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Cationic and Fluorescent "Janus" Dendrimers

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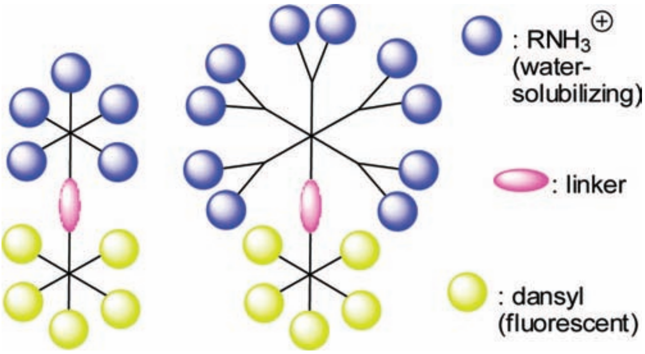
ABSTRACT



Two synthetic routes to "Janus"-type dendrimers possessing ammonium groups on one side and fluorescent dansyl derivatives on the other side are described. These surface-block dendrimers are obtained by the coupling of two different dendrons, built from the hexafunctional cyclotriphosphazene core. Their characterization and their photophysical behavior are reported. The largest compound possesses 10 ammonium groups and 5 dansyl groups; it is potentially useful as a fluorescent label in materials science and biology.

The art of designing dendritic macromolecules progresses toward the synthesis of more and more sophisticated compounds,[1] including those having several types of terminal groups, precisely placed in different areas of the surface. Such compounds can be called "Janus" or surface-block dendrimers. Examples of the synthesis of some of these compounds have already been described,[2] often for using them for self-assembly[3] or as liquid crystals.[4] However, to the best of our knowledge, there is no example to date of surface-block dendrimers bearing fluorescent entities on one side and water-solubilizing functions on the other, which should be useful for labeling materials or biological entities.

The key point for the synthesis of such dendrimers is the coupling of two different dendrons by their core. This strategy is relatively difficult to apply when dealing with reactive terminal groups, due to problems of compatibility with the core functionality. Another problem is the relatively small number of terminal groups for low-generation dendrons: one arm is for future coupling and not for growing, thus it is necessary to build relatively high generations to

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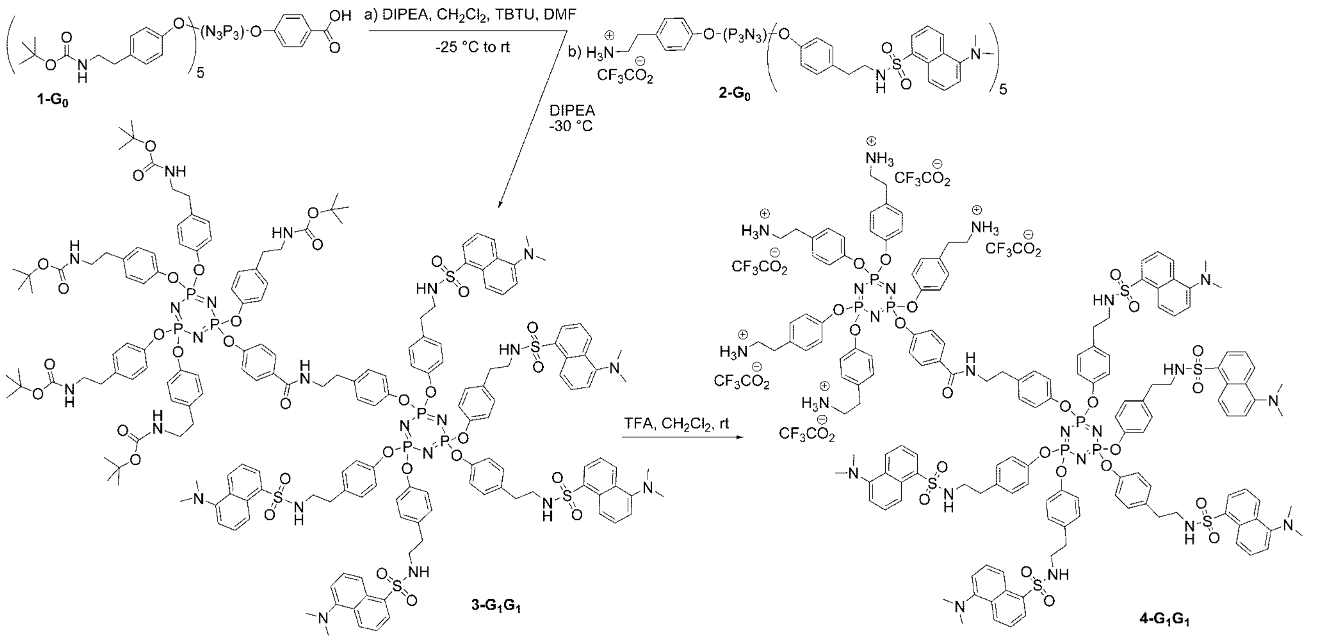
Scheme 1



have a significant number of functional groups. We report here for the first time the use of dendrons built from the hexafunctional cyclotriphosphazene core to rapidly multiply the number of terminal groups.

The strategy is based on the nonsymmetrical functionalization of hexachlorocyclotriphosphazene ($N_3P_3Cl_6$) to synthesize AB_5 (or AB_{5n})[5] type compounds, where A is the function usable for the coupling with another dendron and B is the functional terminal group; thus, five functions remain available for growing, instead of two for "classical" dendrons.

The first strategy is based on peptidic coupling of two dendrons by their core. Dendrons **1-G$_0$** and **2-G$_0$** are designed for this purpose, both elaborated from $N_3P_3Cl_6$.[6] The former possesses five amino groups protected by *tert*-butyloxycarbonyl (Boc) groups and one carboxylic acid function, and the latter possesses five dansyl derivatives and one primary ammonium group. We choose dansyl as the fluorescent label since it was already found suitable for labeling several types of dendrimers.[7] The carboxylic acid group of dendron **1-G$_0$** is activated first with TBTU (*O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate) in the presence of DIPEA (diisopropylethylamine). Then it is reacted with the trifluoroacetic acid salt **2-G$_0$** to create the amide function. Purification of the Janus dendrimer **3-G$_1$G$_1$** by column chromatography is easy due to the very different polarity and Rf value of the coupling product compared to its constituents **1-G$_0$** and **2-G$_0$** (Scheme 1). Dendrimer **3-G$_1$G$_1$** is isolated in 77% yield and characterized by multinucleus NMR, and two signals are observed for many groups in a 2/3 ratio due to the nonsymmetry of the core. The coupling is ascertained by mass spectrometry (positive ion spray) $m/z = 1777.95$ $[M + 2H]^{2+}$. No signal corresponding either to **1-G$_0$** or **2-G$_0$** is detectable, showing both the efficiency of the purification and the strength of the linker.

The surface-block dendrimer **4-G$_1$G$_1$** is obtained in nearly quantitative yield (98%) by the deprotection of the Boc-protected amine terminal groups of **3-G$_1$G$_1$** using trifluoroacetic acid (TFA) (Scheme 1). The completion of the reaction is rapid (60 min) as shown by the total disappearance of the signal corresponding to the *tert*-butyl groups in both ^{1}H and ^{13}C NMR. Dendrimer **4-G$_1$G$_1$** is fairly soluble in water, and its structural integrity (no cleavage of the linker) is shown by MS (positive IS) $m/z = 1527.95$ $[M + 2H]^{2+}$ where M is the neutral form of **4-G$_1$G$_1$**, after elimination of $5CF_3CO_2H$.

The second coupling strategy tested is based on the classical condensation of hydrazines with aldehydes. We chose hydrazines instead of amines (such as **2-G$_0$**, for instance) due to the known better stability of their condensation products in water. Thus, we designed two new dendrons, structurally close to **1-G$_0$** and **2-G$_0$**, but having a different

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(6) The strategy used can be seen in ref 5 and in: Franc, G.; Mazères, S.; Turrin, C. O.; Vendier, L.; Duhayon, C.; Caminade, A. M.; Majoral, J. P. *J. Org. Chem.* **2007**, *72*, 8707–8715.

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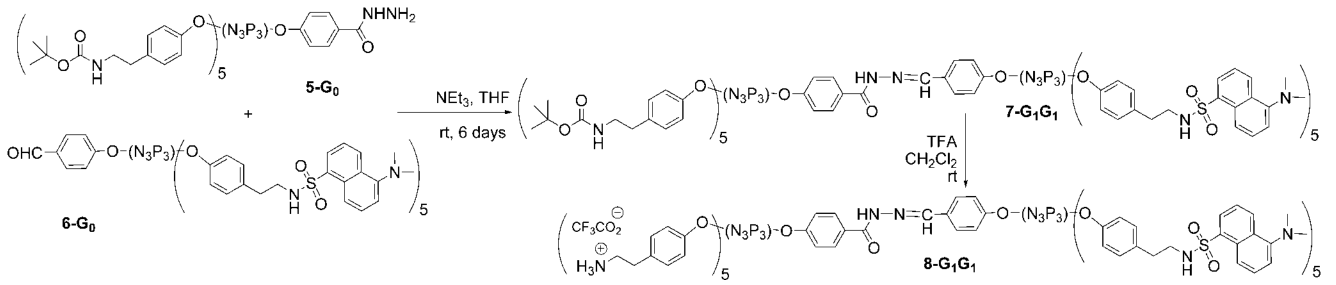
Scheme 2



function at the core, namely a hydrazide for **5-G$_0$** and an aldehyde for **6-G$_0$**. The reaction proceeds slowly at rt and is not complete even after 14 days, as shown both by thin layer chromatography (TLC) and ^{1}H NMR monitoring. Modification of the reaction conditions such as an increased concentration or addition of triethylamine does not accelerate the reaction. However, the surface-block dendrimer **7-G$_1$G$_1$** is easily purified by column chromatography but isolated with a moderate yield (45%) (Scheme 2). The creation of the central hydrazone linkage is shown by the disappearance of the signal corresponding to the aldehyde in ^{1}H and ^{13}C NMR and IR spectrometry. Furthermore, the structure of this compound is demonstrated by MS (MALDI-tof, dithranol): $m/z = 3550$ $[M + H]^+$. As in the previous case, deprotection of the Boc-protected amine terminal groups is carried out using TFA, affording compound **8-G$_1$G$_1$** in nearly quantitative yield (Scheme 2).

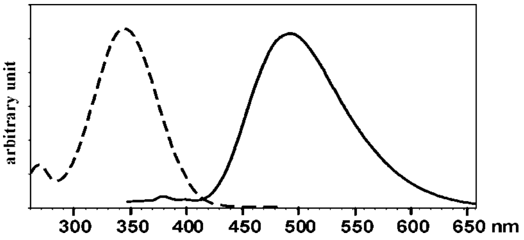


Figure 1. Absorption (- - -) and emission (—) spectra of dendrimer **8-G$_2$G$_1$** in dioxane. These spectra are representative of all the surface-block dendrimers reported in this paper.

The same coupling method is then applied to the first-generation dendron **5-G$_1$** bearing 10 protected amines. Condensation with **6-G$_0$** affords the unsymmetrical second-generation Janus dendrimer **7-G$_2$G$_1$** in 59% yield. The increased size of the dendron has only a little influence on the rate of condensation. The coupling is confirmed by MS (MALDI-tof, dithranol): $m/z = 5813$ $[M + Na]^+$. The deprotection of the amines affords dendrimer **8-G$_2$G$_1$**, possessing 10 ammonium and 5 dansyl groups, characterized by ^{31}P, ^{1}H, and ^{13}C NMR, as for all the other Janus dendrimers. MS (MALDI-ToF, dithranol) does not display the expected molecular peak for the monocharged species (4785) but peaks corresponding to the cleavage of two P−tyramine bonds ($m/z = 4642$), followed by the cleavage of one then two hydrazone linkages ($m/z = 4642$ and 3919), as already reported for phosphorhydrazone-containing dendrimers.[8] These Janus dendrimers were designed in the course of our studies in the fields of materials science[9] and biology,[10] in which fluorescent markers are highly precious monitoring tools.

Table 1. Absorption, Fluorescence Emission, and Quantum Yield of the Janus Dendrimers in Dioxane (Reference: Quinine Sulfate)

compound	absorption maxima (nm)	emission maxima (nm)	quantum yield (%)
3-G$_1$G$_1$	343	493	50
4-G$_1$G$_1$	345	493	46
7-G$_1$G$_1$	344	493	56
8-G$_1$G$_1$	344	495	42
7-G$_2$G$_1$	342	491	42
8-G$_2$G$_1$	345	493	30

The series of compounds possessing Boc-protected amines are soluble in organic solvents, whereas the series of compounds possessing ammonium groups are soluble in water.[11] To compare the fluorescence properties of all

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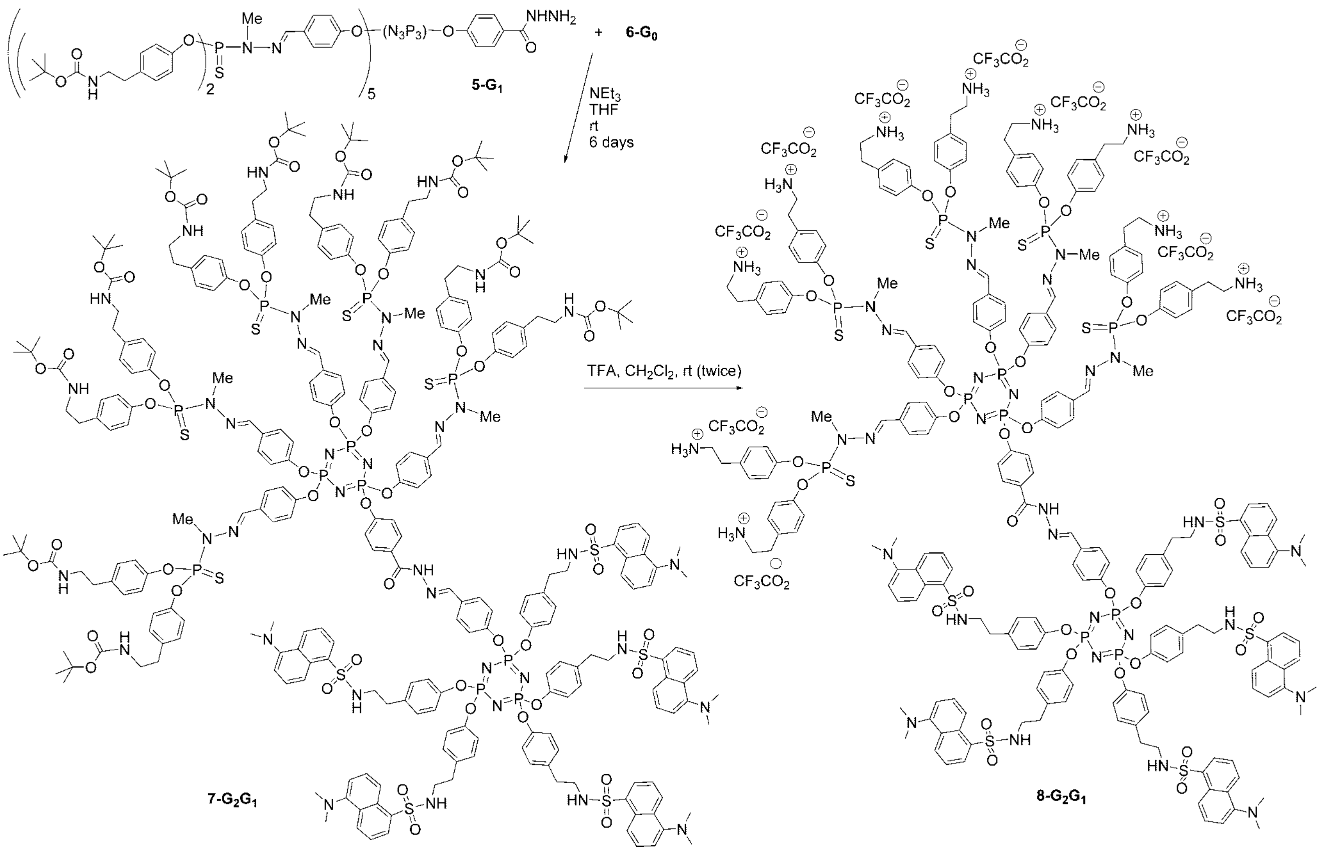
(11) The presence of traces of organic solvent in the interior of the dendrimer is necessary to ensure the solubility in water as we have already shown in: Leclaire, J.; Coppel, Y.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 2304–2305.

Scheme 3



compounds, we choose dioxane as solvent suitable for all of them. All compounds display very similar absorption (342−345 nm) and emission (491−495 nm) maxima wavelengths, well separated ($\Delta\lambda$ = *ca*. 150 nm) (Table 1). As expected for dansyl derivatives, all these compounds exhibit a very large Stokes shift estimated to be 8702−8873 cm^{-1} in dioxane (calculated as $(1/\lambda_{\text{max}\cdot\text{exc}} - 1/\lambda_{\text{max}\cdot\text{em}}) \times 10^7$). As can be seen in Figure 1 for dendrimer **8-G$_2$G$_1$**, there is practically no overlap between the absorption and emission spectra. This is a very interesting characteristic for fluorescent probes that permits an improved separation of the light inherent to the probe and the light dispersed by the sample. The quantum yields are good in all cases but decrease on going from a neutral to a charged form. This might be related to a partial protonation of the dansyl groups.[7] A decrease is also observed when going from a first to a second generation, possibly related to an interaction with the dendritic structure[6] (Table 1). However, in all cases, these quantum yields are similar to those known for dansyl derivatives.

In conclusion, we have described the first examples of water-soluble fluorescent Janus dendrimers and found that these compounds possess a bright fluorescence, which is separated from the absorption area, making it potentially suitable for biological experiments.

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Supporting Information Available: Experimental section (procedures and characterization). Copy of ^{31}P, ^{1}H, and ^{13}C NMR spectra for all dendrimers and MS. This material is available free of charge via the Internet at http://pubs.acs.org.

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