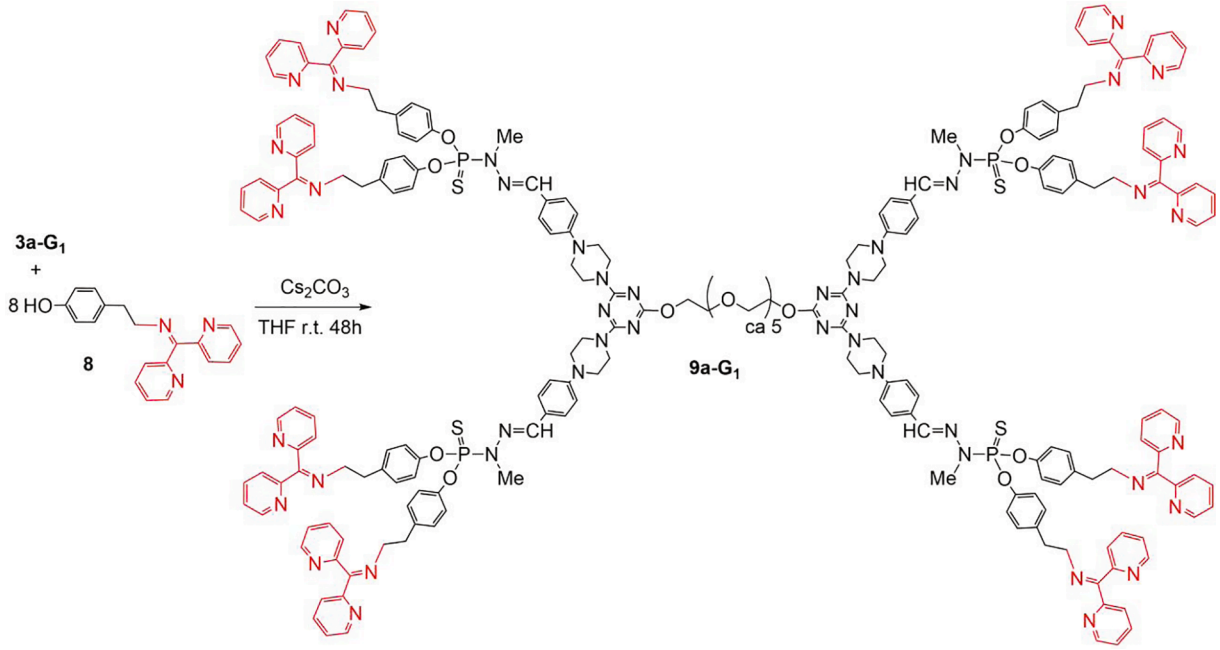
The first PEG-cored phosphorus dendrimers have been synthesized, characterized, and functionalized with nitrogen ligands. A large difference in the reactivity and in the properties has been observed, depending on the PEG length. Dendritic structures incorporating as core the smallest PEG (PEG_{300}) can be easily processed. No difference in reactivity was observed, when compared with "classical" phosphorhydrazone dendrimers built from a N_3P_3 core. However, deceptively PEG_{300} is not large enough to induce solubility in water. The reactions of compounds in which the largest PEGs (medium PEG_{1000} and large PEG_{2000}) were used as core needed several weeks of heating to go to completion, most probably because the terminal "reactive" functions are buried inside the PEG, and thus shielded. So, despite the fact that the presence of a larger PEG could induce solubility in water, at least for the smallest synthesized dendritic wedges, the lengthy reaction time precludes a really practical use of such PEG as core. Incorporation of PEG moiety -only- as core of phosphorus dendrimers was inadequate to attain sufficient water solubility. Probably, it would be more advantageous to include PEG chain within the branches of dendrimers, which could potentially solve also the shielding of terminal functional groups by the long PEG chain. However, the resulting compounds would be more hyperbranched polymers than dendrimers.

On the other hand, due to the very poor solubility of the copper complexes formed with PEG-cored dendrimers, they could not be characterized and exploited. However, this work confirms the usefulness of the 1,3,5-triazine piperazine dialdehyde derivative (compound **2**) to afford colored compounds [40]. Indeed, even if present in relatively small quantities, such as in dendrimer **3a-G'$_2$**, a red powder could be obtained. In contrast, the synthesis of "normal" phosphorhydrazone dendrimers always leads to white powders. Therefore, in our group work is in progress to develop the design of new dendrimers incorporating synthon **2**, as potential tools for staining cells or for coloring hard surfaces.

Experimental section

General

All reactions were carried out in the absence of air using standard Schlenk techniques and vacuum-line manipulations. Commercial samples were used as received. All solvents were dried and purified with MBraun SPS 800 solvent purification system before use. ^{1}H, ^{13}C, and ^{31}P NMR measurements were performed on Bruker AV300 and AV400.



Scheme 8. Synthesis of dendrimer **9a-G$_1$**.

Coupling constants are reported in Hz and chemical shifts in ppm relative to TMS for ^{1}H and ^{13}C NMR. Chemical shifts for ^{31}P NMR spectra are calibrated with phosphoric acid as an internal reference. The first-order peak patterns are indicated as s (singlet), d (doublet), t (triplet), q (quadruplet), qn (quintuplet). Complex non-first-order signals are indicated as m (multiplet); broad signals are indicated as br. ^{13}C NMR signals were assigned using Jmod, HMQC and HMBC sequences when required. Due to the presence of solvents inside the dendrimers, no reliable elemental analyzes could be obtained. The presence of solvents is necessary to ensure the solubility of the dendrimers in the next synthetic step. If they are removed, the dendrimers could not be solubilized again, even when using ultrasounds or heating. Compound **2** was synthesized as published [40], as well as compound **8** [36]. The numbering used for the assignment of NMR signals is shown in Fig. 2.

*Synthesis of dendrimer **3a-G'$_0$***

A solution of PEG$_{300}$, 1.0 g (3.34 mmol) in 10 mL of dichloromethane (DCM) was added dropwise to a solution of 20 mL of DCM containing 3.62 g of **2** (7.35 mmol) and 412 mg of KOH, at T = 40° C. The reaction mixture was heated to reflux for 24 h. After thin layer chromatography (TLC) control, a filtration followed by column purification was performed (DCM/ethyl acetate 3/1 then 10% ethanol, v/v). After evaporation of the solvents under vacuum, 3.17 g of **3a-G'$_0$** as a reddish solid were obtained (79% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 3.48 (br s, H-C$_6$, 16H), 3.66–3.71 (m, H-Cp, 16H), 3.85 (t, H-C$_2$, $^3J_{HH}$ = 5.1 Hz, 4H), 4.00 (br s, H-C$_5$, 16H), 4.49 (t, H-C$_1$, $^3J_{HH}$ = 5.7 Hz, 4H), 6.96 (d, H-C$_8$, $^3J_{HH}$ = 9 Hz, 8H), 7.81 (d, H-C$_9$, $^3J_{HH}$ = 8.7 Hz, 8H), 9.82 (s, H-C$_{11}$, 4H). ^{13}C {^{1}H} NMR (100 MHz, CDCl$_3$): δ (ppm) = 42.8 (s, C$_5$), 47.0 (s, C$_6$), 65.7 (s, C$_1$), 69.2 (s, C$_2$), 70.6 (s, C$_p$), 113.7 (s, C$_8$), 127.5 (s, C$_{10}$),

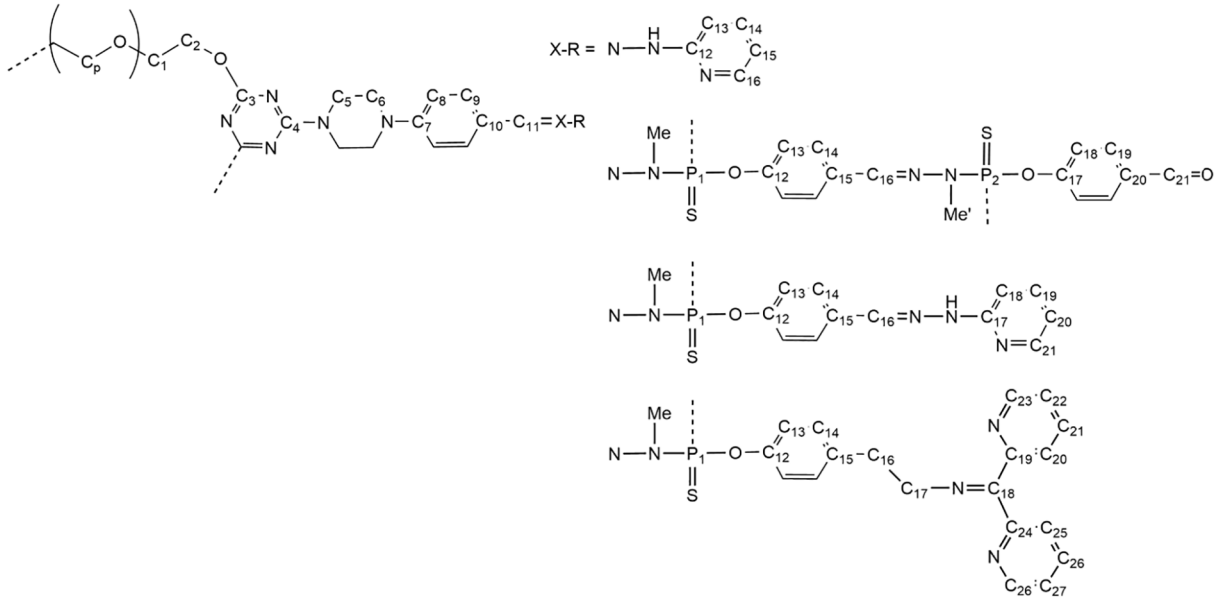


Fig. 2. Numbering used for NMR assignments.

131.9 (s, C_9), 154.8 (s, C_7),166.0 (s, C_4), 170.9 (s, C_3), 190. 4 (s, C_{11}).

*Synthesis of dendrimer **3b-G'$_0$***

A solution of PEG_{1000}, 2.0 g (2.0 mmol) in 10 mL of DCM was added dropwise to a solution of 15 mL of DCM containing 2.01 g of **2** (4.1 mmol) and 230 mg of KOH, at T = 40° C. The reaction mixture was refluxed for 48 h. After separating the salts by centrifugation and evaporating the solvent, 10 mL of water were added to precipitate the excess of **2**. After filtration, the aqueous solution was placed in freeze dryer to remove water. 2.44 g of **3b-G'$_0$** were obtained as a yellow solid (65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.43 (br s, H-C_6, 16H), 3.60–3.67 (m, H-Cp, 80H), 3.78 (t, H-C_2, $^3J_{HH}$ = 5.1 Hz, 4H), 3.94 (br s, H-C_5, 16H), 4.48 (t, H-C_1, $^3J_{HH}$ = 5.7 Hz, 4H), 6.90 (d, H-C_8, $^3J_{HH}$ = 9 Hz, 8H), 7.73 (d, H-C_9, $^3J_{HH}$ = 8.7 Hz, 8H), 9.74 (s, H-C_{11}, 4H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 42.7 (s, C_5), 46.8 (s, C_6), 66.9 (s, C_1), 69.2 (s, C_2), 70.6 (s, C_p), 113.6 (s, C_8), 127.3 (s, C_{10}), 131.9 (s, C_9), 154.8 (s, C_7),166.2 (s, C_4), 170.8 (s, C_3), 190.4 (s, C_{11}).

*Synthesis of dendrimer **3c-G'$_0$***

A solution of PEG_{2000}, 2.0 g (1.0 mmol) in 10 mL of DCM was added dropwise to a solution of 15 mL of DCM containing 1.01 g of **2** (2.05 mmol) and 115.7 mg of KOH, at T = 40° C. The reaction mixture was heated to reflux for 48 h. After separating the salts by centrifugation and evaporating the solvent, 10 mL of water were added to precipitate the excess of **2**. After filtration, the aqueous solution was placed in freeze dryer to remove water. 1.27 g of **3c-G'$_0$** as a yellow oil was obtained (87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.50 (br s, H-C_6, 16H), 3.76 (t, H-Cp, 172H), 3.83 (t, H-C_2, $^3J_{HH}$ = 5.1 Hz, 4H), 4.0 (br s, H-C_5, 16H), 4.62 (t, H-C_1, $^3J_{HH}$ = 5.7 Hz, 4H), 6.96 (d, H-C_8, $^3J_{HH}$ = 9 Hz, 8H), 7.81 (d, H-C_9, $^3J_{HH}$ = 8.7 Hz, 8H), 9.83 (s, H-C_{11}, 4H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 42.9 (s, C_5), 46.8 (s, C_6), 65.7 (s, C_1), 69.2 (s, C_2), 70.6 (s, C_p), 113.8 (s, C_8), 127.7 (s, C_{10}), 131.9 (s, C_9), 154.6 (s, C_7),164.5 (s, C_4), 169.8 (s, C_3), 190.4 (s, C_{11}).

*Synthesis of dendrimer **3a-G$_1$***

In a Schlenk tube containing activated molecular sieves, were placed 800 mg of **3a-G'$_0$** (0.66 mmol) in 5 mL of $CHCl_3$. 15.4 mL of compound **4** (c = 0.215 mol/L) were added dropwise at 0° C. Then the reaction was stirred at room temperature for 24 h. The reaction was monitored by ^{31}P {^{1}H} NMR and ^{1}H NMR. After filtration to remove the molecular sieves, the filtrate was then poured into 200 mL of pentane under argon, to precipitate **3a-G$_1$**, recovered by filtration. The solid recovered was washed using 200 mL of pentane/ether solution (1/1, v / v). A final washing in 200 mL pentane/ether (1/1, v/v) was performed. 734 mg of the reddish **3a-G$_1$** product was then collected and dried under vacuum (yield 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.35 (br s, H-C_6, 16H), 3.51 (d, CH_3, $^3J_{HP}$ = 14.2 Hz,12H), 3.66–3.73 (m, H-Cp, 20H), 3.85 (t, H-C_1, $^3J_{HH}$ = 5.4 Hz, 4H), 4.00 (br s, H-C_5, 16H), 4.47 (t, H-C_2, $^3J_{HH}$ = 5.7 Hz, 4H), 6.99 (d, H-C_8, $^3J_{HH}$ = 8.4 Hz, 8H), 7.26 (s, H-C_{11}, 4H), 7.40 (d, H-C_9, $^3J_{HH}$ = 8.4 Hz, 8H). ^{31}P {^{1}H} NMR ($CDCl_3$): δ (ppm) = 63.40 (s, P). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 31.85 (d, $^2J_{CP}$ = 12.9 Hz, CH_3), 43.0 (s, C_5), 48.3 (s, C_6), 68.0 (s, C_1), 69.2 (s, C_2), 70.6 (s, C_p), 115.6 (s, C_8), 125.5 (s, C_{10}), 128.7 (s, C_9), 142.2 (d, $^3J_{CP}$ = 12.9 Hz, C_{11}), 152.3 (s, C_7),166.1 (s, C_4), 170.5 (s, C_3).

*Synthesis of dendrimer **3b-G$_1$***

In a Schlenk tube containing activated molecular sieves, were placed 1.91 g of **3b-G'$_0$** (0.99 mmol) in 20 mL of $CHCl_3$. Then, 34 mL of compound **4** (c = 0.18 mol/L) were added dropwise at 0° C. The reaction was stirred at 40° C for 3 weeks. The reaction was monitored by ^{31}P {^{1}H} NMR and ^{1}H NMR. Following the disappearance of aldehyde groups, the mixture was filtered, and the filtrate was poured in 200 mL of pentane, in which **3b-G$_1$** precipitated, and was recovered by filtration. Then a washing was performed with 200 mL of pentane/ether solution (1/1, v/v). A final washing with 200 mL of pentane/ether (1/2, v/v) was performed. 1.8 g of a yellowish solid **3b-G$_1$** was then collected and dried under vacuum (68% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.39 (br s, H-C_6, 16H), 3.51 (d, CH_3, $^3J_{HP}$ = 14.3 Hz, 12H), 3.65–3.75 (m, H-Cp, 80H), 3.86 (br s, H-C_1, 4H), 4.14 (br s, H-C_5, 16H), 4.51 (br s, H-C_2, 4H), 7.18 (br s, H-C_8, 8H), 7.72 (m, H-C_{11} and H-C_9, 12H). ^{31}P {^{1}H} NMR (121.5 MHz, CD_2Cl_2): δ (ppm) = 63.16 (s, P).

*Synthesis of dendrimer **3c-G$_1$***

In a Schlenk tube containing activated molecular sieves, were placed 1.05 g of **3c-G'$_0$** (0.36 mmol) in 10 mL of $CHCl_3$. Then 12 mL of compound **4** (c = 0.18 mol/L) were added dropwise at 0° C. Stirring was maintained at a temperature of 40° C for 3 weeks. The reaction was monitored by ^{31}P {^{1}H} NMR and ^{1}H NMR. Following the disappearance of aldehyde groups, the mixture was filtered, and the filtrate was poured in 200 mL of pentane to precipitate **3c-G$_1$**, which was then recovered by filtration. Then a washing was performed with 200 mL of pentane/ether solution (1/1, v/v). A final washing with 200 mL of pentane/ether (1/2, v/v) was performed. 0.94 g of a yellowish solid **3c-G$_1$** was then collected and dried under vacuum (71% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.35 (br s, H-C_6, 16H), 3.51 (d, CH_3, $^3J_{HP}$ = 12.7 Hz, 12H), 3.66–3.76 (m, H-Cp, 172H), 3.85 (br s, H-C_1, 4H), 4.04 (br s, H-C_5, 16H), 4.50 (br s, H-C_2, 4H), 7.03 (d, H-C_8, $^3J_{HH}$ = 8.2 Hz, 8H), 7.69 (br s, H-C_{11} and H-C_9, 12H). ^{31}P {^{1}H} NMR ($CDCl_3$): δ (ppm) = 63.30 (s, P). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 31.85 (d, $^2J_{CP}$ = 13.05 Hz, CH_3), 42.9 (s, C_5), 48.7 (s, C_6), 68.0 (s, C_1), 69.15 (s, C_2), 70.6 (s, C_p), 115.9 (s, C_8), 126.0 (s, C_{10}), 128.75 (s, C_9), 142.2 (d, $^3J_{CP}$ = 18.7 Hz, C_{11}), 151.9 (s, C_7),165.7 (s, C_4), 170.8 (s, C_3).

*Synthesis of dendrimer **3a-G'$_1$***

494 mg (4.05 mmol) of hydroxybenzaldehyde **5** were placed in a Schlenk tube, with 1.56 g of Cs_2CO_3 in 10 mL of THF, to which were added dropwise 750 mg of **3a-G$_1$** (0.40 mmol) dissolved in 5 mL of THF. The reaction mixture was left stirring at room temperature for 3 h. After separating the salts by centrifugation, the solution was poured in 200 mL of pentane, to precipitate **3a-G'$_1$**, which was then recovered by filtration. Then a washing was performed with 200 mL of MeOH. A final washing with 200 mL pentane/ether (1/1, v/v) was performed. 0.7 g of **3a-G'$_1$** as a yellow-orange solid was then collected and dried under vacuum (65% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.27 (br s, H-C_6, 16H), 3.51 (d, CH_3, $^3J_{HP}$ = 11.05 Hz, 12H), 3.50–3.72 (br s, H-Cp, 16H), 3.78 (br s, H-C_1, 4H), 3.94 (br s, H-C_5, 16H), 4.46 (br s, H-C_2, 4H), 6.90 (br s, H-C_8, 8H), 7.40 (d, H-C_{13}, $^3J_{HH}$ = 7.4 Hz, 16H), 7.57 (br s, H-C_9, 8H), 7.62 (br s, H-C_{11}, 4H), 7.85 (d, H-C_{14}, $^3J_{HH}$ = 8.3 Hz, 16H), 9.92 (s, H-C_{16}, 8H). ^{31}P {^{1}H} NMR (121.5 MHz, THF D_8): δ (ppm) = 60.5 (s, P). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 32.9 (d, $^2J_{CP}$ = 13.25 Hz, CH_3), 43.0 (s, C_5), 48.2 (s, C_6), 65.4 (s, C_1), 69.0 (s, C_2), 70.0 (s, C_p), 115.5 (s, C_8), 122.05 (d, $^3J_{CP}$ = 4.8 Hz, C_{13}), 125.5 (s, C_{10}), 128.3 (s, C_9), 131,4 (s, C_{14}), 133.6 (s, C_{15}), 140.9 (d, $^3J_{CP}$ = 13.7 Hz, C_{11}), 152.0 (s, C_7), 155,3 (d, $^2J_{CP}$ = 7,2 Hz, C_{12}), 165.8 (s, C_4), 170.5 (s, C_3), 190.9 (s, C_{16}).

*Synthesis of dendrimer **3a-G$_2$***

In a Schlenk tube containing activated molecular sieves, were placed 500 mg of **3a-G'$_1$** (0.20 mmol) in 10 mL of $CHCl_3$. Then 8.2 mL of compound **4** (c = 0.215 mol/L) were added dropwise at 0° C. The reaction mixture was left stirring at room temperature for 24 h. The reaction was monitored by ^{31}P{^{1}H} NMR and ^{1}H NMR. After filtration, the filtrate was then poured in 200 mL of pentane, to precipitate **3a-G$_2$**, which was then recovered by filtration. Then, a washing was performed with 200 mL of pentane/ether solution (1/1, v/v). 0.65 g of **3a-G$_2$** as a

reddish solid was then collected and dried under vacuum (86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.35 (br s, H-C_6, 16H), 3.37 (s, CH_3, $^3J_{HP}$ = 10.6 Hz, 12H), 3.60 (s, CH_3', $^3J_{HP}$ = 13.75 Hz, 24H), 3.60–3.75 (m, H-Cp, 16H), 3.85 (br s, H-C_1, 4H), 4.00 (s, H-C_5, 16H), 4.50 (br s, H-C_2, 4H), 6.96 (d, H-C_8, $^3J_{HH}$ = 7.5 Hz, 8H), 7.32 (d, H-C_{13}, $^3J_{HH}$ = 8.2 Hz, 16H), 7.55–7.80 (m, H-C_9, H-C_{14}, H-C_{11}, H-C_{16}, 36H). ^{31}P {^{1}H} NMR (162.0 MHz, $CDCl_3$): δ (ppm) = 62.04 (s, P_1), 63.03 (s, P_2).

*Synthesis of dendrimer **3a-G'$_2$***

132 mg (1.08 mmol) of hydroxybenzaldehyde **5** were placed in a Schlenk tube, with 422 mg of Cs_2CO_3 in 10 mL of THF, to which were added dropwise 200 mg of **3a-G$_2$** (0.054 mmol) dissolved in 5 mL of THF. The reaction mixture was left stirring at room temperature for 7 days. After separating the salts by centrifugation, the solution was poured in 200 mL of pentane, to precipitate **3a-G'$_2$**, which was recovered by filtration. Then a washing of the solid with 200 mL pentane/MeOH (4/1, v/v) was performed. 174 mg of **3a-G'$_2$** as a reddish solid were then collected and dried under vacuum (62% yield). ^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 3.27 (br s, H-C_6, 16H), 3.32–3.47 (m, CH_3 and CH_3', 36H), 3.48–3.68 (m, H-Cp, 16H), 3.82–4.07 (m, H-C_1 and H-C_5, 20H), 4.48 (br s, H-C_2, 4H), 6.88 (br s, H-C_8, 8H), 6.95 (d, H-$C_{13,}$ $^3J_{HH}$ = 8.7 Hz, 16H), 7.30 (d, H-C_{13}, $^3J_{HH}$ = 8.3 Hz, 16H), 7.41 (d, H-C_{18}, $^3J_{HH}$ = 6.9 Hz, 32H), 7.55–7.76 (m, H-C_{14}, H-C_9, H-C_{16}, H-C_{11}, 36H), 7.88 (d, H-C_{19}, $^3J_{HH}$ = 8.2 Hz, 32H), 9.96 (s, H-C_{21}, 16H). ^{31}P {^{1}H} NMR (162.0 MHz, CD_2Cl_2): δ (ppm) = 60.42 (s, P_2), 62.60 (s, P_1).

*Synthesis of dendrimer **7a-G'$_0$***

In a Schlenk tube containing activated molecular sieves, were placed 600 mg of **3a-G'$_0$** (0.496 mmol) in 10 mL of THF. Then a solution of 238 mg of 2-hydrazinopyridine **6** (2.18 mmol) in 5 mL of THF was added dropwise. The reaction mixture was left stirring at reflux for 2 days. The reaction was monitored by ^{1}H NMR. After filtration, the filtrate was poured in 200 mL of pentane, to precipitate **7a-G'$_0$**. Then a washing of the solid was performed with 200 mL of pentane/ether solution (5/1, v/v). 586 mg of **7a-G'$_0$** as a reddish solid were then collected and dried under vacuum (75% yield). ^{1}H NMR (300 MHz, CD_2Cl_2): δ (ppm) = 3.31 (br s, H-C_6, 16H), 3.55–3.65 (m, H-C_p, 16H), 3.81 (t, H-C_1, $^3J_{HH}$ = 7.5 Hz, 4H), 4.00 (br s, H-C_5, 16H), 4.46 (t, H-C_2, $^3J_{HH}$ = 8.4 Hz, 4H), 6.77 (m, H-C_{15}, 4H), 6.98 (d, $^3J_{HH}$ = 8.4 Hz, H-C_8, 8H), 7.34 (d, $^3J_{HH}$ = 8.4 Hz, H-C_{13}, 4H), 7.58–7.68 (m, H-C_9 and H-C_{14}, 12H), 7.74 (s, H-C_{11}, 4H), 8.13 (m, H-C_{16}, 4H), 8.43 (s, NH, 4H). ^{13}C {^{1}H} NMR (75 MHz, CD_2Cl_2): δ (ppm) = 43.1 (s, C_5), 48.4 (s, C_6), 65.5 (s, C_2), 69.3 (s, C_1), 70.5 (s, C_p), 106.9 (s, C_{13}), 115.3 (s, C_{15}), 115.6 (s, C_8), 126.2 (s, C_{10}), 127.4 (s, C_9), 137.9 (s, C_{11}), 139.4 (s, C_{14}), 147.7 (s, C_{16}), 151.7 (s, C_{12}), 157.0 (s, C_7), 166.1 (s, C_4), 170.8 (s, C_3).

*Synthesis of dendrimer **7b-G'$_0$***

In a Schlenk tube containing activated molecular sieves, were placed 530 mg of **3b-G'$_0$** (0.277 mmol) in 10 mL of THF. Then a solution of 133 mg of 2-hydrazinopyridine **6** (1.22 mmol) in 5 mL of THF was added dropwise. The reaction mixture was left stirring at 40° C for 9 days. The reaction was monitored by ^{1}H NMR. After filtration, the filtrate was poured in 200 mL of pentane to precipitate **7b-G'$_0$**. Then a washing of the solid was performed with 200 mL of pentane/ether solution (1/2, v/v). 617 mg of **7b-G'$_0$** as a yellow solid were then collected and dried under vacuum (98 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.23 (br s, H-C_6, 16H), 3.50–3.65 (m, H-C_p, 80H), 3.80 (t, H-C_1, $^3J_{HH}$ = 7.5 Hz, 4H), 3.94 (br s, H-C_5, 16H), 4.45 (t, H-C_2, $^3J_{HH}$ = 8.4 Hz, 4H), 6.69 (m, H-C_{15}, 4H), 6.96 (d, $^3J_{HH}$ = 8.5 Hz H-C_8, 8H), 7.31 (d, $^3J_{HH}$ = 8.4 Hz, H-C_{13}, 4H), 7.48–7.60 (m, H-C_9 and H-C_{14}, 12H), 7.71 (s, H-C_{11}, 4H), 8.08 (m, H-C_{16}, 4H), 9.30 (s, NH, 4H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 43.0 (s, C_5), 48.6 (s, C_6), 61.7 (s, C_2), 69.2 (s, C_1), 70.5 (s, C_p), 107.4 (s, C_{13}), 115.05 (s, C_{15}), 115.8 (s, C_8), 126.7 (s, C_{10}), 127.5 (s, C_9), 138.0 (s, C_{11}), 139.5 (s, C_{14}), 147.2 (s, C_{16}), 151.5 (s, C_{12}), 157.2 (s, C_7), 165.9 (s, C_4), 170.7 (s, C_3).

*Synthesis of dendrimer **7c-G'$_0$***

In a Schlenk tube containing activated molecular sieves, were placed 490 mg of **3c-G'$_0$** (0.168 mmol) in 10 mL of THF. Then a solution of 82 mg of 2-hydrazinopyridine (0.751 mmol) in 5 mL of THF was added dropwise. The reaction mixture was left stirring at 40° C for 9 days then at reflux for 10 days. The reaction was monitored by ^{1}H NMR. After filtration, the filtrate was poured in 200 mL of pentane to precipitate **7c-G'$_0$**. Then a washing of the solid was performed with 200 mL of pentane/ether solution (2/1, v/v). 544 mg of **7c-G'$_0$** as a yellow solid were then collected and dried under vacuum (99 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.30 (br s, H-C_6, 16H), 3.66 (m, H-C_p, 176H), 3.85 (t, H-C_1, $^3J_{HH}$ = 7.5 Hz, 4H), 4.00 (br s, H-C_5, 16H), 4.48 (t, H-C_2, $^3J_{HH}$ = 8.4 Hz, 4H), 6.73 (m, H-C_{15}, 4H), 6.96 (d, $^3J_{HH}$ = 8.3 Hz, H-C_8, 8H), 7.34 (d, $^3J_{HH}$ = 8.4 Hz, H-C_{13}, 4H), 7.55–7.65 (m, H-C_9 and H-C_{14}, 12H), 7.73 (s, H-C_{11}, 4H), 8.12 (br s, H-C_{16}, 4H), 8.40 (br s, NH, 4H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) = 43.1 (s, C_5), 48.6 (s, C_6), 65.6 (s, C_2), 69.2 (s, C_1), 70.6 (s, C_p), 107.2 (s, C_{13}), 115.3 (s, C_{15}), 115.8 (s, C_8), 126.5 (s, C_{10}), 127.6 (s, C_9), 138.4 (s, C_{11}), 140.0 (s, C_{14}), 147.6 (s, C_{16}), 151.7 (d, C_{12}), 156.5 (s, C_7), 166.0 (s, C_4), 170.8 (s, C_3).

*Synthesis of dendrimer **7a-G'$_1$***

In a Schlenk tube containing activated molecular sieves, were placed 199 mg of **3a-G'$_1$** (0.070 mmol) in 10 mL of THF. Then a solution of 68 mg of 2-hydrazinopyridine **6** (0.623 mmol) in 5 mL of THF was added dropwise. The reaction mixture was left stirring at room temperature for 7 days. The reaction was monitored by ^{1}H NMR. After filtration, the filtrate was poured in 200 mL of pentane/ether (9/1; v/v), to precipitate **7a-G'$_1$**. Then a washing of the solid was performed with 200 mL of pentane/ether solution (6/4, v/v). 212 mg of **7a-G'$_1$** as a reddish solid were then collected and dried under vacuum (93 % yield). ^{1}H NMR (300 MHz, THF, D_8): δ (ppm) = 3.36 (br s, H-C_6, 16H), 3.52 (d, CH_3, $^3J_{HP}$ = 10.8 Hz, 12H), 3.48–3-55 (m, H-Cp, 16H), 3.64 (t, H-$C_{1,}$ $^3J_{HH}$ = 7.8 Hz, 4H), 3.97 (br s, H-C_5, 16H), 4.45 (t, H-C_2, $^3J_{HH}$ = 5.7 Hz , 4H), 6.68 (d, H-C_{20}, $^3J_{HH}$ = 8.4 Hz, 8H), 7.01 (d, H-C_{13}, $^3J_{HH}$ = 7.4 Hz, 16H), 7.30 (d, H-C_{18}, $^3J_{HH}$ = 8.4 Hz, 8H), 7.54 (d, $^3J_{HH}$ = 8.4 Hz, H-C_{19}, 8H), 7.65 (s, H-C_9, 8H), 7.68 (d, $^3J_{HH}$ = 8.4 Hz, H-C_{14}, 16H), 7.86 (s, H-C_{11}, 4H), 7.92 (s, H-C_{16}, 8H), 8.06 (d, H-C_{21}, $^3J_{HH}$ = 6 Hz, 8H), 9.90 (s, H-N_2, 8H). ^{31}P {^{1}H} NMR (121.5 MHz, THF D_8): δ (ppm) = 60.25 (s, P).

*Synthesis of dendrimer **9a-G$_1$***

180 mg of compound **8** (0.594 mmol) were placed in a Schlenk tube, with 387 mg of Cs_2CO_3 in 10 mL of THF, to which were added dropwise 122 mg of **3a-G$_1$** (0.066 mmol) dissolved in 5 mL of THF. The reaction mixture was left stirring at room temperature for 48 h. The reaction was monitored by ^{31}P {^{1}H} NMR. After separating the salts by centrifugation, the solution was poured in 200 mL of pentane, to precipitate **9a-G$_1$**. Then a washing of the solid was carried out in 200 mL pentane/ether (3/1, v/v). 171 mg of **9a-G$_1$** as a reddish solid were then collected and dried under vacuum (65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.83 (t, H-C_{16}, $^3J_{HH}$ = 7.5 Hz, 16H), 3.49 (br s, H-C_6, 16H), 3.51–3.72 (m, CH_3, H-C_{17}, H-Cp, 44H), 3.84 (t, $^3J_{HH}$ = 5.1 Hz , H-C_2, 4H), 4.0 (br s, H-C_5, 16H), 4.49 (t, H-C_1, $^3J_{HH}$ = 5.7 Hz, 4H), 6.64 (d, H-C_{20}, $^3J_{HH}$ = 8.4 Hz, 8H), 6.93 (d, H-C_8, $^3J_{HH}$ = 8.4 Hz, 8H), 6.95 (d, H-C_{13}, $^3J_{HH}$ = 9 Hz, 16H), 7.12 (d, H-C_{22}, $^3J_{HH}$ = 7.8 Hz, 8H), 7.35–7.44 (m, H-C_{27}, 8H), 7.80–7.91 (m, H-C_9, H-C_{11}, H-C_{26}, H-C_{21}, 28H), 8.17 (d, H-C_{25}, $^3J_{HH}$ = 7.8 Hz, 8H), 8.43 (d, H-C_{28}, $^3J_{HH}$ = 4.1 Hz, 8H), 8.63 (d, H-C_{23}, $^3J_{HH}$ = 4.1 Hz, 8H). ^{31}P {^{1}H} NMR (162.5 MHz, $CDCl_3$): δ (ppm) = 60.45 (s, P). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 32.9 (d, $^2J_{CP}$ = 13.25 Hz, CH_3), 36.3 (s, C_{16}), 42.3 (s, C_5), 46.9 (s, C_6), 55.6 (s, C_{17}), 65.8 (s, C_1), 69.2 (s, C_2), 70.6 (s, C_p), 114.3 (s, C_8), 115.6 (s, C_{13}), 121.9 (s, C_{20}),

123.6 (s, C_{25}), 124.2 (s, C_{27}), 128.7 (s, C_{10}), 130.7 (s, C_{15}), 131.7 (s, C_9), 136.0 (s, C_{21}), 136.4 (s, $C_{11,}$ C_{26}), 148.4 (s, C_{23}), 149.3 (s, C_{28}), 154.6 (s, C_7), 155.4 (s, C_{19}), 156.0 (s, C_{24}), 156.8 (s, C_{12}), 165.6 (s, C_4), 166.6 (s, C_{18}), 170.5 (s, C_3).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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