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Thioacylation Reactions for the Surface Functionalization of Phosphorus-Containing Dendrimers

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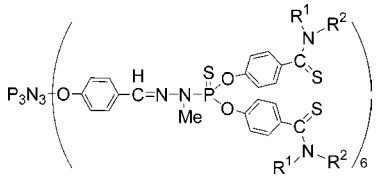
ABSTRACT



The functionalization of phosphorus-containing dendrimers was easily achieved through thioacylation reactions involving new dendrimers capped with dithioester end groups and various functionalized amines. These reactions were successfully applied to the first generation (12 end groups) and the third generation of the dendrimer (48 end groups) and allowed their functionalization by various primary or secondary amines, alcohols, glycols, and azides.

Dendrimers are highly branched and regular macromolecules possessing a large number of unique properties.[1] The synthesis of dendrimers (convergent or divergent) is now well documented even if the search for new improvements is still active, as we recently exemplified.[2] Considerable effort has been devoted also to the functionalization of the periphery of dendrimers to explore new properties and applications. Indeed, the properties of these compounds mainly depend on the type of functional end groups they bear. The type of end groups most generally used for further functionalizations is limited; one can cite mainly NH_2 end groups, and to a lesser extent CO_2H, CHO, P−Cl, and Si−H. One of the common properties of all these end groups is that they are able to react with large classes of easily available (often commercial) functionalized compounds. The other property shared by all these end groups is that they are directly obtained during the normal process of synthesis of dendrimers at each generation. To expand the type of functional groups on the periphery of dendrimers, it is desirable to introduce new types of end groups possessing a high potential of reactivity, even if they are not directly available from the normal process. Ideally, the functionalization should be done in an easy and single step, without any modification of the general methods used for the synthesis and the growth of the dendrimers.

According to these two main considerations, we turned our attention toward the use of dithioesters as end groups on the surface of dendrimers. Dithioesters are well-known to react easily and rapidly with amines (non aromatic); moreover, the thioacylation reaction tolerates a broad variety of other functional groups (such as hydroxyl and carboxyl), and the only byproduct of the reaction is a thiol which can be easily removed during the purification step.[3] Thus, we

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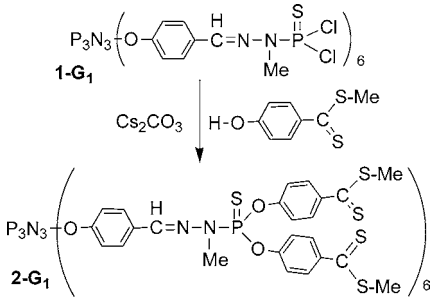
thought that dithioester functionalities should offer a large number of possibilities to graft new functional groups. To the best of our knowledge, dithioester groups were never grafted previously on the surface of any dendrimer. Only the sodium salt of dithiocarbamates were reported by Welton et al. as end groups of PAMAM dendrimers and used for the covalent bonding of metal complexes (Ru).[4]

The type of dendrimers we use in the present work is based on the first method of synthesis of neutral phosphorus-containing dendrimers we reported.[5] It consists of condensation reactions between aldehydes and hydrazides, followed by nucleophilic substitutions on $P(S)Cl_2$ end groups with 4-hydroxybenzaldehyde in basic conditions. Depending on the step considered, these dendrimers have either aldehydes or $P(S)Cl_2$ as reactive end groups. To preserve the general structure and the nature of the backbone of these phosphorus dendrimers during the introduction of the dithioester moieties, we chose *S*-methyl-4-hydroxydithiobenzoate[6] to replace 4-hydroxy benzaldehyde. Thus, with Cs_2CO_3 as base in THF, the phenol linked to the dithioester function is successfully reacted with dendrimers bearing $S{=}PCl_2$ end groups. The reaction is first carried out with the first-generation **1-G$_1$**,[7] leading to compound **2-G$_1$**, isolated in 95% yield as a bright red powder (Scheme 1).

Scheme 1. Grafting of the Dithioester Functions on the Surface of the First-Generation Dendrimer **1-G$_1$**



The same reaction is then applied to the third generation; the reaction is slightly slower than with the first generation, but it affords cleanly dendrimer **2-G$_3$**, which possesses 48 dithioester end groups (Scheme 2). The completion of the reaction is monitored by ^{31}P NMR, which displays a slight deshielding of the phosphorus end groups from $\delta = 63.0$ ppm for **1-G$_3$**[7] to $\delta = 63.9$ ppm for **2-G$_3$**. This dendrimer is isolated in 90% yield, also as a bright red powder.

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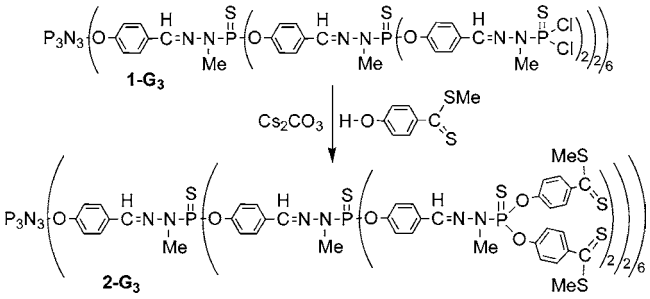
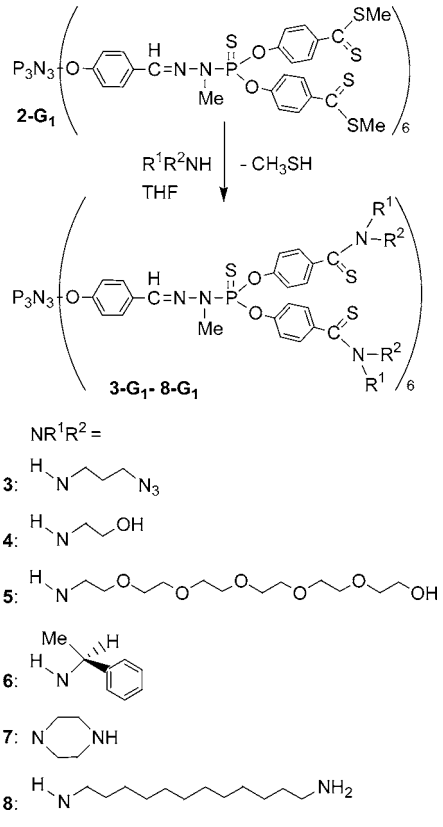
Scheme 2. Grafting of the Dithioester Functions on the Surface of the Third-Generation Dendrimer **1-G$_3$**



As expected, these new phosphorus-containing dendrimers capped with dithioester end groups react cleanly, quantitatively, and rapidly in thioacylation reactions (Scheme 3). Various functionalized amines (**3**−**8**) were selected for this study to determine the scope of this reaction (use of primary and secondary amines) and its compatibility with the presence of other functional groups.

Scheme 3. Thioacylation Reactions with Variously Functionalized Primary or Secondary Amines on the Surface of the First-Generation Dendrimer **2-G$_1$**



The experimental conditions used for the thioacylation reactions depend on the second function borne by the amine. In the case of monoamines possessing an azido (**3**), alcoholic (**4**, **5**), or chiral group (**6**), a moderate excess of the neat

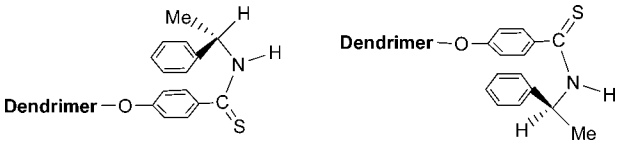


Figure 1. Possible isomers for the π-stacking of end groups for **6-G$_1$**.

amine (10−50% excess) is added to a solution of dendrimer (method A in Table 1). In the case of bis-amino derivatives (**7**, **8**), a reverse dropwise addition of a highly diluted solution of dendrimer onto a large excess of amine is used to avoid intra- and/or intermolecular cross-coupling reactions (method B in Table 1).

All reactions were first applied to the first-generation dendrimer **2-G$_1$**. They proceed quantitatively, generally within a few hours. All compounds remain soluble during the reaction, even in the case of difunctional amines. This behavior shows that there is no bridging between end groups, even when amino alcohols are used in a stoichiometric amount. Indeed, bridging would lead to insoluble materials, which are observed when stoichiometric amounts of diamines are used. The progress of reactions is monitored by ^{31}P NMR on the crude mixture, which displays in all cases a slight but clearly detectable deshielding of the signal corresponding to the end groups. The functionalized dendrimers **3-G$_1$**−

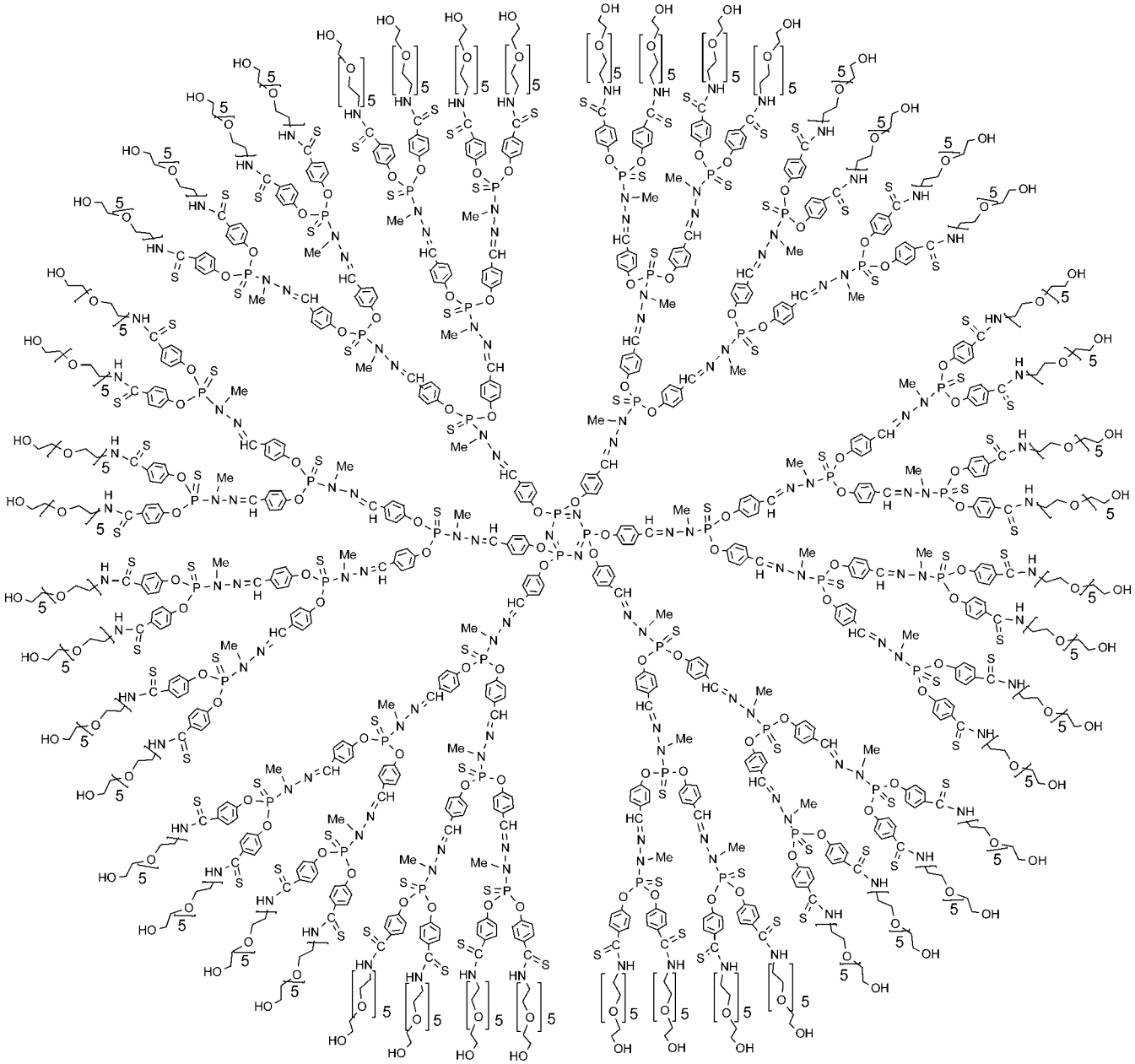


Figure 2. Third-generation dendrimer having 48 thioamidoglycol functions as end groups.

Table 1. Thioamide Synthesis According to Scheme 3[a]

product	amine	equiv of amine/ CS_2Me function	yield (%)	method
3-G$_1$	**3**: $H_2NCH_2CH_2CH_2N_3$[8]	1.35	86	A
4-G$_1$	**4**: $H_2NCH_2CH_2OH$	1.5	96	A
4-G$_3$	**4**: $H_2NCH_2CH_2OH$	40	67	A
5-G$_1$	**5**: $NH_2(CH_2CH_2O)_6H$[9]	1.6	61	A
5-G$_3$	**5**: $NH_2(CH_2CH_2O)_6H$	25	50	A
6-G$_1$	**6**: (*S*)-(−)α-methylbenzylamine	1.2	98	A
7-G$_1$	**7**: piperazine	111	73	B
8-G$_1$	**8**: $H_2N(CH_2)_{12}NH_2$	64	47	B

[a] Method A: a slight excess of amine is added onto a concentrated solution of dendrimer in THF or $CHCl_3$. Method B: a highly diluted solution of dendrimer in THF is added dropwise on a large excess of amine in a small volume of THF (yields are not optimized).

8-G$_1$ are isolated in moderate to high yields after purification, depending on the facility with which excesses of reagents can be eliminated. When a large excess of amine had to be used (method B) the purification was performed by iterative "washing" of the dendrimer with the appropriate solvent. In this way, when using 1,12-diaminododecane we were able to recover 96% of the excess of amine, which can be reused. Due to the process, despite a complete and selective reaction according to ^{31}P NMR of the crude mixture, a moderate yield of **8-G$_1$** is obtained with 1,12-diaminododecane.

Dendrimers **3-G$_1$**−**8-G$_1$** are mainly characterized by multinuclear NMR. Besides the ^{31}P NMR data already mentioned, ^{13}C NMR also appears as a valuable tool, since the thioacylation reaction induces a shielding of the signal corresponding to the C═S group from 227.3 ppm for **2-G$_1$** to ca. 197 ppm for **3-G$_1$**−**8-G$_1$**.[10] A special feature is observed on the ^{13}C NMR spectrum of **4-G$_1$**, which indicates the presence of two isomers in a 2/1 ratio for the signal corresponding to C═S (197.9 and 198.1 ppm) and CH_2N (49.8 and 49.9 ppm). This particular behavior might be ascribed to the occurrence (or not) of hydrogen bonding between O−H···S═C, forming a seven-membered ring. This phenomenon is not observed with the long-chain aminoglycol **5**. The presence of isomers is also detected on the ^{13}C NMR spectrum of **6-G$_1$**, in a 1/1 ratio. Contrary to **4-G$_1$**, most signals are concerned with this isomery, particularly in the aromatic region. Thus, this phenomenon might be due to two types of π-stacking occurring between O−C_6H_4CS and C_6H_5 (relative position of Me, NH and C═S) (Figure 1).

These methodologies are further extended to the third generation of phosphorus-containing dendrimer **2-G$_3$**. The dithioester functions are reacted with the aminoethanol **4** affording dendrimer **4-G$_3$**. As expected, a slight broadening of the signals precludes the observation of isomers in this case. The aminoglycol **5** was also reacted with **2-G$_3$**, affording dendrimer **5-G$_3$** (Figure 2). Despite the 48 glycol functions, dendrimer **5-G$_3$** was not soluble in pure water, but it is soluble in mixtures of water−organic solvent.

In conclusion, phosphorus-containing dendrimers bearing dithioester end groups are useful tools for further functionalizations of the surface. The thioacylation reactions proceed quantitatively and selectively in the presence of other functional groups, even in the case of di-amino derivatives. The amines we have used allow the grafting of primary or secondary amines, azides, alcohols, or glycols, which could be used for further functionalizations. Furthermore, taking into account the huge number of functionalized amines that exist, this method opens the way to new and versatile functionalizations of the surface of dendrimers.

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Supporting Information Available: Synthetic details and characterization of all dendrimers (**2-G$_1$**, **2-G$_3$**, **3-G$_1$**, **4-G$_1$**, **4-G$_3$**, **5-G$_1$**, **5-G$_3$**, **6-G$_1$**, **7-G$_1$**, **8-G$_1$**). ^{31}P NMR spectra of **2-G$_1$**, **2-G$_3$**, **4-G$_1$**, **5-G$_3$**, **6-G$_1$**. ^{1}H NMR spectra of **2-G$_1$**, **4-G$_1$**, **6-G$_1$**. ^{13}C NMR spectra of **2-G$_1$**, **2-G$_3$**, **4-G$_1$**, **5-G$_3$**, **6-G$_1$**. This material is available free of charge via the Internet at http://pubs.acs.org.

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