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Phosphorus dendrimers as new tools to deliver active substances

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Abstract—An active substance having pesticide properties is linked to the surface of phosphorus-containing dendrimers through a linker. Depending on the chemical stability of the linker towards hydrolysis, the release of the active substance can be controlled.

The concept of using dendrimers as new types of carriers of active substances was propound until the very beginning of the research in the field of dendrimers chemistry.[1] Several ways can be imagined to achieve this purpose; for instance, the active substance can be encapsulated within the dendrimer (Fig. 1**A**), or entrapped within a network composed of dendrimers (Fig. 1**B**), or linked to the surface of the dendrimer through a labile bond (Fig. 1**C**) or through a stable bond (Fig. 1**D**).

The term 'active substance' may be applied to any type of molecule having a particular property, for instance to drugs, pesticides, perfumes, dyes, etc. After our paper reporting type **B** interactions between dendrimers and various active substances,[2] we wish to relate here our first investigations concerning the use of phosphorus-containing dendrimers[3] as supports of types **C** and **D** for pesticides.

The main problem in obtaining type **C** or **D** compounds is that the active substance must have at least one functional group available for grafting to the dendrimer. However, even if most pesticides have functional groups, they are generally only slightly reactive or, indeed, non-reactive. Such behaviour can be illus-

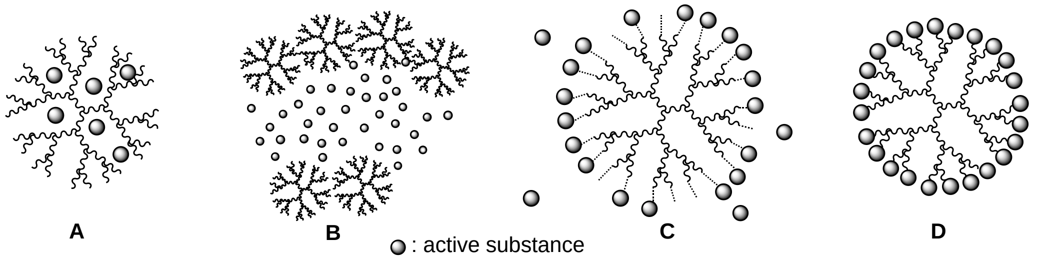
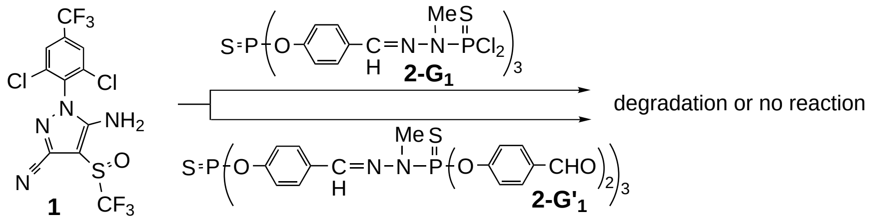


Figure 1.



Scheme 1.

Keywords: dendrimers; pesticides; phosphorus compounds; hydrazones; imines.

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trated with the insecticide **1** (fipronil[4]). Its NH_2 function does not react in substitution reactions with dendrimer **2-G$_1$** ($P(S)Cl_2$ end groups) or in condensation reactions with **2-G$'_1$** (CHO end groups)[3] (Scheme 1). Whatever the solvent, the temperature, the type of acid or base used either no reaction or degradation is observed.

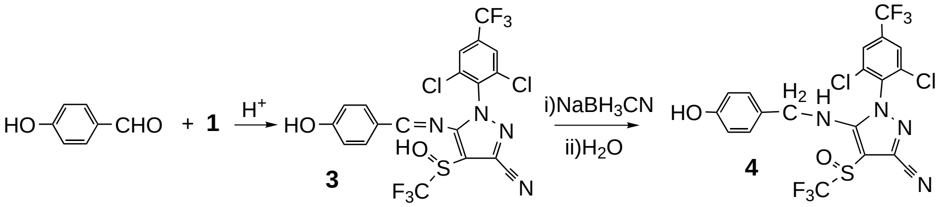
Thus, it appeared necessary to use a difunctional linker between **1** and the dendrimer **2-G$_1$**. In spite of the failure met with **2-G$'_1$**, we decided to try hydroxybenzaldehyde as a linker. Indeed, it should be easier to use drastic conditions with hydroxybenzaldehyde than with the dendrimer and, in case of uncompleted reactions, the purification will be easier. However, **1** does not react with hydroxybenzaldehyde, even in forced conditions (in refluxing toluene or at 180°C without solvent). After a lot of unsuccessful attempts, we finally succeeded by using a strongly acidic resin (Dowex) in refluxing toluene. The reaction never goes to completion, but imine **3**[5] is isolated in low yield (20%) by crystallisation in acetonitrile. The imine bond of **3** is very sensitive towards hydrolysis, but it is easily reduced by $NaBH_3CN$ to afford the stable amine **4**[5] (Scheme 2).

Type **C** dendrimers are obtained by reacting the sodium salt of **3** (**3-Na**[5]) with **2-G$_n$**. These reactions were carried out with first and fourth generations of the dendrimer ($n=1$ and 4) (Scheme 3). As expected, the imine bonds remain sensitive towards hydrolysis after the grafting of **3** to the dendrimer. Thus, compounds **5-G$_n$**[5] are able to gradually release fipronil. Surprisingly, the rate of this release is higher for the fourth generation than for the first one.

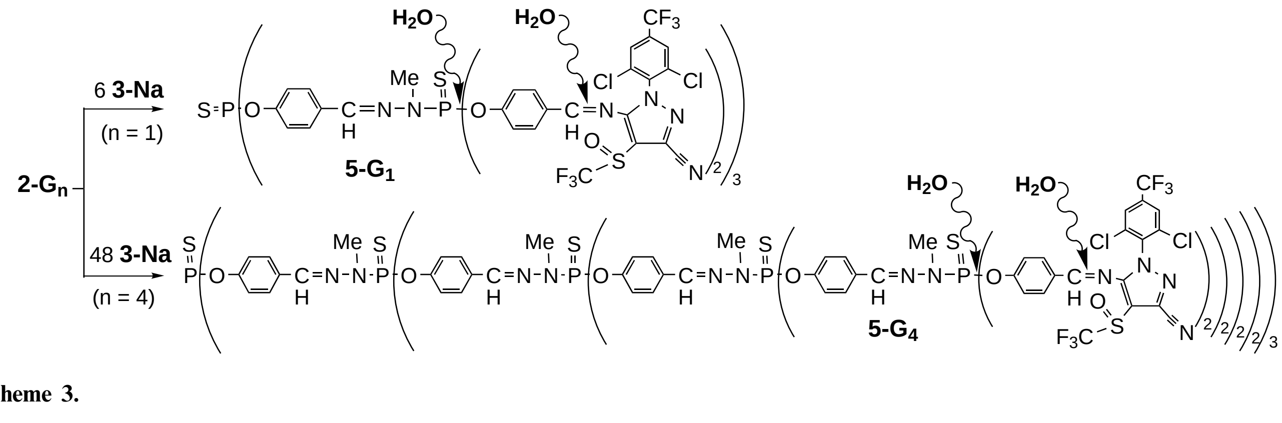
Keeping compounds **5-G$_n$** as powders in contact with air for 35 days induces the release of 12% of fipronil from **5-G$_1$** and 37% from **5-G$_4$** (ratio free fipronil/total fipronil, measured by ^1H NMR). Unexpectedly, a second way of release is also observed, induced by the hydrolysis of the P–O bonds, regenerating compound **3**. We had never observed previously such behaviour, even though we already grafted a lot of phenol derivatives to the surface of phosphorus-containing dendrimers.[6] Thus, fipronil induces a destabilisation of the periphery of the dendrimer, as emphasised by the fact that the other P–OAr bonds of the skeleton of **5-G$_n$** remain intact.

Compounds **5-G$_n$** are very difficult to keep pure even under argon; it means that they could be too sensitive for practical uses. Thus, it appeared important to test the reactivity of the stable compound **4** towards dendrimers. Type **D** dendrimers are easily obtained by reacting the sodium salt of **4** (**4-Na**,[5] synthesised by reaction of 1 equiv. of NaH with the phenol part of **4**) with **2-G$_n$** ($n=1$ and 4) (Scheme 4). Dendrimers **6-G$_n$**[5] are isolated in very good yields as powders. The ^{31}P NMR chemical shift of the most external phosphorus compares well with those found for **5-G$_n$** and confirms that the fipronil derivative is linked exclusively to the dendrimer through a P–O bond (and not through a P–N bond). Compounds **6-G$_n$** present a certain persistence of the pesticide activity. They are much less sensitive towards hydrolysis than **5-G$_n$** and can be kept as a powder for months, at least, in an inert atmosphere and for weeks in air without decomposition. However, the presence of benzylic functions should induce a long-term release of fipronil.

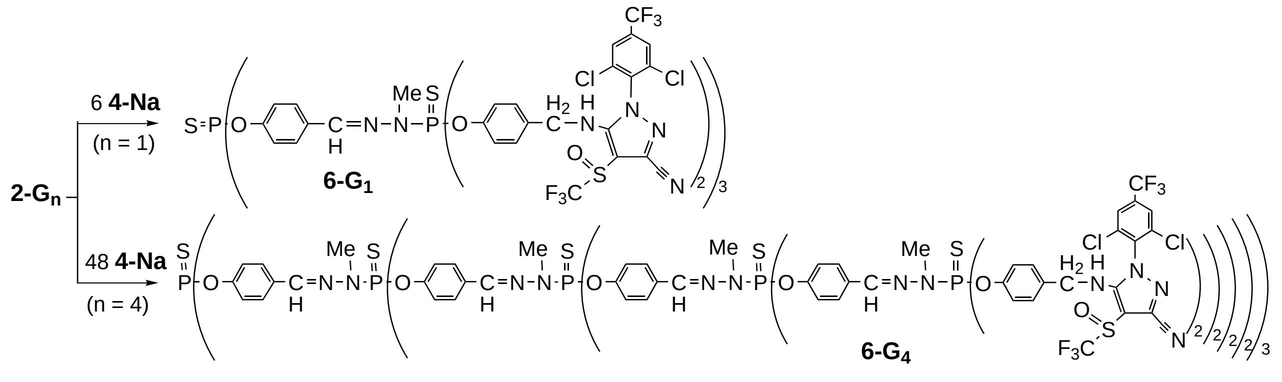
This work opens new perspectives for the controlled-release of active substances. Indeed, we have shown, as expected, that the rate of release depends on the type of linker used and, more surprisingly, that it also depends



Scheme 2.



Scheme 3.



Scheme 4.

on the generation (the size) of the dendrimer. Work is in progress to control the persistence of the pesticide activity in the course of time for both series of compounds and to apply these methods to other types of active substances.

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4. Fipronil, property of the Aventis CropScience company.
5. Compound **3**: 1.8 equiv. of hydroxybenzaldehyde, 1 equiv. of fipronil and 1 equiv. of Dowex 50WX8-400 were heated in toluene (reflux) in a Dean–Stark tube for 24 h. After filtration and evaporation, **3** was isolated in 20% yield by crystallisation in acetonitrile. Compound **3-Na**: a stoichiometric amount of NaH was added to a solution of **3** in THF at room temperature and stirred overnight. **3-Na** was obtained in quantitative yield and directly used to react with the dendrimer. Compound **4**: 1.5 equiv. of $\mathrm{NaBH_3CN}$ was added to a solution of **3** in THF. The mixture was stirred overnight at room temperature, then water was added. The mixture was stirred again for 4 h, filtered, and evaporated to dryness. The resulting powder was extracted with chloroform; the solution was recovered and evaporated to dryness to afford **4** in 78% yield. Compound **4-Na**: same procedure as for **3-Na**. Compound **5-G$_1$**: 6 equiv. (+5%) of **3-Na** and 1 equiv. of **2-G$_1$** were stirred overnight at room temperature in THF. The solvent was evaporated and the resulting powder was washed several times with ether to afford **5-G$_1$** in 85% yield. Compound **5-G$_4$**: same procedure as for **5-G$_1$**, with 48 equiv. of **3-Na**; 84% yield. Compound **6-G$_1$**: same procedure as for **5-G$_1$**, with 6 equiv. of **4-Na**; 87% yield (see Fig. 2 for the numbering used for NMR). $^{31}\mathrm{P}\{^{1}\mathrm{H}\}$ NMR ($\mathrm{CDCl_3}$): 51.6 (s, $\mathrm{P_0}$), 62.2 (s, $\mathrm{P_1}$). $^{1}\mathrm{H}$ NMR ($\mathrm{CDCl_3}$): 3.35 (d, $^{3}J_{\mathrm{HP}}=11$ Hz, 9H, $\mathrm{CH_3}$), 4.09 (br s, 12H, $\mathrm{CH_2}$), 6.41 (br s, 6H, NH), 6.89 (d, $^{3}J_{\mathrm{HH}}=8.5$ Hz, 12H, $\mathrm{C^2H}$), 7.05 (d, $^{3}J_{\mathrm{HH}}=8.5$ Hz, 12H, $\mathrm{C^3H}$), 7.30 (d, $^{3}J_{\mathrm{HH}}=8.0$ Hz, 6H, $\mathrm{C_0{}^2H}$), 7.60 and 7.62 (2 s, 12H, $\mathrm{C_6H_2}$), 7.66 (s, 3H, CH=N), 7.76 (d, $^{3}J_{\mathrm{HH}}=8.0$ Hz, 6H, $\mathrm{C_0{}^3H}$). $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR ($\mathrm{CDCl_3}$): 32.9 (d, $^{2}J_{\mathrm{CP}}=14$ Hz, $\mathrm{CH_3}$), 47.3 (s, $\mathrm{CH_2}$), 110.2 (s, C≡N), 121.5 (d, $^{3}J_{\mathrm{CP}}=4$ Hz, $\mathrm{C_0{}^2}$), 121.7 (q, $^{1}J_{\mathrm{CF}}=274$ Hz, $\mathrm{CF_3Ar}$), 121.8 (d, $^{3}J_{\mathrm{CP}}=4$ Hz, $\mathrm{C^2}$), 125.4 (q, $^{1}J_{\mathrm{CF}}=337$ Hz, $\mathrm{CF_3SO}$), 126.1 (br s, N=$\underline{\mathrm{C}}$-C≡N and CHAr), 126.6 (s, $\underline{\mathrm{C}}$=C-SO), 127.3 (s, $\mathrm{C^3}$), 128.4 (s, $\mathrm{C_0{}^3}$), 132.6 (s, $\mathrm{C_0{}^4}$), 133.2 (s, $\mathrm{C^4}$), 134.8 (q, $^{2}J_{\mathrm{CF}}=35$ Hz, $\underline{\mathrm{C}}$-$\mathrm{CF_3}$), 136.0 (s, C-SO), 136.5 (s, C-Cl), 138.8 (d, $^{3}J_{\mathrm{CP}}=13$ Hz, CH=N), 150.3 (d, $^{2}J_{\mathrm{CP}}=7$ Hz, $\mathrm{C^1}$), 151.2 (d, $^{2}J_{\mathrm{CP}}=8$ Hz, $\mathrm{C_0{}^1}$), 151.6 (s, N-CAr). $^{19}\mathrm{F}$ NMR ($\mathrm{CDCl_3}$): −74.0 (s, $\mathrm{CF_3SO}$), −63.2 (s, $\mathrm{CF_3Ar}$). IR (KBr): 2255 (C≡N). Anal. calcd for $\mathrm{C_{138}H_{78}Cl_{12}F_{36}N_{30}O_{15}P_4S_{10}}$ (3950.3): C, 41.96; H, 1.99; N, 10.63. Found: C, 42.21; H, 2.07; N, 10.54. Compound **6-G$_4$**: same procedure as for **5-G$_1$**, with 48 equiv. of **4-Na**; 90% yield. $^{31}\mathrm{P}\{^{1}\mathrm{H}\}$ NMR ($\mathrm{CD_3CN}$): 51.7 (s, $\mathrm{P_0}$), 61.8 (br s, $\mathrm{P_1}$, $\mathrm{P_2}$, $\mathrm{P_3}$), 62.2 (s, $\mathrm{P_4}$). $^{1}\mathrm{H}$ NMR ($\mathrm{CD_3CN}$): 3.3 (m, 135H, $\mathrm{CH_3}$), 4.26 (d, $^{2}J_{\mathrm{HH}}=16$ Hz, 48H, $\mathrm{CH_2}$), 4.46 (d, $^{2}J_{\mathrm{HH}}=16$ Hz, 48H, $\mathrm{CH_2}$), 5.2 (br s, 48H, NH), 7.10–8.20 (m, 513H, $\mathrm{C_6H_4}$, $\mathrm{C_6H_2}$, CH=N). $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR ($\mathrm{CD_3CN}$): 34.1 (br d, $^{2}J_{\mathrm{CP}}=12$ Hz, $\mathrm{CH_3}$), 49.1 (s, $\mathrm{CH_2}$), 113.0 (s, C≡N), 122.9 (br s, $\mathrm{C_0{}^2}$, $\mathrm{C_1{}^2}$, $\mathrm{C_2{}^2}$, $\mathrm{C_3{}^2}$, $\mathrm{C^2}$), 123.7 (q, $^{1}J_{\mathrm{CF}}=274$ Hz, $\mathrm{CF_3Ar}$), 126.9 (q, $^{1}J_{\mathrm{CF}}=334$ Hz, $\mathrm{CF_3SO}$), 127.6 (s, $\underline{\mathrm{C}}$=C-SO), 128.2 (br s, N=$\underline{\mathrm{C}}$-C≡N and CHAr), 129.6 (br s, $\mathrm{C_0{}^3}$, $\mathrm{C_1{}^3}$, $\mathrm{C_2{}^3}$, $\mathrm{C_3{}^3}$, $\mathrm{C^3}$), 133.8 (s, $\mathrm{C_0{}^4}$, $\mathrm{C_1{}^4}$, $\mathrm{C_2{}^4}$, $\mathrm{C_3{}^4}$), 135.6 (s, $\mathrm{C^4}$), 135.6 (q, $^{2}J_{\mathrm{CF}}=35$ Hz, $\underline{\mathrm{C}}$-$\mathrm{CF_3}$), 136.4 (s, C-SO), 137.9 and 138.0 (2 s, C-Cl), 141.7 (m, CH=N), 151.3 (d, $^{2}J_{\mathrm{CP}}=6$ Hz, $\mathrm{C^1}$), 152.1 (s, N-CAr), 152.7 (br d,

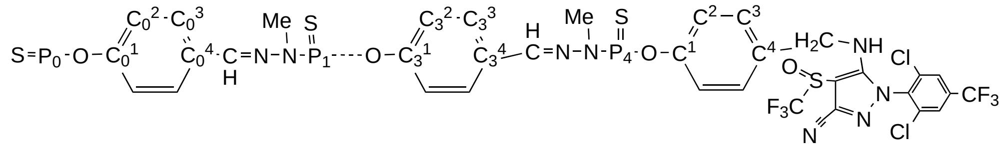

Figure 2. Numbering scheme used for NMR.

$^2J_{CP}=6$ Hz, $C_0{}^1$, $C_1{}^1$, $C_2{}^1$, $C_3{}^1$). ^{19}F NMR (CD_3CN): −73.9 (s, CF_3SO), −63.1 (s, CF_3Ar). IR (KBr): 2255 (C≡N). Anal. calcd for $C_{1272}H_{792}Cl_{96}F_{288}N_{282}O_{141}P_{46}S_{94}$ (35596): C, 42.92; H, 2.24; N, 11.09. Found: C, 43.21; H, 2.35; N, 10.91.

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