PHOSPHORUS CONTAINING DENDRIMERS:
SURFACE CHEMISTRY AND APPLICATIONS

Final Technical Report

by

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Ferrous scrap is not a critical material -- important, yes; essential yes; significant, yes; but not critical. I say that not to minimize the importance of scrap as a major raw material in iron and steelmaking. Rather, scrap is in such abundance throughout our nation, and is so readily available in such quantities that nothing so ubiquitous can be critical by definition. The critical fact of scrap iron is its need for a market.

Scrap is available to be made into new steel, but there are few uses for scrap other than to be recycled into that new iron and steel. Thus, scrap is not a critical material but a market is critical for that material.

The opportunities to expand the recovery of iron and steel discards are tremendous as are the benefits of such expansion, and both will be realized when iron and steelmakers increase their demand for scrap to charge their melting furnaces.

The reservoir of iron and steel discards in the United State is enormous -- hundreds of millions of tons of material that will become either an asset or a liability to our economy -- that represent an incredible conservation potential or a conservation disaster -- depending on the choice made for metallics in future steelmaking.
IF WE ARE NOT ABLE TO RECOVER THESE METALLIC UNITS FOR RECYCLING INTO NEW PRODUCTS, BY DEFAULT THEY BECOME BOTH AN ECONOMIC AND SOCIAL LIABILITY TO THE JURISDICTIONS IN WHICH THEY ARE LOCATED. WHEN VACANT CITY LOTS AND COUNTRY ROADSIDES BECOME THE DUMPING GROUNDS FOR DERELECT AUTOMOBILES, UNWANTED REFRIGERATORS AND THE LIKE, CITIZENS GENERALLY DEMAND ACTION BY THEIR LOCAL GOVERNMENT TO "GET RID OF THE JUNK." THE RESULT IS AN EXPENDITURE OF TAX DOLLARS TO DISPOSE OF WHAT COULD BE, BUT BY CHOICE IS NOT, AN INDUSTRIAL RAW MATERIAL.

THE ROLE FOR OBSOLETE SCRAP BEGINS WITH THE COLLECTOR, WHO TRANSPORTS IT TO THE SCRAP PLANT FOR PROCESSING AND THEN SHIPMENT AS A PREPARED PRODUCT TO STEEL MILLS AND FOUNDRIES. IN THIS SCENERIO, SCRAP IS TRANSFORMED INTO AN ECONOMIC AND ENVIRONMENTAL ASSET. CERTAINLY IT MAKES MORE SENSE IF SCRAP CAN BE HANDLED THROUGH THE PRIVATE SECTOR GENERATING JOBS, MAKING EXPENDITURES FOR GOODS AND SERVICES, EARNING PROFITS, AND PAYING TAX REVENUES, RATHER THAN BEING A DRAIN ON OUR TAX DOLLARS WHEN IT IS MERELY DISPOSED OF, NOT RECYCLED. HOW COULD ANYONE DISAGREE.

BUT IN REGARD TO THE TOPIC FOR THIS MORNING, IN ADDITION TO CONSERVING ONE AND ONE HALF MILLION TONS OF IRON ORE, EPA FOUND THAT WHEN ONE MILLION TONS OF SCRAP IRON ARE USED TO MAKE NEW STEEL, AIR POLLUTION EFFLUENTS ARE REDUCED 86 PERCENT -- 208 MILLION POUNDS; WATER POLLUTION IS REDUCED 76 PERCENT.
Summary

The synthesis of phosphorus containing dendrimers is described up to the fifth generation (96 terminal groups). The surface chemistry of these dendrimers allows the grafting of various functionalities such as phosphate (6 O-P(O)(OEt)$_2$ groups), aminophosphate (up to 96 N-P(O)(OEt)$_2$ groups), aminophosphite (up to 96 N-P(OEt)$_2$ groups), functionalized phosphonate (up to 96 HC(OH)P(O)(OR)$_2$ (R = Et, (CH$_2$)$_{11}$CH$_3$), up to 96 HC(N-Pr)P(O)(OEt)$_2$, or up to 48 CH=CH-P(O)(OEt)$_2$), phosphorus ylide (6 C(O)CH=P(Ph)$_3$), carboxylic acid (up to 24 CH=CH-C(O)OH), and tetraazamacrocycle (up to 12 cyclam). These surface functionalities have been chosen due to the wellknown properties of the corresponding monomers and/or polymers in various areas such as adhesives, flame retardants, fuel additives, sequestering agents...

Key words

dendrimers, surface functionalities, phosphate, aminophosphate, aminophosphite, functionalized phosphonate, phosphorus ylide, carboxylic acid, tetraazamacrocycle
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# List of Appendixes:

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Publications issued from this report:

I - Phosphate, phosphite, ylide and phosphonate terminated dendrimers  

II - Application of the Horner-Wadsworth-Emmons reaction to the functionalization of dendrimers: Synthesis of amino acid terminated dendrimers  
A - Introduction

Dendrimers[1] constitute a new class of macromolecules whose size, shape, and molecular weight are rigorously controlled. Furthermore, their highly branched structure which induce the formation of internal voids and the occurrence of all the reactive functions on the surface make dendrimers unique among polymers.

The synthesis of organic dendrimers and silicon containing dendrimers are well explored areas, which now come out to the study of properties and applications of these compounds. Concerning phosphorus containing dendrimers, the expertise of our research group is unrivalled in the world (60% of all the papers ever published to date in this field come from our group)[2]. The methods of synthesis of phosphorus containing dendrimers we have developed present several significant advantages: cheap industrially available starting materials, quantitative yields, possibility to check easily the construction of the dendrimer by $^{31}$P NMR, solubility in several common organic solvents, and stability towards hydrolysis and bases.

The objectives of the present study was to take advantage of the large number of reactive functions located on the surface of dendrimers to graft various new functional groups susceptible to bring properties in several fields, mainly adhesives, flame retardant, additives, or sequestering agents. For this purpose, we have tried to graft several types of phosphorus containing groups such as phosphates, aminophosphates, aminophosphites, phosphorus ylides, with emphasis on functionalized phosphonates, whose properties of the monomers and/or corresponding polymers are well known in most of the fields evoked above, and in many other fields. The grafting of carboxylic acids and tetraazamacrocycles should also induce properties in the field of adhesives and sequestering agents.

The present report describes only fruitful experiments. All unsuccessful attempts which have been included in the four interim reports are not included in this final report. All the dendrimers described have been isolated and fully characterized by NMR ($^{31}$P, $^1$H, and $^{13}$C), IR, elemental analyses, in some cases by mass spectrometry, and by X-ray diffraction for a small molecule.
B - Results

I - Synthesis of dendrimers

Dendrimers from generation 0 to generation 5 were prepared by the repetition of a two steps procedure: nucleophilic substitution of chlorine by hydroxybenzaldehyde, and Schiff condensation reaction (Scheme 1, Table 1, Figure 1).

\[
\text{Scheme 1}
\]

<table>
<thead>
<tr>
<th>Generation n (Cl)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (CHO)</td>
<td>1-([G_1])</td>
<td>1-([G_2])</td>
<td>1-([G_3])</td>
<td>1-([G_4])</td>
<td>1-([G_5])</td>
</tr>
<tr>
<td>Number of Cl or CHO</td>
<td>6</td>
<td>12</td>
<td>24</td>
<td>48</td>
<td>96</td>
</tr>
<tr>
<td>Molecular weight (terminal Cl)</td>
<td>909</td>
<td>2389</td>
<td>5349</td>
<td>11269</td>
<td>23108</td>
</tr>
<tr>
<td>Molecular weight (terminal CHO)</td>
<td>1423</td>
<td>3417</td>
<td>7405</td>
<td>15381</td>
<td>31331</td>
</tr>
</tbody>
</table>

Table 1: Some characteristic data concerning dendrimers 1-\([G_1]\) - 1-\([G_5]\) (terminal P-Cl bonds) and 1-\([G’_1]\) - 1-\([G’_5]\) (terminal CHO groups).
II - Anchorage of phosphorus groups

II - 1 - Anchorage of aminophosphate groups

The strategy investigated for the grafting of aminophosphate groups consists of the reaction of dendrimers 1-[G'1] and 1-[G'5] (generations 1 and 5, respectively) with a new phospho monohydrazide 2 (Scheme 3). Compound 2 is prepared by reacting the chlorophosphonate (EtO)₂P(O)Cl with methylhydrazine (Scheme 2).

\[
\begin{array}{c}
\text{(EtO)}_2\text{P(O)}\text{Cl} + 2 \text{HN(Me)}-\text{NH}_2 \rightarrow \text{(EtO)}_2\text{P(O)}-\text{N(Me)}-\text{NH}_2 \\
\text{HN(Me)}-\text{NH}_2\cdot\text{HCl} \rightarrow \text{(EtO)}_2\text{P(O)}-\text{N(Me)}-\text{NH-P(O)}(\text{OEt})_2 \\
\end{array}
\]

Scheme 2

The reaction of formation of 2 is performed at low temperature (-80°C) to avoid the formation of a by-product such as 3 which can be formed via condensation of 2 with (EtO)₂P(O)Cl.

\[
\text{Dend-}\left(\text{C=O}\right)_y \xrightarrow{\text{y (EtO)}_2\text{P(O)}-\text{N(Me)}-\text{NH}_2} \xrightarrow{\text{Dend-} \left(\text{CH}_3\right)} \xrightarrow{\text{C=N-}} \xrightarrow{\text{3-CH}_2\cdot\text{CH}_3} \xrightarrow{\text{4-} \left[\text{G}_1\right]} \xrightarrow{\text{y = 6}} \xrightarrow{\text{4-} \left[\text{G}_5\right]} \xrightarrow{\text{y = 96}}
\]

Scheme 3

The new dendrimers 4-[G₁] and 4-[G₅] possessing 6 or 96 terminal aminophosphate groups respectively are obtained as white powders (Figure 1).

II - 2 - Anchorage of aminophosphate groups

Grafting of aminophosphate groups was successfully performed by reacting dendrimers 5-[G₁] and 5-[G₅] possessing 6 and 96 terminal N(CH₃)H groups respectively with the chlorophosphite (EtO)₂PCL (Scheme 5, Figure 1). Arborols 5-[G₁] and 5-[G₅] were easily prepared by reacting 1-[G'₁] and 1-[G'₅] with methyldiazine (Scheme 4).

\[
\text{Dend-}\left(\text{C=O}\right)_y \xrightarrow{\text{y H₂N-N(Me)H}} \xrightarrow{\text{Dend-} \left(\text{CH}_3\right)} \xrightarrow{\text{y = 6}} \xrightarrow{\text{5-[G₁]}} \xrightarrow{\text{y = 96}} \xrightarrow{\text{5-[G₅]}}
\]

Scheme 4

\[
\text{Dend-} \left(\text{C=NH-NH}\right)_y \xrightarrow{\text{y (EtO)}_2\text{P(O)} \cdot \text{NEt}_3, \text{HCl}} \xrightarrow{\text{Dend-} \left(\text{CH}_3\right)} \xrightarrow{\text{y = 6}} \xrightarrow{\text{6-[G₁]}} \xrightarrow{\text{y = 96}} \xrightarrow{\text{6-[G₅]}}
\]

Scheme 5

Dendrimers 6-[G₁] and 6-[G₅] are sensitive to hydrolysis and oxidation. Cleavage of the terminal nitrogen-phosphorus bond allows to recover 5-[G₁] and 5-[G₅] with the formation of (EtO)₂P(O)H.
Figure 1
II - 3 - Anchorage of phosphate groups

The formation of a dendrimer possessing terminal phosphate groups involves
i) the preparation of dendrimers having terminal NH$_2$ groups 7-[G$_1$] - 7-[G$_5$] (Scheme 6)
ii) the synthesis of a new ligand (EtO)$_2$P(O)Oc$_6$H$_4$CHO 8 (Scheme 8)
iii) the reaction of 7-[G$_1$] - 7-[G$_5$] with 8 to give dendrimers 9-[G$_1$] - 9-[G$_5$] (Scheme 7).

Scheme 6

\[
\text{Dend} \left( \begin{array}{c}
\text{C} \\
\text{H}
\end{array} \right)_y \xrightarrow{\text{H}_2\text{N-NH}_2} \text{Dend} \left( \begin{array}{c}
\text{C} \\
\text{H}
\end{array} \right)_y
\]

(y = 6, 12, 24, 48, 96)

1-[G$_1$], 1-[G$_2$], 1-[G$_3$], 1-[G$_4$], 1-[G$_5$]

7-[G$_1$], 7-[G$_2$], 7-[G$_3$], 7-[G$_4$], 7-[G$_5$]

Derivative 8 is prepared as follows:

Scheme 8

\[
\text{EtO-P(O)} \xrightarrow{\text{EtO-P(O)-Cl}} \text{EtO-P(O)} + \text{Na-O-} \xrightarrow{-\text{NaCl}} \text{EtO-P(O)}
\]

7-[G$_1$], 7-[G$_2$], 7-[G$_3$], 7-[G$_4$], 7-[G$_5$] \rightarrow \text{unsoluble compounds}

Scheme 7

The dendrimer 9-[G$_1$] (72% yield) incorporates six terminal phosphate groups. Unfortunately the reaction of 1-[G'$_5$] with 96 equivalents of 8 affords insoluble material. Therefore, such a condensation reaction was attempted with 8 and dendrimers of generation 2 (7-[G$_2$]) 3 (7-[G$_3$]) or 4 (7-[G$_4$]). In all cases insoluble powders were obtained and characterizations were not possible.

It appears that the introduction in the framework of the molecule of CH=N-N=CH sequences dramatically reduces the solubility of the resulting products preventing from rigorous characterization.

II - 4 - Anchorage of phosphorus ylide groups

Addition of terminal NH groups of the dendrimer 5-[G$_1$] on the carbon carbon double bond of the cumulene Ph$_3$P=C=C=O 10 was undertaken (Scheme 9).

Scheme 9

Temptative extension of this type of reaction to higher generations (5-[G$_2$], 5-[G$_3$]) led only to insoluble materials.
Terminal ylide groups of $11\cdot[G_1]$ remain very reactive. For example, a Wittig reaction can be performed by reacting $11\cdot[G_1]$ with crotonaldehyde $\text{CH}_3\text{CH}=$CH-CHO affording dendrimer $12\cdot[G_1]$ (Scheme 10).

$$
\text{Dend} \left( \begin{array}{c}
\text{C} \equiv \text{N} \text{N} \text{C} \equiv \text{C} \text{P} \text{Ph} \\
\text{H} & \text{H} \\
11\cdot[G_1]
\end{array} \right) \xrightarrow{6 \ \text{CH}_3\text{CH}=$CH-CHO} \text{Dend} \left( \begin{array}{c}
\text{C} \equiv \text{N} \text{N} \text{C} \equiv \text{C} \text{H} \equiv \text{C} \text{H}=$\text{C} \text{H} \equiv \text{CH} \equiv \text{CH}_3 \\
\text{H} \\
12\cdot[G_1]
\end{array} \right)
$$

Scheme 10

II - 5 - Anchorage of phosphonate groups

II - 5 - a - Addition to terminal aldehyde groups

Several tries were performed to graft in good yields phosphonate groups on the terminal aldehyde groups (Scheme 11, Figure 1).

$$
\text{Dend} \left( \begin{array}{c}
\text{C} \equiv \text{O} \\
\text{H} \\
1\cdot[G_1], 1\cdot[G_2] \\
1\cdot[G_3], 1\cdot[G_4], 1\cdot[G_5]
\end{array} \right) \xrightarrow{\text{H-P(O)(OEt)}_2 \ \text{(excess)}} \text{Dend} \left( \begin{array}{c}
\text{O} \equiv \text{P} \text{O} \text{C} \equiv \text{O} \\
\text{H} \equiv \text{C} \equiv \text{H} \equiv \text{C} \equiv \text{H} \\
13\cdot[G_1], 13\cdot[G_2] \\
13\cdot[G_3], 13\cdot[G_4], 13\cdot[G_5]
\end{array} \right)
$$

Scheme 11

This type of reaction was done in several conditions. After several attempts, the best method was the following one: the dendrimer was dissolved in a mixture of [(EtO)$_2$P(O)H, NEt$_3$], at room temperature, the phosphonate acting as reagent and solvent. This experiment gave the best results and allowed us to graft from 6 to 96 phosphonates groups (see Table 2).

<table>
<thead>
<tr>
<th>Generation n =</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of terminal phosphonate groups (-\text{CH(OH)}\cdot\text{P(O)(OEt)}_2)</td>
<td>6</td>
<td>12</td>
<td>24</td>
<td>48</td>
<td>96</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>2252</td>
<td>5074</td>
<td>10719</td>
<td>22010</td>
<td>44589</td>
</tr>
</tbody>
</table>

*Table 2: Characteristic data concerning dendrimers with \(-\text{CH(OH)}\cdot\text{P(O)(OEt)}_2\) terminal groups.*

It should be mentioned the interest of this reaction which leads to phosphonate end groups but also to secondary alcohols end groups which should be of help for adhesive properties.
The same type of addition reaction was performed with another phosphonate \((\text{C}_{12}\text{H}_{25}\text{O})_2\text{P(O)H}\) to avoid problems of solubility encountered with \((\text{EtO})_2\text{P(O)H}\): compound with 96 \(\text{CH(OH)}\)-\(\text{P(O)(OEt)}_2\) groups start to be poorly soluble in common organic solvents and NMR data were collected in CD$_3$OD.

The grafting of \((\text{C}_{12}\text{H}_{25}\text{O})_2\text{P(O)}\) groups was undertaken on dendrimers 1-[G$^1$] and 1-[G$^5$] (Table 3) in the same experimental conditions than that used with \((\text{C}_{2}\text{H}_{5}\text{O})_2\text{P(O)H}\) and afforded compounds now easily soluble in CH$_2$Cl$_2$ or CHCl$_3$ (Scheme 12, Figure 1).

\[
\begin{align*}
\text{Dend} & \quad \xrightarrow{\text{H-P(O)(O-(CH$_2$)$_{11}$-CH$_3$)$_2$ (excess)}} \quad \text{Dend} \\
1-[\text{G}^1] & \quad \text{14-[G$_1$]} \\
1-[\text{G}^5] & \quad \text{14-[G$_5$]}
\end{align*}
\]

Scheme 12

<table>
<thead>
<tr>
<th>Generation n =</th>
<th>1</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound number</td>
<td>14-[G$_1$]</td>
<td>14-[G$_5$]</td>
</tr>
<tr>
<td>Number of terminal phosphonate groups</td>
<td>6</td>
<td>96</td>
</tr>
<tr>
<td>CH(OH)-P(O)(OC$<em>{12}$H$</em>{25}$)$_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular weight</td>
<td>3935</td>
<td>7152</td>
</tr>
</tbody>
</table>

**Table 3:** Dendrimers with terminal CH(OH)-P(O)(OC$_{12}$H$_{25}$)$_2$ groups

**II - 5 - b - Addition to terminal imino groups**

New dendrimers with terminal imino groups were prepared as follows (Scheme 13):

\[
\begin{align*}
\text{Dend} & \quad \xrightarrow{y \ \text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_3} \quad \text{Dend} \\
1-[\text{G}^1] & \quad \text{15-[G$_1$]} \\
1-[\text{G}^5] & \quad \text{15-[G$_5$]}
\end{align*}
\]

Scheme 13

Dendrimers 15-[G$_1$] and 15-[G$_5$] possessing 6 or 96 terminal imino groups respectively were further reacted with \((\text{EtO})_2\text{P(O)H}\) again used as solvent. This reaction allowed to obtain new dendrimers 16-[G$_1$] and 16-[G$_5$] arising from oxidative addition of the P-H bond on imine functions (Scheme 14, Table 4, Figure 1).
Table 4: Dendrimers with terminal -CH(NHC₃H₇)-P(O)(OC₂H₅)₂ groups

<table>
<thead>
<tr>
<th>Generation n =</th>
<th>1</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound number</td>
<td>16-[G₁]</td>
<td>16-[G₅]</td>
</tr>
<tr>
<td>Number of terminal phosphonate groups</td>
<td>6</td>
<td>96</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>2498</td>
<td>48535</td>
</tr>
</tbody>
</table>

II - 5 - c - Horner-Wadsworth-Emmons reaction on terminal aldehyde groups

Vinylphosphonates moieties (from 6 to 48 units) were grafted on the surface of phosphorus containing dendrimers according to the reactions indicated in scheme 15.

Scheme 15

The reaction consists of the generation of the carbanionic species [(EtO)₂P(O)]⁺ which is further reacted with terminal aldehyde groups. The reaction proceeded in very mild conditions and allowed to obtain new dendrimers 17-[G₁] and 17-[G₄] as white powders.

III - Acid terminated dendrimers

After several unsuccessful attempts to graft phosphorus acids such as P(O)(OH)₂ groups on the surface of dendrimers, we turned our efforts to the synthesis of dendrimers possessing carboxylic acid chain ends.

The strategy used, outlined in scheme 16, is also a Horner-Wadsworth-Emmons reaction.
Reactions proceed nicely and give first the CH=CHC(O)OLi derivatives (soluble in water, but not isolated), then the new acidic terminated macromolecules $18\cdot[G_1]$ and $18\cdot[G_3]$ possessing six or 24 terminal CO$_2$H groups, which are isolated after treatment with formic acid. It is noteworthy that only the trans isomers are obtained.

**IV - Grafting of tetraazamacrocycles**

We planned to prepare new dendrimers possessing both phosphorus groups and nitrogen macrocycles with the aim to have strong useful ligands able to bring new properties due to the presence of various groups on phosphorus and free NH groups.

In order to find the good experimental conditions for reactions involving P(S)Cl$_2$ end groups of dendrimers, we reacted first the monomer $19$ with macrocycles $20$, $22$ and $24$ (Schemes 17 and 18). In a typical experiment a dichloromethane solution of $19$ (1 equiv.) 1,4,8,11-tetraazacyclotetradecane $20$ (cyclam, 1 equiv) and potassium carbonate (2 equiv.) was stirred for 4 days at room temperature. After workup the macrocycle $21$ was isolated in 55% yield (Scheme 17).

$^1$H and $^{13}$C NMR data appeared in agreement with the proposed structure and seemed to rule out the form $21'$ in which a diazaphosphorinane unit (six membered ring) is created.

Similarly the treatment of $19$ with 1,4,8,11-tetraazacyclodecane $22$ in the same experimental conditions led to the macroyclic species $23$ or $23'$ (Scheme 18). In this case $^1$H and $^{13}$C NMR did not allow us to choose between forms $23$ and $23'$ but allowed to exclude form $23''$. On the other hand $19$ reacted unequivocally with 1,4,8,11-tetraazacyclotetradecane -5,7 dione $24$ to give the macrocycle $25$ characterized by X-ray diffraction (see Figure 2).
Figure 2: Structure of macrocycle 25 determined by X-ray diffraction studies
Such experiments were extrapolated to the reaction of the dendrimer of generation 1, 1-[G\textsubscript{1}] with macrocycles 20, 22 and 24 (Scheme 19). The expected tris macrocyclic species 26-[G\textsubscript{1}], 28-[G\textsubscript{1}] (or 28'-[G\textsubscript{1}]), and 29-[G\textsubscript{1}] were obtained in 64-70% yield. Here also NMR data did not allow us to choose between the two possible forms 28-[G\textsubscript{1}] or 28'-[G\textsubscript{1}].

We have already demonstrated that the reactivity of functional groups grafted on the surface of dendrimers of high generations is similar to those of the same functional groups anchored at the periphery of the dendrimer of generation 1. Therefore, the anchorage of 12 units of macrocycle 20 on the surface of the dendrimer of generation 3, 1-[G\textsubscript{3}] (12 terminal P(S)Cl\textsubscript{2} groups) was attempted, and allowed to isolate dendrimer 26-[G\textsubscript{3}]. Remarkably, no cross linking reactions are detected (Scheme 20).
C - Conclusion

We have succeeded in grafting various functional groups on the surface of phosphorus containing dendrimers, up to the fifth generation in most cases (up to 96 terminal functional groups). The nature of the terminal groups strongly influence the solubility of dendrimers. Thus, the first generation with 6 CH(OH)P(O)[O(CH₂)₁₁CH₃]₂ end groups is soluble in pentane (the fifth is not), whereas dendrimers with CH(OH)P(O)(OEt)₂ end groups are soluble in methanol, and dendrimers with CH=CH-C(O)OLi end groups (not isolated) are soluble in water. Other common solvents usable, depending on the nature of the end groups, are toluene, benzene, ether, dichloromethane, chloroform, tetrahydrofuran, dioxane, or acetonitrile.

All the dendrimers isolated possess terminal end groups which confer to these macromolecules the expected properties mainly in the field of adhesives, flame retardants, additives, or sequestering agents. Furthermore, it is clear that the procedures experimented for this work should be extended to other types of functional groups to be grafted on the surface, but also in the internal cavities of some of the internaly functionalized dendrimers we now develop in the group.

It should be also emphasized that, as we have received the authorization to publish from the US Army Office, most of this work will appear in two papers: the work concerning all phosphorus end groups (excluding vinylphosphonates) is in press in the Journal of Organic Chemistry[3a], and the work concerning the Wadsworth-Horner-Emmons reaction, which has been extended to other functional groups, is accepted as a feature article in Synthesis[3b].
D - Literature Cited

[1] – for reviews on dendrimers, see for example:

(m) Bardají, M.; Kustos, M.; Caminade, A.M.; Majoral, J.P.; Chaudret B. Organometallics 1997, 16, 403.
[3] - Publications issued from this report

(a) Phosphate, phosphite, ylide and phosphonate terminated dendrimers

(b) Application of the Horner-Wadsworth-Emmons reaction to the functionalization of dendrimers: Synthesis of amino acid terminated dendrimers
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List of Participating Scientific Personnel

- Dr. Jean-Pierre Majoral (20 %)
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Phosphate-, Phosphite-, Ylide-, and Phosphate-Terminated Dendrimers

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Many types of tri- and tetracoordinated phosphorus derivatives have been grafted on the surface of dendrimers, starting from aldehyde terminal functions. Depending on the solubility of the resulting phosphorylated dendrimers, these experiments have been carried out on generation 1 (six end groups) for phosphate- (4-[G1]), phosphinite- (6-[G1]), and ylide-terminated (11-[G1]) dendrimers and up to generation 5 (96 end groups) for aminophosphate- (8-[G1], 8-[G2]), aminophosphite (10-[G1], 10-[G2]), and functionalized phosphonate-terminated (14-[G1]-14-[G4], 15-[G1], 15-[G2], 17-[G1], 19-[G1], 19-[G2] dendrimers. Most of the phosphate-terminated dendrimers present an unexpected long-range phosphorus–phosphorus coupling constant through seven bonds (3.8 < 1JPP < 4.5 Hz).

Introduction

Tetracoordinated organophosphorus derivatives such as phosphates and phosphites offer a wide range of applications as pesticides, insecticides, herbicides, catalysts, lubricants, adhesives, flame retardants, etc. For many uses, these compounds are grafted on polymers or are polymerized themselves. Owing to their potential applications, we decided to graft several types of tetracoordinated organophosphorus derivatives on a new class of monodisperse and highly branched polymers, namely dendrimers.1 Our efforts were first directed toward the grafting of phosphates and then mainly toward the grafting of phosphites, since both types of compounds generally have similar properties, but differ in that phosphites have a different solubility and a greater stability toward hydrolysis. We have also grafted on dendrimers several other types of organophosphorus derivatives such as aminophosphites, phosphinites, aminophosphites, and even ylides.

Results and Discussion

The family of dendrimers we used is built from PS-C18 as core by the repetition of two reactions, which creates OCH2CH(NN Me)P(S) linkages.2 These compounds possess 6, 12, 24, 48, or 96 terminal functions for generations 1, 2, 3, 4, or 5, respectively. These functions are either Cl or benzaldehyde groups, the latter being the starting groups for the synthesis of all the organophosphorus-terminated dendrimers described in this paper (Figure 1).

Scheme 1

In first attempts, we tried to graft phosphate groups in two steps from the dendrimer 1-[G1]. The first step is a condensation with hydrazine, used in very large excess, to afford compound 2-[G1]. The second step is another condensation, with the phosphate 3, easily obtained by reaction of hydroxybenzaldehyde sodium salt with (EtO)3P(O)Cl (Scheme 1). The synthesis of dendrimer 4-[G1] is monitored by 31P NMR, which shows a slight deshielding of the signal corresponding to the (EtO)3P(O) moieties on going from 3 (δ31P = -7 ppm) to 4-[G1] (δ31P = -6.7 ppm). Additional proofs of the condensation reaction are given by 1H NMR, with the total disappearance of signals corresponding to CHO and NH2 groups. Furthermore, 13C NMR indicates the presence of two very close singlets (δ13C = 160.5 and 160.8 ppm) corresponding to the azine –CH=NN–CH– linkages of the dendrimer 4-[G1].

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Figure 1. Fifth generation of the dendrimer with various end groups.

We tried to extend this reaction to higher generations 4-[G₄] (n: generations 2–5). Unfortunately, the condensation results in all cases in the formation of powders, insoluble in water and in common organic solvents. However, the same condensation reaction can be applied to graft other phosphorus derivatives such as phosphinites. Indeed, the phosphinite 5, obtained by reaction of hydroxylbenzaldehyde and triethyamine and diphenylchlorophosphine, is easily condensed with dendrimer 2-[G₁] to afford the phosphinite-terminated dendrimer 6-[G₁] (Scheme 2). The condensation induces a slight shielding of the signal corresponding to the Ph₂PO moieties in ³¹P NMR on going from 6 (δ²¹P = 112.3 ppm) to 6-[G₁] (δ²¹P = 111.5 ppm) and the total disappearance of signals corresponding to CHO and NH₂ groups in H NMR. In this case also, we tried to obtain higher generations of the phosphinite-terminated dendrimers, for instance 6-[G₃], but we observed the same phenomenon of insolubility that we already noted for dendrimers 4-[G₃] (n > 1), probably due to the presence of many diarylazine groups. To overcome this problem, we decided to avoid the formation of this linkage and, therefore, to find other strategies to graft phosphorus derivatives on the dendrimer.

We tried first another condensation reaction, with aldehyde groups on the dendrimer and NH₂ groups on the phosphorus derivative to be grafted, such as H₂NN-(Me)P(0)(OEt)₂. This compound, obtained by reaction of methylhydrazine with CIP(O)(OEt)₂, reacts easily with the first generation of the dendrimer 1-[G₁] (6 CHO end groups) but also with the fifth generation 1-[G₅] (96 CHO end groups) (Scheme 3, Figure 1). In both cases, the quantitative formation of the hydrazonophosphate-terminated dendrimer 8-[G₅] is monitored by ³¹P NMR. Indeed, we observed the total disappearance of the signal corresponding to 7 (δ²¹P = 8.7 ppm) on behalf of the appearance of a new signal (δ²¹P = 2.8 ppm) corresponding to the P=O groups of 8-[G₅]. Furthermore, the signal of the phosphorus atoms on the external layer of the dendrimer (P₁ for [G₁], P₃ for [G₃]) is slightly deshielded on going from 1-[G₅] to 8-[G₅] (Δδ = 2.2 ppm). The total disappearance of signals corresponding to CHO and NH₂ groups in H NMR confirms the quantitative formation of dendrimers 8-[G₅] as crude product. It is worth noting that the fifth generation of the dendrimer 8-[G₅], which possesses 96 hydrazonophosphate groups, remains perfectly soluble in several organic solvents such as THF, chloroform, dichloromethane, etc.

Obviously, many types of phosphorus derivatives can be grafted on the surface of the dendrimers in this way, provided the formation of the phosphorohydrazide H₂NNMeP(X)R₂ could be accomplished. This is the case with most PIV derivatives (X = O, S, N...) but is extremely difficult and even impossible with PIII derivatives. In-
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Scheme 5

![Scheme 5](image)

we tried to obtain the same type of compound from the second generation 9-[G₄]. Unfortunately, the corresponding ylide-terminated dendrimer 11-[G₄] was found to be insoluble in water and in a variety of organic solvents.

However, we decided to test the reactivity of the first generation 11-[G₄] in the Wittig reaction, toward benzaldehyde and crotonaldehyde. Benzaldehyde reacts at room temperature to afford compound 12-[G₄] in quantitative yield as a crude product (Scheme 5). The reaction is monitored by $^3$P NMR, which indicates the total disappearance of the ylide signal on behalf of the appearance of the signal corresponding to Ph₃P(O) ($\delta_{^3P} = 24$ ppm). After removal of the triphenylphosphine oxide, $^1$H NMR indicates a slight deshielding of the signal corresponding to the CH₃NCO groups, but the signals of the CH=CH linkages are overlapped by the aromatic signals and did not allow us to determine the geometry of the ethylenic linkage. However, $^{13}$C NMR indicates the formation of both cis and trans isomers; indeed, each carbon atom of the CH₃NCO(O)CH=CH- linkages gives two close singlets, approximately in a 1:3 ratio, whereas for all the other parts of the dendrimer 12-[G₄], each carbon gives a single set of signals. According to the known tendency of stabilized ylides to give predominantly trans isomers in the Wittig reaction, we tentatively assign the largest signals to the trans isomer.

This assignment is corroborated by the study of the reaction of crotonaldehyde (trans isomer) with 12-[G₄] (Scheme 5). In this case also, $^{13}$C NMR displays the formation of two isomers, characterized by the presence of two signals for each carbon atom of the CH₃NCO(O)CH=CHMe linkages in an approximate 1:9 ratio. The attribution of these signals to the cis-trans and trans-trans isomers, respectively, is unambiguous in this case owing to $^1$H two-dimensional NMR experiments. Indeed, two doublets in a 1:9 ratio are observed for the H₃ protons of the CH₃NCO(O)CH=CHMe linkages: $^3$H = 6.80 (d, $J_{CH} = 10.0$ Hz), and 7.12 (d, $J_{CH} = 15.0$ Hz) ppm. The value of the coupling constants allows us to attribute unambiguously the former signals to the minor cis-trans isomer and the latter to the major trans-trans isomer.

The last type of phosphorus derivatives we tried to graft on dendrimers is phosphonates. In all cases, the

method of synthesis we used consists of the addition of P=H bonds on polaron double bonds of the dendrimer. In our first attempts, we tried to graft phosphonate groups by addition of diethyl phosphate to the aldehyde functions of dendrimer 1-[G₄] in several conditions, using THF as solvent. It is well known that this type of reaction is catalyzed by bases; thus, we used either CaF, NEt₃, or DBU as catalysts, heating for several days at 65 °C. In all cases, we observed only a partial reaction, even after heating for 2 weeks (when CaF is used), or a degradation (when DBU is used). On the other hand, when a large excess of diethyl phosphate is used without solvent, and in the presence of CaF as catalyst under heating, the reaction with 1-[G₄] goes to completion. However, the resulting α-hydroxy methylphosphonate-terminated dendrimer 14-[G₄] is difficult to purify in these conditions, both from CaF and from the large excess of diethyl phosphate.

We also tried to use NEt₃ as catalyst (20–40%) without solvent, the dendrimer 1-[G₄] being dissolved in the mixture Et₃N/ EtOH/P(O)OH. In these conditions, the reaction proceeds rapidly and quantitatively at room temperature, and the resulting phosphonate-terminated dendrimer 14-[G₄] is more easily purified (Scheme 6). However, the 31P NMR spectrum of compound 14-[G₄] appears surprisingly complex. Indeed, beside the singlet corresponding to the phosphorus of the core (δ 31P = 51.8 ppm, P₀), we observed two signals centered at δ = 21.3 ppm, corresponding to P(O)OEt₂, and three signals centered at δ = 62.0 ppm, corresponding to the phosphorus of the first generation P₁ (Figure 2a). At first glance, these signals could be due to the formation of three diastereoisomers (one racemic and two meso forms) for each branch of the dendrimer, as the addition of PH groups to aldehydes creates chiral carbon centers (Figure 3). However, the relative intensity for each set of signals (1:2:1 for δ = 62.0 ppm and 1:1 for δ = 21.3 ppm) and the line separation seems to be in agreement with the presence of a triplet and a doublet, with a coupling constant of 3.9 Hz, which should correspond to the coupling of P₃(S) with P(O) through seven bonds! This surprising result prompted us to verify this hypothesis by selective phosphorus-decoupling NMR experiments. The selective irradiation of the signal at δ = 62.0 ppm clearly induces the transformation of the signal at δ = 21.3 ppm from a doublet to a singlet (Figure 2b). Furthermore, the selective irradiation of the signal at δ = 21.3 ppm also transforms the signal at δ = 62.0 ppm to a singlet. These experiments confirm the existence of the 1JₚP coupling constant in compound 14-[G₄]. Very few coupling constants through so many bonds have been reported in the literature, most of them concerning through-space couplings, which are unlikely for compound 14-[G₄] for sterical reasons. However, a phosphorus–phosphorus coupling constant over seven bonds has already been measured for a compound whose structure is closely related to that of 14-[G₄]: the analysis of the outer 13C satellites in the 31P NMR spectrum of (Et₂)₃P(O)CH₂CH₂CH₂P(O)(OEt)₂ gave 1JₚP = 7.8 Hz, a value attributed to a large II-electron contribution. The value directly obtained in the case of 14-[G₄] (1JₚP = 3.9 Hz) compares well with these data.

Figure 2. (a) 31P(1H) NMR spectra of dendrimer 14-[G₄]. (b) 31P(1H) NMR spectra of dendrimer 14-[G₄] with selective irradiation of the signal at δ = 62 ppm.

Figure 3. Racemic and meso forms for each branch of dendrimers 14-[G₄].

Scheme 6

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\begin{align*}
14-[G₄] & \xrightarrow{y = 6 \text{ for } [G₄]} 1-[G₄] \\
14-[G₄] & \xrightarrow{y = 96 \text{ for } [G₄]} 1-[G₄]
\end{align*}
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from \(y = 6\) for \([G₄]\) to \(y = 96\) for \([G₄]\).
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**Scheme 7**

The grafting of phosphonate groups can be extended to higher generations without any problem of solubility. We have carried out this reaction under the same conditions for all the generations from 1 to 5 and, thus, isolated dendrimers 14-[G1]–14-[G2], with up to 96 phosphonate end groups (Scheme 6). In all cases, we observed a doublet in the $^{31}$P NMR spectra at $\delta = 21$ ppm (3.8 < $^{3}J_{PP} < 4.5$ Hz) for the PO(O)(OE)2 groups, whereas the signal at $\delta = 62$ ppm becomes a broad singlet for generations higher than 2, presumably due to the formation of an increasing number of stereoisomers. The full transformation of the aldehyde groups in alcohol for all compounds is characterized in $^1$H NMR by the total disappearance of the singlet of the aldehyde groups on behalf of the appearance of a doublet at ca. 5 ppm corresponding to the C=OH groups. The presence of chiral carbon atoms also complicates the $^1$H and $^{13}$C NMR spectra for all generations, as this renders the CH$_2$CH$_2$ groups diastereotopic. This is clearly seen in $^{13}$C NMR spectra by the presence of two distinct doublets at ca. 63–65 ppm corresponding to the OCH$_2$CH$_2$ groups.

The facility of the synthesis of dendrimers 14-[G1]–14-[G2] incited us to try to extend this reaction to other phosphonates and to other end groups on the dendrimers. For instance, the long chain phosphonate HP(O)(O)(CH$_2$)$_n$CH$_3$ also reacts with dendrimers 1-[G1] and 1-[G2] to afford dendrimers 15-[G1] and 16-[G2] (Scheme 7). These compounds possess the same spectral characteristics already noted for dendrimers 14-[G1]–14-[G2], in particular, a $^{3}J_{PP} = 3.8$ Hz is clearly observed on the $^{31}$P NMR spectrum of 15-[G1]. The presence of several long-chain hydrocarbons modifies the solubility of the dendrimer: for instance, compound 16-[G1] is soluble in pentane, whereas none of the dendrimers we already synthesized is.

We also tried the addition of phosphonates on a dendrimer with $\alpha,\beta$-unsaturated aldehydes as end groups, 16-[G1]. This compound is obtained in THF at 40 °C by reacting 6 equiv of the sodium salt of 4-hydroxy-3-methoxy-intramaldehyde with (S)P(O)CH$_2$CH$_2$=NN(Me)P(S)CH$_2$ (Scheme 8). Addition of HP(O)(O)(OE)$_2$ on 16-[G1] affords dendrimer 17-[G1], which possesses six unsaturated alcohol–phosphonate end groups. In this case, no phosphorus–phosphorus coupling constant through nine bonds is observed on the $^{31}$P NMR spectrum of 17-[G1]. $^1$H NMR shows the total disappearance of the CHO groups on behalf of the appearance of a doublet of doublet at $\delta = 4.6$ ppm ($^{3}J_{HP} = 13.4$ Hz, $^{2}J_{HH} = 5.0$ Hz) corresponding to C–OH. As expected, no reaction occurred on the CH=CH bonds.

IR spectra of compounds 14-[G1]–14-[G2], 15-[G1], 15-[G2], and 17-[G1] exhibit classical $\nu_{OH} = 3270$ cm$^{-1}$, demonstrating the presence of a hydrogen bond between hydroxyl and phosphoryl groups.

Finally, we also tried to add phosphonates to imine terminal functional groups, as it is known that this type of reaction proceeds approximately under the same conditions as the addition to aldehydes. For this purpose, we synthesized first the imine-terminated dendrimers 18-[G1] and 18-[G2], easily obtained by condensation of propyamine with dendrimers 1-[G1] and 1-[G2], respectively (Scheme 9). Addition of HP(O)(O)(OE)$_2$ on dendrimers 18-[G1] and 18-[G2] affords dendrimers 19-[G1] and 19-[G2], respectively. In this case also, the phosphorus–phosphorus coupling constant through seven bonds ($^{3}J_{PP} = 4.5$ Hz) is clearly observed on the $^{31}$P NMR spectra of both generations. The reaction has gone to completion, as demonstrated by the total disappearance of the imine functions ($\delta = 8.20$ ppm) in $^1$H NMR. The addition to the imine bonds is chemoselective; no reaction occurs on the hydrazone functions of the skeleton of the dendrimer, either in this experiment or in all the previous cases.

**Conclusion**

We have experimented with several strategies to graft tri- and tetracoordinated phosphorus derivatives on dendrimers of generation one–five, depending on the solubility of the resulting dendrimer. It can be inferred from all these experiments that the solubility of the dendrimers depends essentially on the type of substituents grafted on the surface. Indeed, azinephosphates, azinephosphinite, and ylide linkages on the periphery dramatically reduce the solubility of dendrimers possessing more than six end groups. On the other hand, the grafting of long-chain hydrocarbons increases the solubility of the dendrimer in organic solvents. However, it can

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be pointed out that each end group seems to behave independently as far as the reactivity is concerned. Moreover, the reactivity of the ylide-terminated dendrimer with aldehydes follows the rules elaborated for classical Wittig reactions in organic chemistry.

The phosphonate-terminated dendrimers appears to be very interesting, as all of them remain soluble in common organic solvents, even for high generations. Furthermore, the addition reaction we used allows several variations, both in the nature of the phosphonate to be grafted and in the nature of the polar double bond on the surface of the dendrimer. It is also worth noting that this reaction creates additional functions on the surface of the dendrimer, besides the phosphonate groups: alcohols or secondary amines groups, whose reactivity should be interesting to investigate. Furthermore, these compounds possess a rare and unexpected long-range phosphorus—phosphorus coupling constant through seven bonds for the (SIPCO)H3CR(OR)2 linkages (R = OH, NHPR; R' = Et, (CH2)3CH)2.

To summarize, this work clearly demonstrates for the first time that it is possible to anchor to the surface of dendritic molecules a large variety of phosphorus ylides, phosphates, phosphinites, hydrazonophosphates, hydrazonophosphites, phosphorus ylides, and phosphonates (from 6 to 96 units) of each, them having potentially a great interest in different fields. Indeed, biologically important phosphates are known (nucleotides, phospholipides, nucleosides, polyphosphates, phosphates sugar).

Phosphate monomers are used in some catalytic processes (acylonitrile dimersization) and in the well-known Arbuzov rearrangement,11 while phosphorus ylides play a key role in Wittig reactions.11 Moreover, phosphonate monomers have found wide applications in general organic synthesis.6,13,14 (Horner—Wadsworth—Emmons condensation, Diels—Alder reactions, Michael additions, etc.), and they can be used as versatile intermediates for the preparation of a number of heterocycles.11

Work is in progress to study the properties of these new phosphonate-terminated dendrimers in some of the areas reported above and to extend the scope of reactions developed in this paper to other phosphate derivatives.

**Experimental Section**

**General Methods.** All manipulations were carried out with standard high vacuum or dry argon atmosphere techniques. 1H, 31P(H), and 31P(C) NMR spectra were recorded on Bruker AC 200 or W 250 or AMX 400 spectrometers, using CDCl3 as solvent, except where noted. 31P NMR chemical shifts are reported in ppm relative to 85% H3PO4. Coupling constants (J) are reported in Tables 1 and 2.

**Synthesis of Compound 3.** To a solution of 4-hydroxylbenzaldehyde (0.50 g, 3.47 mmol) in THF (10 mL) was added EtO2P(O)Cl (0.50 mL, 3.47 mmol). The resulting mixture was stirred for 1 h at room temperature and then filtered to give an oil that was used without further purification.

3a: colorless oil; 70% yield (0.627 g); 1H NMR δ 7.0 (7, j = 6.0 Hz); 6.9 (7, j = 2.0 Hz), 7.08 (s, J = 3.7 Hz, 2H), 7.08 (s, J = 8.5 Hz, 2H), 7.58 (s, J = 8.5 Hz, 2H), 9.65 (s).

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11C NMR δ 16.0 (d, J = 7), 32.0 (d, J = 10), 32.9 (d, J = 16), 63.4 (d, J = 6), 121.5 (d, J = 3), 127.6, 128.1, 132.0, 132.5, 136.3 (d, J = 18), 138.8 (110 ms), 159.7 (d, J = 7), 161.1 (115 ms). Anal. Caled for C₄₅₀H₃₆₂N₁₅O₂₅P₁₆Ca₂: C, 48.36, H, 5.29; N, 11.24. Found: C, 48.17; H, 5.14; N, 11.07.

**General Procedure for the Synthesis of Aminophosphate-Terminated Dendrimers 10-[Ga] and 10-[Ga].** To a solution of 0.20 g of dendrimer 3-[Ga] (n = 1, 0.075 mmol; n = 5, 0.0064 mmol) in THF (10 ml) were added chlorodiethylphosphine (n = 1, 130 μl, 0.90 mmol; n = 5, 9.8 μl, 0.677 mmol) and triethylamine (n = 1, 126 μl, 0.90 mmol; n = 5, 100 μl, 0.677 mmol). The resulting mixture was stirred for 2 h at room temperature and then filtered and evaporated to dryness to give a white powder, very sensitive to humidity.

10-[Ga] white powder; 40% yield (0.070 g); 31P NMR δ 5.25, 62.8, 139.2; 1H NMR δ 1.22 (t, J = 7.0, 3H), 2.93 (d, J = 1.0, 18H), 3.33 (d, J = 10.4, 9H), 3.71—3.85 (m, 24H), 7.15—7.77 (m, 45H); 13C NMR δ 16.7 (d, J = 6), 28.4, 32.9 (d, J = 13), 59.7 (d, J = 17), 121.4 (d, J = 4), 126.9, 128.3, 132.5, 136.3 (J = 28), 138.2 (d, J = 12), 159.3 (d, J = 17), 50.8 (d, J = 5); Anal. Caled for C₄₅₀H₃₆₂N₁₅O₂₅P₁₆Ca₂: C, 49.87; H, 5.75; N, 10.90. Found: C, 49.73; H, 5.71; N, 10.72.

10-[Ga] white powder, 64% yield (0.102 g); 31P NMR δ 62.6, 62.7, 138.6; 1H NMR δ 1.15—1.27 (m, 7H), 2.85 (d, J = 1.87, 28H), 3.25 (d, J = 11.6, 27H), 3.70—3.86 (m, 84H), 7.11—7.60 (m, 94H); 13C NMR δ 18.7 (d, J = 5), 28.4, 32.9 (d, J = 12), 59.6 (d, J = 17), 121.1 (d, J = 6), 126.9, 128.0, 132.0, 132.6, 132.3 (d, J = 28), 138.3—140.0 (m), 149.9 (d, J = 7), 151.1 (d, J = 9). Anal. Caled for C₄₅₀H₃₆₂N₁₅O₂₅P₁₆Ca₂: C, 49.99; H, 5.47; N, 11.62. Found: C, 49.76; H, 5.32; N, 5.11.

**Synthesis of Ylide-Terminated Dendrimer 11-[Ga].** To a solution of (triphenylphosphanylidene)ethylen (0.120 g, 0.397 mmol) in THF (7 ml) was added 9-[Ga] (0.105 g, 0.066 mmol) in THF (5 ml) at room temperature. The resulting mixture was stirred for 24 h at room temperature and then evaporated to dryness. The resulting powder was washed with 3 × 10 ml of THF/ether/pentane (1/2/2).

11-[Ga] yellow powder; 78% yield (0.175 g); 31P NMR δ 13.8, 52.8, 62.6; 1H NMR δ 3.3 (s, 18H), 3.3 (J = 11.5, 9H), 4.2 (br s, J = 25, 6H), 7.1—7.7 (m, 13H); 13C NMR δ 26.8, 32.4 (d, J = 13), 32.5 (d, J = 127), 120.9 (d, J = 126), 127.5, 128.0 (d, J = 12), 129.7 (d, J = 13), 131.1, 132.4 (d, J = 10), 133.7, 134.0 (d, J = 12), 150.4 (d, J = 17), 150.3 (d, J = 9), 170.3 (d, J = 12); IR (KBr) 1663 cm⁻¹ (νP). Anal. Caled for C₄₅₀H₃₆₂N₁₅O₂₅P₁₆Ca₂: C, 67.21; H, 4.87; N, 7.01. Found: C, 67.62; H, 4.87; N, 7.01.

**Reaction of Dendrimer 11-[Ga] with Aldehydes.** To a solution of 0.211 mmol (0.002 mmol of dendrimer 11-[Ga] in 10 ml) was 0.040 mmol of aldehyde (1.0 ml) or crotonaldehyde (0.031 ml, 0.37 mmol). The resulting mixture was stirred overnight at room temperature (benzaldehyde) or for 1 week at 40 °C (crotonaldehyde). The solvent was evaporated under vacuum to give a yellow powder that was washed with 3 × 10 ml of THF/ether/pentane (1/2/2).

**General Procedure for the Synthesis of Phosphate-Terminated Dendrimers 15-[Ga] and 15-[Ga].** To 0.200 g of dendrimer 11-[Ga] (n = 1, 0.140 mmol; n = 5, 0.0064 mmol) were added dialueryl phosphorus (5 × 10 ml) and then the resulting mixture was stirred for 3 days at room temperature (for 15-[Ga]) or for 5 days at room temperature then for 2 days at 45 °C (for 15-[Ga]). The resulting mixture was washed several times with ether/pentane to give a white powder.


**General Procedure for the Synthesis of Imine-Terminated Dendrimers 18-IG[1] and 18-IG[2]**

To a solution of 0.250 g of 1-IG[1] (n = 1, 0.176 mmol; n = 5, 0.0038 mmol) in THF (10 mL) was added propylamine (n = 1, 0.180 mL, 2.112 mmol; n = 5, 0.130 mL, 1.530 mmol) in the presence of molecular sieves (4 Å). The mixture was stirred at room temperature for 24 h and then filtered and evaporated to dryness. The resulting powder was washed with ether.

18-IG[1]: white powder; 61% yield (0.179 g); 13C NMR δ 52.4, 61.9; 1H NMR δ 0.90 (t, J = 6.7, 18H), 1.67 (m, 12H), 3.35 (d, J = 10, 9H), 3.51 (m, 12H), 7.26–7.70 (m, 39H), 8.20 (t, 6H);

18-IG[2]: white powder; 46% yield (0.130 g); 13C NMR δ 61.9, 62.5; 1H NMR δ 0.86 (s, 28H), 1.61 (s, 19H), 2.38 (br, s, 279H), 3.47 (br, s, 292H), 7.21–7.65 (m, 489H), 8.15 (s, 96H); 13C NMR δ 11.7, 23.8, 32.9 (d, J = 14), 63.2, 121.4 (d, J = 4), 128.3, 129.2, 132.4, 133.5, 138.0 (d, J = 0), 151.0 (d, J = 7), 152.0 (d, J = 9), 153.9; IR (KBr) 1647 cm⁻¹ (v(C=O)).

**Synthesis of Dendrimer 16-IG[1]**

To 0.300 g (0.33 mmol) of (S)-5-OCH₃CH=CH-NH(NMe)PS₂C₆H₄Cl₂ in THF (30 mL) was added 0.420 g (2.27 mmol) of 4-hydroxy-3-methoxycinnamaldehyde sodium salt. The resulting mixture was stirred for 5 days at 40 °C and then centrifuged. The solution was evaporated to dryness to give a powder that was washed twice with pentane/ether (1/1).

16-IG[1]: yellow powder; 48% yield (0.278 g); 13C NMR δ 59.7, 62.0; 1H NMR δ 3.40 (d, J = 9.9, 9H), 3.73 (m, 18H), 6.51 (d, J = 16.0, 6H), 7.00–7.34 (m, 33H), 7.55 (d, J = 16.0, 6H), 9.54 (d, J = 7.0, 6H), 13C NMR δ 32.5 (d, J = 12, 55), 111.7, 121.1, 121.5, 122.3, 128.1, 131.7, 132.6, 137.9 (d, J = 15), 142.3 (d, J = 8), 150.6 (d, J = 8), 151.3 (d, J = 6), 193.4; IR (KBr) 1677 cm⁻¹ (v(C=O)).

**Synthesis of Phosphonate-Terminated Dendrimers 19-IG[1] and 19-IG[2]**

To 0.280 g (0.160 mmol) of dendrimer 16-IG[1] were added triethylphosphite (30 μL) and diethyl phosphite (the quantity necessary to dissolve 16-IG[1]; 0.5 mL). The mixture was stirred overnight at room temperature and then evaporated under vacuum to give an oil that was washed with acetone to give a powder.

17-IG[1]: yellow powder; 18% yield (0.074 g); 13C NMR δ 21.3, 52.3, 62.1; 1H NMR δ 1.26 (m, 36H), 2.62 (br s, 6H), 3.40 (d, J = 10.0, 9H), 3.75 (s, 18H), 4.13 (m, 24H), 4.61 (dd, J = 13.4, 5.0, 6H), 6.21 (d, J = 15.7, 6H), 6.67 (dd, J = 15.7, 6.0, 6H), 6.86–7.67 (m, 33H, C₆H₄); 13C NMR δ 16.5 (d, J = 6), 22.7 (d, J = 12), 56.0, 63.2 (d, J = 6), 69.3 (d, J = 162), 110.7, 119.1, 121.3, 122.2, 124.1, 128.3, 130.0, 134.3, 137.4 (d, J = 16), 139.9, 150.8 (d, J = 8), 151.2 (d, J = 6); IR (KBr) 3270 cm⁻¹ (v(C=O)).

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Application of the Horner-Wadsworth-Emmons Reaction to the Functionalization of Dendrimers: Synthesis of Amino Acid Terminated Dendrimers

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Abstract:

The Horner-Wadsworth-Emmons reaction of the first, third and fourth generation of aldehyde terminated dendrimers 1-[Gn] (n = 1: 6 CHO, n = 3: 24 CHO, n = 4: 48 CHO groups, respectively) with phosphonates unsubstituted at the carbon α to the phosphoryl group 2a-i affords in moderate yield dendrimers bearing various α,β-unsaturated functional groups on the surface, including amino acid derivatives.

Key words: Dendrimer, arborol, phosphonate, Horner-Wadsworth-Emmons reaction, amino-acid
The design of highly branched macromolecules with well defined structure and constitution, namely dendrimers\(^1\) gives rise to an increasing interest in several fields of chemistry, including biochemistry. For instance, natural amino acids have been included several times in the skeleton of dendritic structures, or grafted on the surface. In previous examples, amino acids such as \(\alpha,\omega\)-diamino carboxylic acids (mainly lysine) were used as building blocks in divergent syntheses up to the tenth generation.\(^2\) Later, oligonucleotides were used in convergent syntheses.\(^3\) Small lysine dendrimers have also been a support for the grafting of peptides,\(^4\) carboranes and peptides,\(^5\) or \(\alpha\)-thiosialosides\(^6\) onto the surface, whereas poly(ethylene oxide) has been grafted to the core.\(^7\) Several antibodies have also been linked to the surface of organic dendrimers such as PAMAM dendrimers.\(^8\)

All the above-mentioned papers deals with the use of "oligomeric" amino acids; in contrast, only one series of reports concerns the synthesis of dendrimers possessing monomeric amino acids on the surface. They were obtained by the modification of poly (propylene imine) dendrimer end-groups with bulky amino acids, which resulted in a "dendritic box" able to encapsulate small molecules.\(^9\) We recently described the synthesis of phosphorus containing dendrimers possessing either \(\text{PCl}_2\) or aldehyde end-groups\(^10\) and the grafting on the surface of various types of functional groups.\(^11\) Pursuing our investigations in the field of functionalized dendrimers, it appeared interesting to try to graft natural amino acids onto the surface. Amino acid could be grafted directly by a Schiff reaction with the aldehyde end-groups, but the resulting imine bonds would be too sensitive to hydrolysis. In order to get amino acids firmly bounded to the dendrimers, we decided to use the Horner-Wadsworth-Emmons reaction\(^12\) which creates a carbon carbon double bond, starting from the phosphorylated amino acids of general formula \((\text{EtO})_2\text{P(O)CH}_2\text{C(S)[amino acid]}\) that we recently described.\(^13\)

To demonstrate the versatility of the Horner-Wadsworth-Emmons reaction applied to dendrimers, we carried out preliminary experiments with the first (1-\([G_1]\)) , third (1-\([G_3]\)) , or fourth (1-\([G_4]\)) generation of the dendrimer (6, 24, or 48 aldehyde end-groups, respectively) and with the salts of the ester, phosphonate, thioamide, and carboxylic acid derivatives of phosphonates 2a-e. Subsequent reactions were carried out with the salts of the amino acid derivatives of phosphonates 2f-i. Two different synthetic procedures have been applied,
depending on the absence or presence of carboxylic acid on compounds 2. In the former case, one equivalent of sodium hydride is added to the phosphonates 2a-d to afford the corresponding phosphonate salts. Then, the dendrimer is added to this salt, used in situ and stirred overnight. All these experiments are carried out with the first generation of the dendrimer 1-[G1] (Scheme 1). This procedure affords dendrimers 3a-[G1] – 3d-[G1] in quantitative yield as crude products, and in moderate yield after workup (see Table 1).

All these compounds have been characterized by 31P, 1H, and 13C NMR (Table 1), IR, and elemental analyses. The reaction induces a slight deshielding of the signal corresponding to the external phosphorus (P1) of the dendrimer, from 60.1 ppm for 1-[G1] to 60.9-61.4 ppm for 3a-[G1] – 3d-[G1]. Furthermore, the formation of the carbon carbon double bond is unambiguously proved by the total disappearance of the aldehyde signals on 1H and 13C NMR, and IR spectra, and by the appearance of new signals corresponding to the HC=CH linkage. Indeed, two new doublets appears in the 1H NMR spectrum of compound 3a-[G1] at δ = 6.34 and 7.61 ppm (3JHH = 16 Hz), corresponding to CH=CH-CO and CH=CH-CO, respectively. The value of the coupling constant indicates a E-configuration for all the HC=CH linkages. The formation of the alkene moieties is also confirmed by the 13C NMR spectrum, with the appearance of two singlets at δ = 118.4 (CH=CH-CO) and 143.3 ppm (CH=CH-CO). A similar trend is observed for dendrimer 3b-[G1] which possesses six unsaturated phosphonate functions. In this case, the 1H NMR spectrum is slightly complicated by the presence of the phosphonate moieties. Indeed, the signal corresponding to CH=CH-P(O) appears as a doublet of doublet, with two equivalent coupling constants (δ = 6.15 ppm, 2JHP = 3JHH = 17.3 Hz), whereas the signal corresponding to CH=CH-P(O) appears as a single doublet (δ = 7.47 ppm, 3JHH = 17.3 Hz). The formation of the carbon carbon double bond is also demonstrated by the presence of two doublets in the 13C NMR spectrum at δ = 113.9 ppm (1JCP = 191 Hz) for CH=CH-P(O) and δ = 147.3 ppm (2JCP = 7 Hz) for CH=CH-P(O).

The above mentioned data indicate for both compounds 3a-[G1] and 3b-[G1] the unique formation of the E isomer of the double bond. A different behaviour is observed for compounds 3c-[G1] and 3d-[G1]. Indeed, beside the expected signals corresponding to the E isomers, several other signals appear in the 1H and 13C NMR spectra of both compounds, as already
observed in some cases for alkene bonds obtained by Wittig reactions on dendrimers.\textsuperscript{11c} For example, the \textsuperscript{1}H NMR spectrum of 3c-[G\textsubscript{1}] displays a AB system at $\delta = 6.20$ and 6.26 ppm, with $^{3}\text{J}_{\text{HH}} = 12.0$ Hz. The smaller value of the coupling constant and the shielding of the signals indicate the formation of the Z isomer.\textsuperscript{13} Integration of these signals compared to that of the E isomer gives approximately 10/90 for the Z/E ratio. Both isomers are also detected on the \textsuperscript{13}C NMR spectrum of 3c-[G\textsubscript{1}]. The signal corresponding to the Z isomer appears at higher field than for the E isomer ($\delta = 124.9$ and 126.0 ppm for Z and E CH=CH-C(S), respectively; $\delta = 128.0$ and 140.4 ppm for Z and E CH=CH-C(S), respectively). The same behaviour is observed for dendrimer 3d-[G\textsubscript{1}]. In this case, integration of the Z and E signals of the alkene bond in \textsuperscript{1}H NMR indicates the formation of a higher proportion of Z isomer (30/70 for the Z/E ratio). Obviously, isomers of compounds 3c-[G\textsubscript{1}] and 3d-[G\textsubscript{1}] cannot be purified, as both E and Z isomers are linked to the same dendrimer.

All these experiments have been extended to the third 1-[G\textsubscript{3}] or fourth 1-[G\textsubscript{4}] generation of the dendrimer which possesses 24 or 48 aldehyde end groups (Scheme 2, Figure 1). These reactions are slightly slower than for the first generation and need two days at room temperature to go to completion. The reactions are monitored by \textsuperscript{31}P NMR which indicates the total disappearance of the signal of the external phosphorus (P\textsubscript{3}; $\delta = 60.1$ ppm for 1-[G\textsubscript{3}]; P\textsubscript{4}; $\delta = 60.0$ ppm for 1-[G\textsubscript{4}]) on behalf of a new singlet slightly deshielded (P\textsubscript{3}; $\delta = 60.9$ ppm for 3d-[G\textsubscript{3}]; P\textsubscript{4}; $\delta = 61.0$-61.4 ppm for 3a-[G\textsubscript{4}] - 3c-[G\textsubscript{4}]). The reaction of all the aldehyde groups is confirmed by \textsuperscript{1}H and \textsuperscript{13}C NMR, and IR spectra with the total disappearance of the signals corresponding to these linkages. Furthermore, beside the signals corresponding to the skeleton of the dendrimer, \textsuperscript{1}H and \textsuperscript{13}C NMR spectra display signals characteristic of the CH=CH-R moieties, as already seen for the first generation (Table 1). Dendrimers 3a-[G\textsubscript{4}] and 3b-[G\textsubscript{4}] possess a all-E configuration, as noted for 3a-[G\textsubscript{1}] and 3b-[G\textsubscript{1}], whereas a mixture of E and Z configuration is observed for 3c-[G\textsubscript{4}] and 3d-[G\textsubscript{3}]. The Z/E ratio seems to depend on the generation used for compounds 3d (Z/E $\equiv$ 30/70 for 3d-[G\textsubscript{1}]; 50/50 for 3d-[G\textsubscript{3}]) but not for compounds 3c (Z/E $\equiv$ 10/90 for 3c-[G\textsubscript{1}] and 3c-[G\textsubscript{4}]). It must be noted that the precision of the technique used, \textsuperscript{1}H NMR, is hampered by the occurrence of signals of
the \( E \ CH=CH \) linkage within the area corresponding to the \( C_6H_4 \) and \( CH=N \) signals of the dendrimer skeleton.

After these preliminary experiments, we have tried to apply the same procedures to phosphonates bearing acid or amino acid substituents 2e-i. In these cases, two equivalents of base are required: one reacts with the carboxylic acid, the other creates the carbanion \( \alpha \) to the phosphonate. A first attempt was carried out with phosphonate 2f (glycine derivative) and two equivalents of sodium hydride. The reaction with the first generation is slow and necessitates to be heated. In this case, the monitoring by \( ^{31}P \) NMR indicates the partial cleavage of the skeleton of the dendrimer, thus compound 3f-[\( G_1 \)] is extremely difficult to isolate in these conditions. We encountered analogous problems with the salt of phosphonate 2g (alanine derivative) obtained by reaction with one equivalent of triethylamine, and one equivalent of sodium hydride.

To overcome these problems, we decided to use two equivalents of butyllithium, which should give a more reactive carbanion. The reaction is carried out first with dendrimer 1-[\( G_1 \)] and the simplest acid derivative of phosphonate 2e in tetrahydrofuran (Scheme 3). A yellow precipitate is observed when the reaction has gone to completion, and no phosphorus derivative remains in solution. The precipitate is solubilized in water and checked by \( ^{31}P \) NMR. It contains the water soluble dendrimer with six \( CH=CH-COOLi \) end groups, and (EtO)\(_2\)P(O)OLi. In order to separate the dendrimer from (EtO)\(_2\)P(O)OLi, formic acid is slowly added. A precipitate appears rapidly, and the mixture is acidified up to pH = 3-4. This value allows to maximize the amount of dendrimer 3e-[\( G_1 \)] which precipitates; lower pH values precipitates also (EtO)\(_2\)P(O)OH and induces the cleavage of the skeleton of the dendrimer. Compound 3e-[\( G_1 \)] thus obtained is soluble in several organic solvents such as tetrahydrofuran. This compound is characterized by all the techniques already used for the other dendrimers, and particularly by \( ^1H \) NMR, which indicates the formation of only one isomer for all the \( CH=CH \) bonds. The value of the chemical shift (two doublets at \( \delta = 6.56 \) and 7.74 ppm) and the value of the coupling constant (\( ^3J_{HH} = 16 \) Hz) correspond to the \( E \) isomer.

The use of two equivalents of butyl lithium has been extended then to the reaction involving the phosphonate derivatives of glycine (2f), L-alanine (2g), L-phenylalanine (2h), L-methionine
(2i), and dendrimer 1-[G₁] (Scheme 3). In all cases, water soluble dendrimers with 
HC=CHC(S)NHCHR′COOLi end groups (R′ = H, Me, CH₂Ph, CH₂CH₂SMe) are obtained 
but not isolated, then acidified to give in moderate yields dendrimers 3f-[G₁] – 3i-[G₁]. 
These dendrimers which possess six HC=CHC(S)NHCHR′COOH end groups are soluble in 
THF. ¹H and ¹³C NMR spectra of compounds 3f-[G₁] – 3i-[G₁] indicate in all cases the 
formation of both E and Z isomers of the carbon carbon double bonds. The presence of isomers 
is also detected on the level of N-H groups. The Z/E ratio, measured by integration of ¹H NMR 
spectra, is similar in all cases, roughly 10/90 (see Table 1 and Scheme 3). These compounds are 
stable in solution or as powders, provided the solvent is not totally eliminated. Indeed, the total 
removal of last traces of solvents causes the dendrimer to become impossible to solubilize again 
in organic solvents or in water. This phenomenon, which has not been observed for dendrimers 
3a-e, is presumably due to the formation of inter- and intra-molecular hydrogen bonds between 
NH and COOH groups.

The extension of the reaction to the third and fourth generation of the dendrimer has been carried 
out with the dilithium salts of phosphonates 2e-i in THF (Scheme 3). The dendrimer 
precipitates very often before the reaction has gone to completion. This can be seen easily when 
a sample of this precipitate is dissolved in water and checked by ³¹P NMR. Beside the signal at 
δ = 61.0-61.4 ppm, corresponding to the phosphorus of the external layer (P₃ or P₄) linked to 
two OC₆H₄CH=CHC(S)NHCHR′COOLi moieties, another singlet at δ = 60.5 ppm, 
corresponding to the external phosphorus linked to one OC₆H₄CHO and one 
OC₆H₄CH=CHC(S)NHCHR′COOLi moieties is observed. However, the reaction can be 
continued in heterogeneous conditions. In these conditions, the reaction rate is slower, but 
nevertheless the reaction goes to completion after several days. A work up similar to the one 
used for the first generation allows to isolate dendrimers 3e-[G₃], 3f-[G₄], 3g-[G₃], 3h- 
[G₄], and 3i-[G₄] (Figure 1). The absence of any signal corresponding to the CHO groups in 
¹H and ¹³C NMR, as well as in IR spectra confirms that all the branches of the dendrimer have 
reacted. ¹H NMR spectra indicate the formation of both E and Z isomers of the CH=CH bond 
for all the dendrimers having thioamide functions. A higher proportion of Z isomer is generally 
observed for the third and fourth generation than for the first generation (compare Z/E = 15/85
for 3g-[G3], 3i-[G4], and 35/65 for 3f-[G4], 3h-[G4], to Z/E = 10/90 for 3f-[G1] – 3i-[G1]).

The reasons of the variations observed for the Z/E ratio, particularly for the amino acid derivatives which differ only by one substituent in γ position relative to the reactive site (compounds 2f-i) are not fully understood. One may presume that steric crowding plays a role, as the Z proportion increases in most cases with the generation. Electronic effects also influence the Z/E ratio, as Z isomers are observed only when thioamide substituents are linked to the phosphonate (compounds 2c-d, 2f-i). Furthermore, the nature of the base used to generate the phosphonate salt is also an important factor. Indeed, the Z/E ratio measured for dendrimer 3g-[G1] generated from the reaction of 2g with one equivalent of triethylamine and one equivalent of sodium hydride is 30/70, whereas the Z/E ratio measured for the same dendrimer generated from the reaction of 2g with two equivalents of butyllithium is 10/90.

The presence of chiral amino acids on the surface of dendrimers could have induced interesting optical rotation properties, as we have already shown for dendrimers terminated with chiral methyl benzyl amine.14 Unfortunately, the formation of both E and Z isomers of the double bond for compounds 3f-[Gn] – 3i-[Gn] precludes any study in this field. However, this paper demonstrates that the use of the Horner-Wadsworth-Emmons reaction constitutes a new way of grafting various functional groups on the surface of dendrimers.

Experimental Section

General

All manipulations were carried out with standard high vacuum or dry argon atmosphere techniques. 1H, 31P and 13C NMR spectra were recorded on Bruker AC 80 and AC 200 spectrometers. 31P NMR chemical shifts are reported in ppm relative to 85% H3PO4. The numbering used for NMR is depicted on Scheme 4. Dendrimers 1-[G1] – 1-[G4]10 and phosphonates 2c,2d,2f-2i13 are synthesized according to published procedures. Phosphonates 2a, 2b, 2e are purchased from Aldrich. Satisfactory elemental analyses were obtained for all new compounds.
**General procedure for the synthesis of dendrimers 3a-[G₁] – 3d-[G₁], 3d-[G₃], and 3a-[G₄] – 3c-[G₄]:**

To a solution of phosphonate 2a-d (0.420 mmol) in THF (5 mL) was added NaH (0.420 mmol, 10 mg). The resulting mixture was stirred for 30 min. at room temperature. After evolution of H₂, a solution of dendrimer 3-[Gₙ] (n = 1, 0.070 mmol, 100 mg; n = 3, 0.0175 mmol, 130 mg; n = 4, 0.00875 mmol, 135 mg) in THF (5 mL) was added to the solution of the phosphonate salt at room temperature and stirred overnight (1-[G₁]) or for two days (1-[G₃], 1-[G₄]), then the solution was evaporated to dryness. The resulting powder was washed with water to eliminate (EtO)₂P(O)ONa and to afford compounds 3a-[G₁], 3b-[G₁], 3a-[G₄], and 3b-[G₄] which were obtained as white powders. Compounds 3c-[G₁], 3d-[G₁], 3c-[G₄], and 3d-[G₃] were recovered as yellow powders after purification by column chromatography on silica gel (eluent THF).

**General procedure for the synthesis of dendrimers with carboxylic acid end groups 3e-[G₁] – 3i-[G₁], 3e-[G₃], 3g-[G₃], 3f-[G₄], 3h-[G₄], and 3i-[G₄]:**

To a solution of phosphonate (0.420 mmol) in THF (5 mL) were added 2 equivalents of butyllithium 1.6 M (0.840 mmol, 530 µL) at -60°C. The resulting solution was stirred for 30 min. at this temperature. A solution of dendrimer 1-[Gₙ] (n = 1, 0.070 mmol, 100 mg; n = 3, 0.0175 mmol, 130 mg; n = 4, 0.00875 mmol, 135 mg) in THF (5 mL) was added to the solution of the phosphonate salt at this temperature, then the mixture was allowed to warm up to room temperature and stirred overnight (1-[G₁]) or for two days (1-[G₃], 1-[G₄]). A yellow precipitate appeared. A small sample of the precipitate was dissolved in water and checked by ³¹P NMR. If only one signal appeared for the phosphorus of the external layer (P₁ for [G₁], P₃ for [G₃], P₄ for [G₄]), all the precipitate was isolated by centrifugation and dissolved in water. If two signals appeared for the phosphorus of the external layer, the reaction has not gone to completion. In this case, the sample was thrown away and a small amount of butyllithium (10% of the initial quantity) was added to the heterogeneous mixture, which was stirred for two days more. Then, another small sample of the precipitate was taken, dissolved in water and
checked by $^{31}$P NMR, to verify that the reaction has gone to completion. The precipitate was then isolated by centrifugation and dissolved in water. In all cases, formic acid was added dropwise to lower the pH from 9 to 3-4 (the use of more acidic conditions induced the cleavage of the dendrimer). A yellow precipitate appeared at acidic pH; it was recovered by centrifugation. This precipitate was then washed with ether and afforded dendrimers $3\text{e}$$-[G_1]$ – $3\text{i}$$-[G_4]$, $3\text{e}$$-[G_3]$, $3\text{f}$$-[G_4]$, $3\text{g}$$-[G_3]$, $3\text{h}$$-[G_4]$, and $3\text{i}$$-[G_4]$ as yellow powders.

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| Table 1: |  |
|---|---|---|---|
| a-[G₄] | Yield (P₀), 51.7 | $^{31}\text{P NMR}$ | $^{1}\text{H NMR}$, $\delta$ (THF), $\delta$, $J$ (Hz) |
| a-[G₄] | 1.25 (m, 144H, CH₂-CH₃), 3.30 (d, $J = 8.6$, 135H, P₁₄-N-CH₃), 4.17 (m, 96H, CH₂-CH₃), 6.30 (d, $J = 15.9$, 61.0 (P₄), N-CH₃), 48H, CH=CH-CO), 7.00-7.60 (m, 465H, C₆H₆, CH=N), 62.0 (P₂), CH=CH-CO) | a 14.1 (s, CH₂-CH₃), 32.8 (d, $J = 13$, P₁₄-N-CH₃), 60.4 (s, CH₂-CH₃), 118.1 (s, CH=CH-CO), 121.7 (d, $J = 4$, C₀₂, C₁², C₂², C₃², C₄²), 128.1 (br s, C₀³, C₁³, C₂³, C₃³), 129.2 (s, C₄³), 131.6 (br s, C₄₄), 131.8 (br s, C₀⁴, C₁⁴, C₂⁴, C₃⁴), 138.5-139.0 (m, CH=N), 143.1 (s, CH=CH-CO), 150.5-150.7 (m, C₀₁, C₁¹, C₂¹), 151.3 (d, $J = 8$, C₃¹), 151.7 (d, $J = 8$, C₄¹), 166.6 (s, C=O) |
| b-[G₁] | Yield (P₀), 18.1 | $^{31}\text{P NMR}$ | $^{1}\text{H NMR}$, $\delta$ (THF), $\delta$, $J$ (Hz) |
| b-[G₁] | 1.31 (t, $J = 7.1$, 36H, CH₂-CH₃), 3.35 (d, $J = 10.6$, 9H, P₁₄-N-CH₃), 4.01-4.16 (m, 24H, CH₂-CH₃), 6.15 (dd, $J = 51.7$ (P₀), J = 17.3, 6H, CH=CH-P(O)), 7.18-7.77 (m, 39H, C₆H₆, CH=N), 61.1 (P₁), CH=CH-P(O)) | a 16.2 (d, $J = 7$, CH₂-CH₃), 32.9 (d, $J = 13$, P₁₄-N-CH₃), 61.7 (d, $J = 5$, CH₂-CH₃), 113.9 (d, $J = 191$, CH=CH-P(O)), 121.4 (d, $J = 4$, C₀₂), 121.7 (d, $J = 5$, C₁²), 128.3 (s, C₀³), 128.9 (s, C₁³), 131.8 (s, C₀⁴), 132.3 (d, $J = 4$, C₁¹), 138.7 (d, $J = 14$, CH=N), 147.3 (d, $J = 7$, CH=CH-P(O)), 151.0 (d, $J = 7$, C₀¹), 151.6 (d, $J = 7$, C₁¹) |
Table 1 (Continued):

b-[G₄] 37 18.1  

- 1.30 (t, J = 6.8, 288H, CH₂-CH₃), 3.31 (br d, J = 8.4, 135H, P₁₄-N-CH₃), 4.00-4.10 (m, 192H, CH₂-CH₃), 6.13 (P(O)), 51.7 (P₀), (dd, J = J = 17.5, 48H, CH=CH-P(O)), 7.19-7.67 (m, 61.2 (P₄), 465H, C₆H₄, CH=N, CH=CH-P(O))

61.6 (P₁), 61.7 (br s, P₂, P₁)

a 16.2 (d, J = 7, CH₂-CH₃), 32.8 (br d, J = 13, P₁₄-N-CH₃), 61.7 (d, J = 5, CH₂-CH₃), 113.9 (d, J = 192, CH=CH-P(O)), 121.7 (br d, J = 4, C₀², C₁², C₂², C₃², C₄²), 128.2 (br s, C₀³, C₁³, C₂³, C₃³), 128.9 (s, C₄³), 131.8 (d, J = 4, C₄⁴), 132.3 (br s, C₀⁴, C₁⁴, C₂⁴, C₃⁴), 139.0 (br d, J = 14, CH=CH), 147.3 (d, J = 5, CH=CH-P(O)), 151.2 (br d, J = 6, C₀¹, C₁¹, C₂¹, C₃¹), 151.6 (d, J = 7, C₄¹)

a 1.72 (br s, 36H, N-CH₂-(CH₂)₃), 3.35 (d, J = 10.6, 9H, P₁-N-CH₃), 3.73 (br s, 12H, N-CH₂), 4.28 (br s, 12H, N-CH₂), 6.20 (d, J = 12.0, (6*0.1)H, CH=CH-C(S)Z), 6.26 (d, J = 12.0, (6*0.1)H, CH=CH-C(S)Z), 7.14 (d, J = 15.0, (6*0.9)H, CH=CH-C(S)Z), 7.50 (d, J = 15.3, (6*0.9)H, CH=CH-C(S)Z), 7.11-7.75 (m, 39H, C₆H₄, CH=N)

a 24.0, 24.6, 25.3 [3s, N-CH₂-(CH₂)₃], 32.9 (d, J = 13, P₁-N-CH₃), 51.5 (s, N-CH₂), 51.6 (s, N-CH₂), 121.4 (d, J = 4, C₀²), 121.6 (d, J = 5, C₁²), 124.9 (s, CH=CH-C(S)Z), 126.0 (s, CH=CH-C(S)Z), 128.0 (s, CH=CH-C(S)Z), 128.3 (s, C₀³), 128.6 (s, C₁³), 132.4 (s, C₀⁴), 132.8 (s, C₁⁴), 138.5 (d, J = 14, CH=CH), 140.4 (s, CH=CH-C(S)Z), 150.9 (d, J = 7, C₁¹), 151.0 (d, J = 9, C₀¹), 193.9 (s, C=S), 194.6 (s, C=S)

C-[G₄] 25 51.6 (P₀), 61.4 (P₁)

- 1.65 (br s, 288H, N-CH₂-(CH₂)₃), 3.28 (d, J = 8.9, 135H, P₁₄-N-CH₃), 3.73 (br s, 96H, N-CH₂), 4.20 (br s, 96H, N-CH₂), 6.20 (br s, (96*0.1)H, CH=CH-C(S), CH=CH-C(S)Z), 6.91-7.65 (m, 369H, C₆H₄, CH=N), 6.94 (d, J = 15.0, (48*0.9)H, CH=CH-C(S)Z), 7.45 (d, J = 15.0, (48*0.9)H, CH=CH-C(S)Z)

a 24.2, 25.4, 26.8 [3s, N-CH₂-(CH₂)₃], 32.9 (m, P₁₄-N-CH₃), 51.6 (s, N-CH₂), 51.8 (s, N-CH₂), 121.7 (br s, C₀², C₁², C₂², C₃², C₄²), 125.5 (s, CH=CH-C(S)Z), 126.1 (s, CH=CH-C(S)Z), 128.3 (br s, C₀³, C₁³, C₂³, C₃³), 128.8 (s, C₄³), 129.0 (s, CH=CH-C(S)Z), 132.1 (br s, C₀⁴, C₁⁴, C₂⁴, C₃⁴), 132.9 (s, C₄⁴), 140.6 (s, CH=CH-C(S)Z), 138.9-139.2 (m, CH=N), 151.0 (d, J = 7, C₄¹), 151.3 (d, J = 6, C₀¹, C₁¹, C₂¹, C₃¹), 193.9 (s, C=S), 194.6 (s, C=S)
Table 1 (Continued):

<table>
<thead>
<tr>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-[G1] 20</td>
</tr>
<tr>
<td>d-[G3] 20</td>
</tr>
<tr>
<td>e-[G1] 15</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Table 1 (Continued):</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>e- [G₃] 15 51.8 (P₀), 61.0 (P₃), 61.5 (P₂), 61.9 (P₁)</td>
</tr>
<tr>
<td>3.53 (d, J = 10.2, 63H, P₁₋₃-N-CH₃), 6.60 (d, J = 16.0, 24H, CH=CH-CO)</td>
</tr>
<tr>
<td>7.25-7.96 (m, 201H, C₆H₄, CH=NH, OH), 7.77 (d, J = 16.0, 24H, CH=CH-CO)</td>
</tr>
<tr>
<td>b 32.9 (d, J = 13, P₁₋₃-N-CH₃), 119.3 (s, CH=CH-CO), 122.2 (d, J = 4, C₀, C₁, C₂, C₃), 128.5 (s, C₀, C₁, C₂, C₃), 128.6 (br s, C₁, C₂, C₃), 129.8 (s, C₁), 132.6 (s, C₃), 133.0 (br s, C₄), 133.1 (s, C₅), 133.6 (s, C₀), 140.2 (d, J = 13, CH=NX), 143.5 (s, CH=CH-CO), 152.1 (d, J = 6, C₀, C₁, C₂, C₃), 152.5 (d, J = 7, C₇, C₈), 167.4 (s, CO)</td>
</tr>
<tr>
<td>f- [G₁] 25 51.6 (P₀), 61.0 (P₁)</td>
</tr>
<tr>
<td>3.52 (d, J = 10.7, 9H, P₁-N-CH₃), 4.43 (d, J = 5.5, 12H, N-CH₂), 4.60 (d, J = 4.8, 12H, N-CH₂), 6.35 (d, J = 12.5, 6<em>0.1H, CH=CH-C(S)Z), 6.44 (d, J = 12.5, 6</em>0.1H, CH=CH-C(S)Z), 7.17 (d, J = 15.0, 6<em>0.9H, CH=CH-C(S)E), 7.38 (d, J = 7.7, 12H, C₁²H), 7.48 (d, J = 7.9, 6H, C₆²H), 7.69 (d, J = 8.4, 12H, C₁⁴H), 7.90 (d, J = 15.0, 6</em>0.9H, CH=CH-C(S)E), 7.95 (d, J = 7.7, 6H, C₆²H), 7.93 (br s, 9H, CH=NX, OH), 9.24 (br s, 6<em>0.9H, NH²E), 9.49 (br s, 6</em>0.1H, NH²Z)</td>
</tr>
<tr>
<td>b 32.9 (d, J = 12, P₁-N-CH₃), 47.2 (s, N-CH₂), 121.9 (d, J = 5, C₀, C₁²), 122.2 (d, J = 4, C₁²), 127.3 (s, CH=CH-C(S)Z), 128.1 (s, CH=CH-C(S)E), 128.9 (s, C₀, C₁²), 129.5 (s, C₁²), 131.7 (s, CH=CH-C(S)Z), 133.5 (s, C₁⁴), 133.7 (s, C₀⁴), 139.9 (d, J = 13, CH=NX), 140.4 (s, CH=CH-C(S)E), 151.9 (d, J = 9, C₀, C₁¹), 152.1 (d, J = 10, C₁¹), 170.3 (s, CO), 195.3 (s, C=S²E), 196.7 (s, C=S²Z)</td>
</tr>
<tr>
<td>f- [G₄] 10 51.7 (P₀), 61.0 (P₄), 61.2 (P₁, P₂), 61.6 (P₃)</td>
</tr>
<tr>
<td>3.46 (m, 135H, P₁₋₄-N-CH₃), 4.42 (d, J = 4.2, 96H, N-CH₂), 4.60 (d, J = 4.2, 96H, N-CH₂), 6.33 (d, J = 12.5, 6<em>0.35H, CH=CH-C(S)Z), 6.41 (d, J = 12.5, 6</em>0.35H, CH=CH-C(S)Z), 7.14 (d, J = 15.2, 6<em>0.35H, CH=CH-C(S)E), 7.00-7.90 (m, 465H+(48</em>0.65H), C₆H₄, CH=NX, CH=CH-C(S)E, OH), 9.26 (br s, 48<em>0.65H, NH²E), 9.49 (br s, 48</em>0.35H, NH²Z)</td>
</tr>
<tr>
<td>b 32.9 (m, P₁₋₄-N-CH₃), 46.5 (br s, N-CH₂), 121.6 (br s, C₀, C₁², C₁²), 121.9 (br s, C₂), 122.2 (br s, C₂), 127.4 (s, CH=CH-C(S)Z), 128.4 (s, CH=CH-C(S)E), 128.6 (m, C₀, C₁², C₁², C₂, C₃), 129.5 (br s, C₄, 131.6 (s, CH=CH-C(S)Z), 133.0 (br s, C₀, C₁², C₂, C₃, C₄), 140.5 (m, CH=NX, CH=CH-C(S)E), 150.7 (br s, C₀, C₁, C₂, C₃), 152.0 (d, J = 6, C₁²), 170.0 (s, CO), 197.5 (s, C=S²E), 198.4 (s, C=S²Z)</td>
</tr>
<tr>
<td>g-[G1]</td>
</tr>
<tr>
<td>Table 1 (Continued):</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>h-([G_4]) 10 51.6 (P), 61.4 (P), 61.9 (br s, P, p, P)</td>
</tr>
<tr>
<td>b 32.9 (d, (J = 14), P(_{1.4})-N-CH(_3)), 36.5 (br s, CH(_2)Ph), 58.9 (s, CH-CO), 121.6 (br s, C(_0)^2, C(_1)^2), 122.2 (br s, C(_2)^2, C(_3)^2, C(_4)^2), 127.0 (s, CH=CH-C(S)^E), 127.9 (s, CH=CH-C(S)^Z), 128.6 (br s, C(_0)^3, C(_1)^3, C(_2)^3, C(_3)^3, C(_4)^3, p-C(_6)H(_5)), 129.5 (s, o-C(_6)H(_5)), 129.9 (s, m-C(_6)H(_5)), 131.5 (s, CH=CH-C(S)^Z), 133.0 (br s, C(_0)^4, C(_1)^4, C(_2)^4, C(_3)^4, C(_4)^4), 137.4 (s, i-C(_6)H(_5)), 138.5-142.8 (m, CH=N, CH=CH-C(S)^E), 150.6 (m, C(_0)^1, C(_1)^1, C(_2)^1, C(_3)^1), 152.0 (d, (J = 7), C(_4)^1), 172.2 (br s, CO), 194.8 (s, C=S^E), 196.0 (s, C=S^Z)</td>
</tr>
<tr>
<td>i-([G_1]) 15 51.6 (P), 61.0 (P)</td>
</tr>
<tr>
<td>b 14.9 (s, S(_2)CH(_3)), 30.5 (s, CH(_2)S), 32.0 (s, CH-CH(<em>2)), 32.9 (d, (J = 12), P(</em>{1.1})-N-(CH_3)), 57.6 (s, CH-CH(_2)), 121.9 (d, (J = 4), C(_0)^2), 122.2 (d, (J = 5), C(_1)^2), 126.9 (s, CH=CH-C(S)^Z), 128.3 (s, CH=CH-C(S)^E), 128.9 (s, C(_0)^3), 129.5 (s, C(_1)^3), 131.7 (s, CH=CH-C(S)^Z), 133.5 (s, C(_1)^4), 133.7 (s, C(_0)^4), 140.0 (d, (J = 13), CH=N), 140.7 (s, CH=CH-C(S)^E), 151.8 (d, (J = 8), C(_0)^1), 152.1 (d, (J = 7), C(_1)^1), 173.2 (br s, CO), 195.1 (s, C=S^E), 198.5 (s, C=S^Z)</td>
</tr>
</tbody>
</table>
Table 1 (Continued):

<table>
<thead>
<tr>
<th>i-[G₄]</th>
<th>10</th>
<th>51.6 (P₀), 61.0 (P₄), 61.6 (P₁, P₂, P₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.15 (br s, 144H, SCH₃), 2.32 (m, 96H, CH-CH₂), 2.66 (m, 96H, CH₂S), 3.51 (d, J = 6.5, 135H, P₁₄-N-CH₃), 5.53 (m, 48H, CH-CH₂), 6.35 (m, (96<em>0.15)H, CH=CH-C(S)ₓ, CH=CH-C(S)ₓ), 7.04-7.86 (m, 465+(96</em>0.85)H, C₆H₄, CH=N, OH, CH=CH-C(S)ₓ, CH=CH-C(S)ₓ), 9.40 (br s, (48<em>0.85)H, NHₓ), 9.50 (br s, (48</em>0.15)H, NHₓ)</td>
</tr>
</tbody>
</table>

|        | 7 | 14.9 (s, SCH₃), 30.6 (m, CH₂S), 31.0 (m, CH-CH₂), 32.9 (m, P₁₄-N-CH₃), 57.0 (m, CH-CH₂), 121.6 (m, C₀ₓ, C₁ₓ, C₂ₓ, C₃ₓ), 122.2 (br s, C₄ₓ), 127.0 (s, CH=CH-C(S)ₓ), 128.6 (br s, CH=CH-C(S)ₓ), C₀ₓ, C₁ₓ, C₂ₓ, C₃ₓ, 129.5 (br s, C₄ₓ), 131.5 (s, CH=CH-C(S)ₓ), 133.1 (br s, C₀ₓ, C₁ₓ, C₂ₓ, C₃ₓ, C₄ₓ), 140.8 (m, CH=N, CH=CH-C(S)ₓ), 150.7 (d, J = 7, C₀ₓ, C₁ₓ, C₂ₓ, C₃ₓ), 152.0 (br s, C₄ₓ), 168.3 (br s, CO), 195.0 (s, C=Sₓ), 198.5 (s, C=Sₓ) |

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a in CDCl₃
b in THF D₈
Z Z-isomers
E E-isomers
Scheme 1
Scheme 2
\[ \text{Et-}\text{O-} \overset{\text{O}}{\text{P-CH}_2-Y-\text{COOH}} \]
\[ \overset{\text{Et-}}{\text{O-}} \overset{\text{2e-i}}{ \text{Et-} \overset{\text{O-}}{\text{P-CH}_2-Y-\text{COOH}} } \]

\[ 2 \text{ BuLi} \]

\[ 1-[G_1], 1-[G_3], 1-[G_4] \]

\[ \overset{\text{H}}{\text{C=}} \overset{\text{Y-COO\text{Li}^\text{+}}}{\text{C-}} \overset{\text{H}}{\text{Li}^\text{+}} \]

\[ \text{HCOOH} \]

\[ 3e-[G_n] \rightarrow 3i-[G_n] \]

\[ x: 6 \text{ for } [G_1], 24 \text{ for } [G_3], 48 \text{ for } [G_4] \]

<table>
<thead>
<tr>
<th>3 (% of Z isomer)</th>
<th>e-[G_1] (0)</th>
<th>f-[G_1] (10)</th>
<th>e-[G_3] (0)</th>
<th>f-[G_3] (15)</th>
<th>e-[G_4] (35)</th>
<th>f-[G_4] (35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y-COOH</td>
<td>O</td>
<td>O</td>
<td>C-O-H</td>
<td>C-O-H</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>g-[G_1] (10)</td>
<td>h-[G_1] (10)</td>
<td>i-[G_1] (10)</td>
<td>g-[G_3] (15)</td>
<td>h-[G_3] (35)</td>
<td>i-[G_3] (15)</td>
<td>i-[G_4] (15)</td>
</tr>
</tbody>
</table>

Scheme 3
Numbering used for NMR:

Scheme 4
1-[G₄]

Figure 1