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ARTICLE *in* EUROPEAN JOURNAL OF ORGANIC CHEMISTRY · SEPTEMBER 2009

Impact Factor: 3.07 · DOI: 10.1002/ejoc.200900458

DOI: 10.1002/ejoc.200900458

gem-Bisphosphonate-Ended Group Dendrimers: Design and Gadolinium Complexing Properties

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Keywords: Dendrimers / Gadolinium / Magnetic properties / Michael addition / Bisphosphonate

The synthesis of the first *gem*-bisphosphonate-ended group dendrimers is described using nucleophilic substitution of terminal $P(S)Cl_2$ units of phosphorus dendrimers of generation 1 to 3 with protected aminophenols followed by deprotection of amino groups and Michael addition with vinylidene tetraisopropyl bisphosphonate. These dendrimers were found to act as chelating agents towards Gd ions.

Introduction

Dendrimers are monodisperse and three-dimensional nanometre-sized structures built from monomers around a plurifunctional core by an iterative process permitting a perfect control of their size and topology.[1] They allow a multivalent presentation of a given active molecular motif in a highly defined fashion. The ability to synthesize such architectures in such a rigorous way opens large avenues for their applications in different fields ranging from biology and medicine to material sciences and catalysis. Among the different types of dendrimers, those incorporating phosphorus[2–6] were found to be extremely versatile "soft matter" bringing specific properties for example as two photons tracers for in vivo imaging,[7–10] for gene transfection[11,12] or antiprion activity.[13–15] Their crucial role for the elaboration of new materials as dendronized nanolatexes,[16] nanotubes,[17,18] fibres,[19] antiviral supramolecular assemblies,[20,21] DNA chips,[22,23] microcapsules,[24] chemical sensors[25] was also pointed out while enhanced catalytic performance of ligands were observed when multiple copies of these monomers were incorporated on the surface of P-dendrimers.[26]

Phosphorus-containing dendrimers capped with amino bismethylene phosphonates or phosphonic acids of type **A** were found to induce a remarkable bioactivity promoting the activation of human monocytes and the selective multiplication of human Natural Killer (NK) cells.[27–29] These phosphonate groups were also found useful for the grafting to TiO_2 surfaces and the elaboration of chemical sensors.[30] In marked contrast nothing is reported concerning the design and consequently the use of dendrimers bearing *gem*-bisphosphonates or 1,1-bisphosphonic acids of type **B**, these monomers being known for their exceptionally high affinity for the bone mineral hydroxy-apatite and their role against osteoroporosis.[31] To the best of our knowledge only a dendron of generation one **C** (Figure 1) composed of four bisphosphonic acid moieties was designed for improved targeting of proteins to bone.[32]

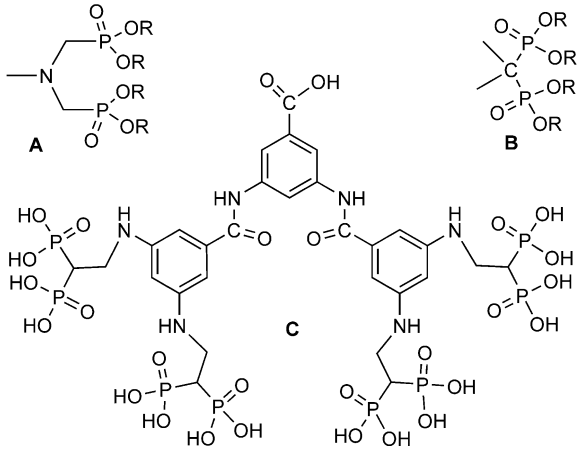

Figure 1. Amino bis-methylene phosphonate (**A**), *gem*-bisphosphonate (**B**) and multivalent *gem*-bisphosphonate dendron (**C**).

On the basis of these observations we report hereafter several ways of synthesis of unique phosphorus dendrimers capped with *gem*-bisphosphonates, and their behaviour as

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900458.

efficient multi-pincers for gadolinium as preliminary illustration of their complexing properties. Discussion regarding the magnetic properties of these novel macromolecular species will be also addressed.

Results and Discussion

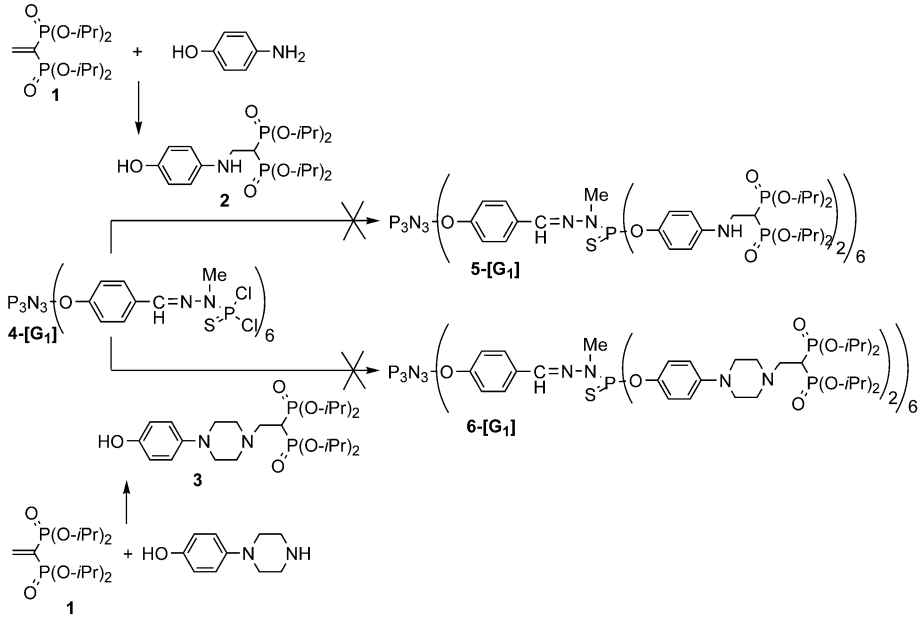
We already demonstrated that $P(S)Cl_2$ end groups of dendrimers easily react with phenols in the presence of base.[2] Indeed this is one of the key reactions used for the preparation of phosphorus dendrimers. Therefore our first efforts were directed to the synthesis of phenols bearing bisphosphonate moieties. To this end, Michael type additions between 4-aminophenol or 4-(hydroxyphenyl)piperazine and vinylidene tetraisopropyl bisphosphonate **1** were undertaken (Scheme 1). Phenol *N*-bisphosphonate monomers **2** and **3** were obtained readily as a viscous oil (**2**, 95% yield) or a crystalline solid (**3**, 84% yield). Unfortunately nucleophilic substitution on terminal $P(S)Cl_2$ groups of the dendrimer of generation 1, **4-[G$_1$]** either with **2** or **3** does not afford the desired dendrimers **5-[G$_1$]** and **6-[G$_1$]**. A retro Michael addition takes place, regardless of the experimental conditions used.

To overcome these difficulties a different divergent strategy was used consisting of the protection of the amino group of 4 aminophenol with classical Boc leading to the phenol **7** which was grafted onto the surface of **4-[G$_1$]** in basic conditions (Cs_2CO_3, THF, overnight, yield of 81%). Deprotection of the Boc groups on the resulting dendrimer **8-[G$_1$]** using standard conditions leads readily to the polycationic dendrimer **9-[G$_1$]** with a yield of 100%. Disappearance of the signal of the *tert*-butyl groups in ^{1}H NMR at δ = 1.48 ppm confirms complete deprotection. Dendrimer **9-[G$_1$]** is then left to react in presence of caesium carbonate and 4 equiv. of the vinylidene bisphosphonate **1** per amino group to afford, after purification, the first phosphorus dendrimer capped with *N*-*gem*-bisphosphonate units **5-[G$_1$]** in 64% yield (Scheme 2). The slow reaction needed two days to go to completion and was monitored by ^{31}P NMR which shows the partial disappearance of the signal due to **1** (δ^{31}P = 10.9 ppm) in behalf of a new signal at δ = 19.9 ppm characteristic of the *gem*-bisphosphonate moieties in **5-[G$_1$]**. ^{1}H and ^{13}C NMR spectroscopic data also corroborate the structure of **5-[G$_1$]**. Typically the signal of the carbon in α position to phosphorus appears as a triplet ($^1J_{CP}$ = 132.1 Hz) at δ = 37.76 ppm (δ = 134.56 ppm, $^1J_{CP}$ = 168 Hz in **1**) and the C(Ar)N signal shifts from 132.3 ppm in **9-[G$_1$]** to 145.1 ppm in **5-[G$_1$]** in ^{13}C NMR spectroscopy.

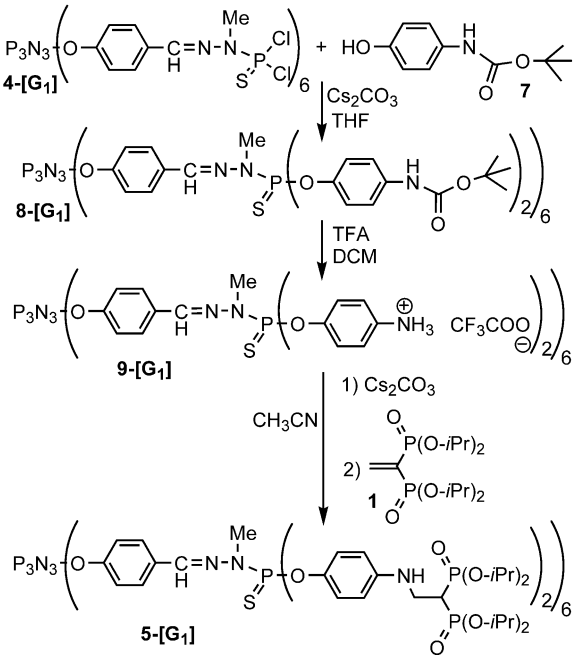
Subsequently we extended this method to the use of the Boc-protected 4-(hydroxyphenyl)piperazine **10**. Grafting was undertaken under the same conditions (Scheme 3) leading successively to generation-one dendrimers, **11-[G$_1$]**, **12-[G$_1$]** and finally **6-[G$_1$]** bearing twelve aza-*gem*-bisphosphonate end groups. As expected three signals were obtained in ^{31}P NMR for **6-[G$_1$]** at respectively 9.2 (P=N core), 20.5 (P=O, surface), 64.3. (P=S, branches) ppm. ^{1}H and ^{13}C NMR spectroscopic data validate the complete functionalization of the periphery for **6-[G$_1$]**.

The same successful strategy was also applied for the construction of generation-two dendrimers. **11-[G$_2$]**, **12-[G$_2$]** and **6-[G$_2$]** (24 terminal *gem*-bisphosphonate units) starting from **4-[G$_2$]** (Scheme 4), and finally for dendrimers of generation 3, **11-[G$_3$]**, **12-[G$_3$]** and **6-[G$_3$]** [48 terminal *gem*-bisphosphonate units (see Supporting Information)].

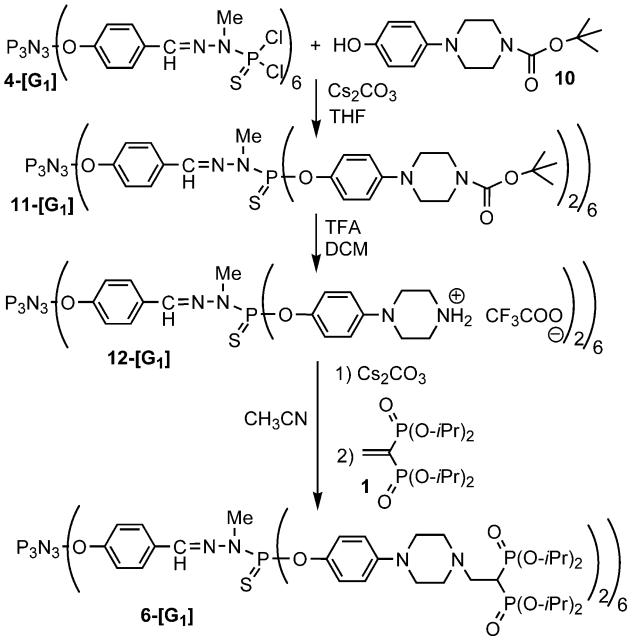
Having in hand these new dendrimers we started preliminary experiments concerning their complexing properties. For several reasons, we decided to investigate the complexation with gadolinium salts. First, the gadolinium ion with its half-filled 4f orbitals and its $^8S_{7/2}$ ground state (S = 7/2, L = 0) is the only 4f ion without first-order orbital momen-



Scheme 1. Synthesis of *gem*-bisphosphonate containing phenols **2** and **3**. Grafting failures on **4-[G$_1$]**.

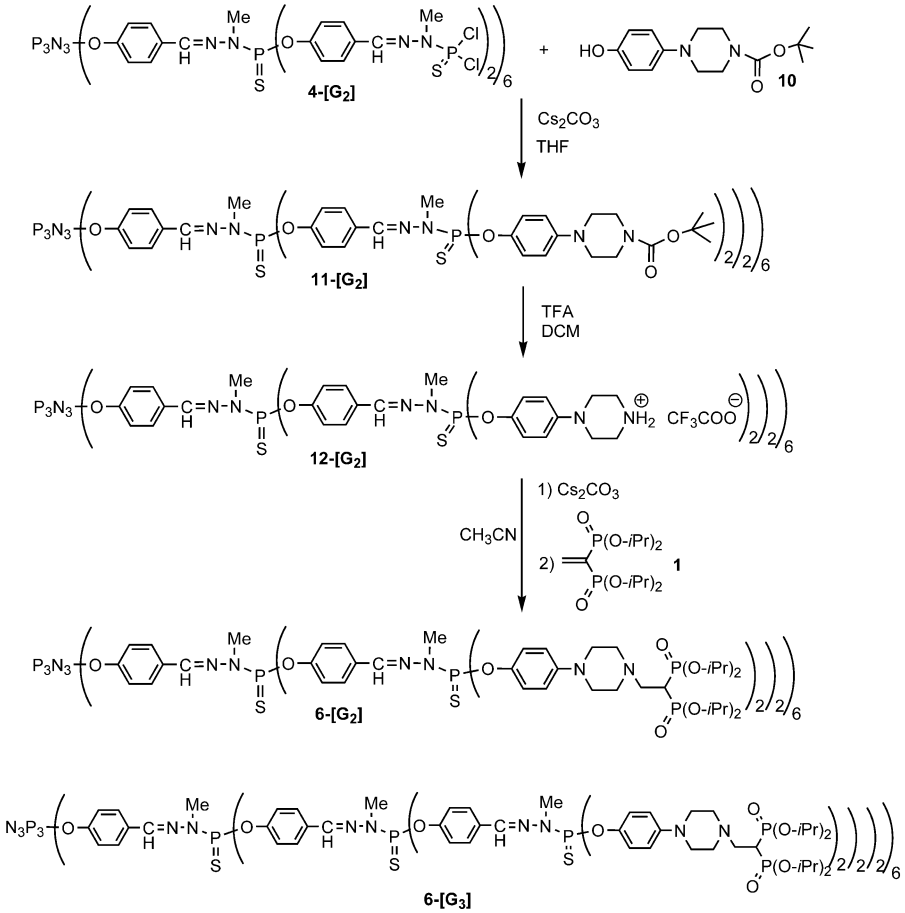


Scheme 2. Multistep synthesis of the dendrimer **5-[G_1]**.



Scheme 3. Synthesis of the piperazino *gem*-bisphosphonate dendrimer **6-[G_1]**.

tum. This huge advantage makes the Gd ion a key element to solve several magnetic problems. It can be used as a magnetic probe to give supporting information in the absence of structural data and the interaction parameters are easily deduced from the experimental data by use of an isotropic Hamiltonian. The second reason lies to the fact that most



Scheme 4. Synthesis of the piperazino bisphosphonate dendrimers of generation 2 and 3: **6-[G_2], 6-[G_3]**.

of the used contrast agents are based on gadolinium ion Gd^{3+}. In the field of dendrimers, there are a few reports dealing with complexation with Gd,[33,34] the group of Wiener was the first to describe a dendrimer-based contrast agent for magnetic resonance imaging (MRI), using a [Gd(DTPA)] complex covalently bound to polyamidoamine dendrimers (DTPA: diethylenetriaminepentacetic acid),[35,36] while other reports described the use of a dendrimer-based MRI contrast agent consisting on a trimesic acid core on which second-generation lysine dendrons bearing 24 Gd ions are anchored.[37–39] Another reason for the choice of complexation of Gd is the ability of phosphonate and bisphosphonate monomers to complex such an element.[40] Therefore it was tempting to undertake such experiments with the unique *gem*-bisphosphonate dendrimers reported in this work.

Dendrimers **6-[G_1]**, **6-[G_2]** and **6-[G_3]** possess 12, 24 and 48 *gem*-bisphosphonate functions, respectively. Their complexation by gadolinium ions was accomplished according to the same experimental protocol, which is briefly described hereafter. Supposing that each phosphonate pair is able to coordinate one gadolinium ion, an acetonitrile solution containing a slight excess of gadolinium triflate [$Gd(SO_3CF_3)_3{\cdot}6H_2O$, **13**] was added dropwise to an acetonitrile solution of the dendrimer. The resulting solution was stirred for 48 h leading after work-up to a powder that was filtered off and dried (yield 32–40%). IR data confirm the presence of water with large bands at 3461 (**6-[G_1] Gd_{12}**), 3437 (**6-[G_2] Gd_{24}**) and 3436 cm^{-1} (**6-[G_3] Gd_{48}**). Strong C–F stretching bands due to triflate counterions (1225, 1197 cm^{-1}) appear in a region where several bands (mainly P=O) from the dendrimers are present (1224–1103 cm^{-1}). Nevertheless strong bands at 1027 and 634 cm^{-1} do confirm their presence in the different dendrimer-Gd entities. It is well established that the gadolinium magnetic interactions in entities containing Gd ions are weak and only active at low temperature. So, measurement of the magnetic susceptibility at room temperature gives information on the amount of Gd ions present per dendrimer. If we consider that 12 gadolinium ions are linked to dendrimer **6-[G_1]**, the expected value of the $\chi_M T$ product, χ_M being the magnetic susceptibility and T temperature, must be equal to 94.5 $cm^3\,mol^{-1}\,K$ (27.5 BM). The experimental $\chi_M T$ product of 94.0 $cm^3 mol^{-1}$ (27.4 BM) at 300 K is in good agreement with the expected value, as shown in Figure 2. This product decreases slightly from 300 to 50 K (85.1 $cm^3\,mol^{-1}\,K$, 26.1 BM) and more abruptly between 25 and 2 K (45.1 $cm^3\,mol^{-1}\,K$, 19.0 BM). This last decrease corresponds to antiferromagnetic Gd–Gd interactions and confirms that at least some of the Gd ions do interact, surely through Gd–O–Gd bridges.

Very similar curves have been obtained with Gd complexes of the second and third generation. They are given in Figures S1 and S2 (S). This is particularly true for the **6-[G_3] Gd_{48}** entity, where the magnetic moment varies from 55.6 BM at 300 K to 44.7 BM at 2 K. A theoretical value of 55.0 BM was expected for 48 Gd ions in the isolated species (Figure S2).

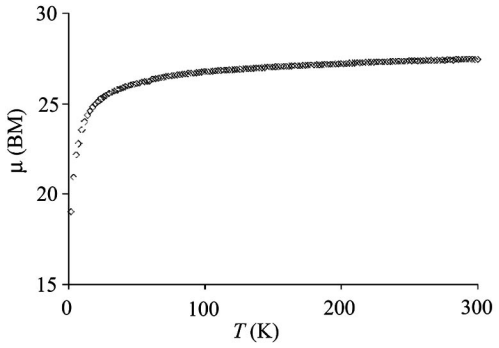
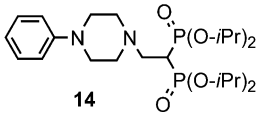


Figure 2. Temperature dependence of the magnetic moment μ for **6-[G_1] Gd_{12}**.

From these magnetic data, it is clear that antiferromagnetic Gd–Gd interactions are a common feature of the three Gd dendrimer entities. Such interactions can have an intra- or inter-dendrimer origin. In order to better understand the magnetic behaviour of these Gd dendrimers, a simple synthon **14** corresponding to the terminal dendrimer arms has been prepared and reacted with Gd ions. After several attempts using different Gd salts, crystals were isolated in presence of gadolinium acetate and gadolinium hexafluoroacetylacetonate $Gd(hfa)_3{\cdot}2H_2O$. The molecular structure of the resulting complex **15** is shown in Figure 3.



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Obviously the molecular entity is binuclear, with four acetato or trifluoroacetato anions acting as bridging ligands through their carboxylato groups, hfa and bisphosphonate ligands chelating each gadolinium ion (Gd and Gd^i). Two acetate functions are in the usual $\eta^1{:}\eta^1{:}\mu$ mode while the two others form bridges in the less common $\eta^2{:}\eta^1{:}\mu$ fashion.[41] In the $\eta^1{:}\eta^1{:}\mu$ mode, the bridging acetates are a mix up of trifluoroacetate and acetate anions in the 0.25:0.75 ratio, trifluoroacetate coming from hexafluoroacetylacetone decomposition. In the latter case, $\eta^2{:}\eta^1{:}\mu$ bridge, one oxygen atom (O19, $O19^i$) is terminally bound to the related gadolinium ion (Gd, Gd^i) and the second oxygen (O18, $O18^i$) is involved in a monoatomic bridge between the two lanthanide ions. Due to the inversion centre the Gd(O18, $O18^i$)Gd^i double bridging network is perfectly planar. The second bridge through the atoms Gd, O16, C16, O17, Gd^i, $O16^i$, $C16^i$ and $O17^i$ is not planar. The dihedral angle between the two planes, Gd(O18, $O18^i$)Gd^i and mean Gd(O16, C16, O17)Gd^i plane, is equal to 87.75(6)° while the nine-coordinated gadolinium ions are separated by 3.9816(3) Å. There are two dinuclear units in the unit cell distinguished by their $\eta^2{:}\eta^1{:}\mu$ acetate bridges and the six-membered Gd-bisphosphonate cycles. The six-membered Gd-bisphosphonate cycles are in a boat conformation in one unit and in a skew boat conformation in the second unit, with very similar bond lengths. On the contrary, the

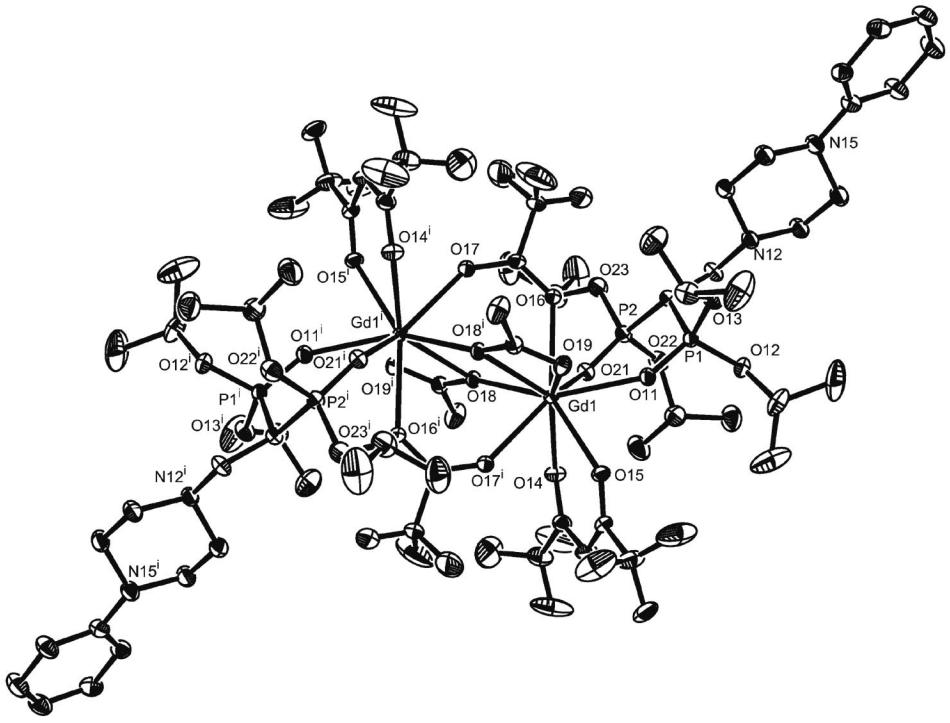

Figure 3. Molecular structure of complex **15** with the thermal ellipsoids drawn at the 30% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths and distance [Å]: Gd1–O18 2.329(2), Gd1–O18^{i} 2.580(2), Gd1–O19 2.460(2), Gd1–O16 2.443(2), Gd1–O17 2.387(2), Gd1–O14 2.449(2), Gd1–O15 2.447(2), Gd1–O11 2.397(2), Gd1–O21 2.451(2), Gd1···Gd1^{i} 3.9816(3).

Gd–O bond lengths of the η^2:η^1:μ acetate bridge do vary, 2.358(2) and 2.507(2) Å instead of 2.329(2) and 2.580(2) Å for the η^2 oxygen atom and 2.492(2) against 2.460(2) Å for the η^1 oxygen atom. So the Gd···Gd^{i} distance in the skew-boat conformation is slightly shorter, 3.9582(3) Å, than in the boat conformation [3.9816(3) Å] shown in Figure 3. The dinuclear units are well isolated from each other, with intermolecular distances greater than 11.2 Å. The main interest of this dinuclear structure consists in showing that the bisphosphonate pincer does not act as a bridging ligand but prefers to act as a chelate for each gadolinium ion.

The magnetic behavior of the dinuclear complex is quite reminiscent of what was observed for the Gd dendrimer entities. At 300 K, $\chi_M T$ (Figure 4) is equal to 15.8 $cm^3 mol^{-1} K$ which is the value attributable to two non-interacting spin carriers, each being characterized by $S = 7/2$ and $g = 2.0$. Lowering of the temperature causes $\chi_M T$ to decrease to 14.6 $cm^3 mol^{-1} K$ at 2 K. Fitting the experimental data to the equation[42] deduced from the isotropic spin Hamiltonian $\boldsymbol{H} = -JS_{Gd1} \cdot S_{Gd2}$ yields $J = -0.01$ cm^{-1} and $g = 2.00$, with an agreement factor R equal to 2.0 10^{-4} ($R = \Sigma[(\chi_M T)_{obs} - (\chi_M T)_{calc}]^2/\Sigma[(\chi_M T)_{obs}]^2$). The weak J parameter results from a delicate balance between two contributions of opposite signs and slightly different magnitudes. Indeed, the double usual η^1:η^1:μ bridging mode[43] is known to favour antiferromagnetic interactions while the less common η^2:η^1:μ bridge is associated to ferromagnetic interactions.[44] Supposing that Gd ions are associated by pairs in **6-[G$_1$] Gd$_{12}$**, the equation[42] defined above gives an interaction parameter J equal to –0.11 cm^{-1}, in perfect agreement with expected J values.[45] As we know that solutions of positive ions are acidic in protic solvents[46] and that Ln salts contain water molecules, we can easily imagine that some water molecules give hydroxo anions able to bridge the Gd ions and to replace an equivalent number of non coordinating triflate anions.

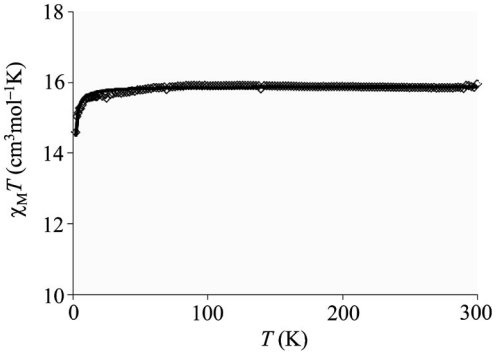

Figure 4. Temperature dependence of the $\chi_M T$ product for complex **15**.

All these data suggest that the Gd dendrimers chelates are better represented as polymeric networks, the Gd units acting as anchoring centres for dendrimers. The poor solubility observed for the complexes seems to be in agreement with the existence of such polymeric networks.

Conclusions

Synthetic strategies leading to the first *gem*-bisphosphonate-ended dendrimers are reported. They imply nucleophilic substitutions of the terminal $P(S)Cl_2$ groups of phosphorus dendrimers of generation 1 to 3 with protected aminophenols followed by deprotection of amino groups and Michael type addition with vinylidene tetraisopropyl bisphosphonate. Preliminary experiments show that the novel dendrimers studied in this work are able to coordinate Gd ions thanks to the presence of *gem*-bisphosphonate functions. Contrary to the phosphonic acids that can introduce bridges between Gd ions,[47] these synthons act as unique chelating agents toward the Gd ions. Furthermore, it appears that the number of Gd ions introduced in the isolated units is equal to the number of *gem*-bisphosphonate pairs. Eventually, the magnetic measurements demonstrate clearly that the Gd ions are not coordinated to these pairs as isolated ions but that at least some of these ions are bridged through oxygen atoms that are not P=O functions, as shown by the structural determination given in the paper. Studies concerning properties of these Gd dendrimers complexes are under active investigation.

Experimental Section

General: All manipulations were carried out with standard high-vacuum and dry-argon techniques. Chemicals were purchased from Sigma–Aldrich or Strem and used without further purification; solvents were dried and distilled by routine procedures. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded at 25 °C with Bruker AC 200, ARX 250, AV 300, DPX 300, AMX 400 or AV500 spectrometers. References for NMR chemical shifts are 85% H_3PO_4 for ^{31}P NMR, and $SiMe_4$ for ^1H and ^{13}C NMR spectroscopy. The attribution of ^{13}C NMR signals has been done using *J*mod, two-dimensional ^1H-^{13}C HSQC, ^1H-^{13}C HMBC, and ^1H-^{31}P HMQC, Broad Band or CW ^{31}P decoupling experiments when necessary. The numbering scheme used for NMR is depicted on Figure 5.

Magnetic susceptibility data were collected on powdered samples with a Quantum Design MPMS SQUID magnetometer under a 0.1 T applied magnetic field. All data were corrected for diamagnetism of the ligands estimated from Pascal's constants.[48]

Compound **1** was a gift from Rhodia PPD and was purified by chromatography (SiO_2, acetone/pentane, 1:1): $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121.5 MHz): δ = 10.84 (s, P=O) ppm. ^1H NMR ($CDCl_3$, 200.13 MHz): δ = 1.21–1.34 [m, 24 H, $CH(CH_3)_2$], 4.63–4.77 [m, 4 H, $CH(CH_3)_2$], 6.88 (distorted dd, J_{HP} = 33.6, 34.0 Hz, 2 H, CH_2=C) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.46 MHz): δ = 23.76 [d, $^3J_{CP}$ = 15.8 Hz, $CH(CH_3)_2$], 71.24 [s, $CH(CH_3)_2$], 134.56 (t, $^1J_{CP}$ = 168 Hz, CH_2=C), 147.25 (d, $^2J_{CP}$ = 7.5 Hz, CH_2=C) ppm.

2: 4-Hydroxyaniline (150 mg, 1.37 mmol) and **1** (0.5 g, 1.40 mmol) were left to react in THF (4 mL) at 50 °C for 2 h. After reaction completion (^{31}P NMR monitoring), the solution was filtered through celite to remove any residual insoluble starting material. After removal of the residual solvent, an oil was obtained and washed twice with pentane (5 mL) to afford **2** as black oil in 95% yield (606 mg). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 101.25 MHz): δ = 20.08 (s, P=O) ppm. ^1H NMR ($CDCl_3$, 250.13 MHz): δ = 1.26–1.31 [m, 24 H, $CH(CH_3)_2$], 2.54 (tt, $^3J_{HH}$ = 5.7, $^2J_{HP}$ = 23.5 Hz, 1 H, CH_2CH), 3.60 (td, $^3J_{HH}$ = 5.7, $^3J_{HP}$ = 15.7 Hz, 2 H, CH_2CH), 4.63–4.81 [m, 4 H, $CH(CH_3)_2$], 6.51 (d, $^3J_{HH}$ = 6.75 Hz, 2 H, $C_0{}^3H$), 6.71 (d, $^3J_{HH}$ = 6.75 Hz, 2 H, $C_0{}^2H$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.46 MHz): δ = 23.76–24.07 [m, $CH(CH_3)$], 37.53 (t, $^1J_{CP}$ = 134 Hz, CH_2CH), 41.87 (s, CH_2CH), 71.57–71.83 [m, $CH(CH_3)_2$], 115.68 (s, $C_0{}^2$), 116.23 (s, $C_0{}^3$), 139.41 (s, $C_0{}^1$), 150.17 (s, $C_0{}^4$) ppm.

3: (4-Hydroxyphenol)piperazine (150 mg, 0.841 mmol) and **1** (305 mg, 0.855 mmol) were left to react in THF (4 mL) at 50 °C during 5 h. After reaction completion (^{31}P NMR monitoring), the solution was filtered through celite to remove any residual insoluble starting material. After removal of the residual solvent, solid obtained was washed twice with pentane (5 mL) and then crystallized with a mixture *n*-pentane/diethyl ether (3:1, with the minimum amount of ether) 3 times to afford **3** as a rose-tinted crystalline powder in 84% yield (378 mg). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 81.015 MHz): δ = 23.93 (s, P=O) ppm. ^1H NMR ($CDCl_3$, 250.133 MHz): δ = 1.26–1.31 [m, 24 H, $CH(CH_3)_2$], 2.58 (tt, $^3J_{HH}$ = 6.5, $^2J_{HP}$ = 30.6 Hz, 1 H, CH_2CH), 2.65 (t, $^3J_{HH}$ = 4.2 Hz, 2 H, C^bH), 2.93 (dt, $^3J_{HH}$ = 6.5, $^3J_{HP}$ = 15.0 Hz, 2 H, CH_2CH), 2.98 (t, $^3J_{HH}$ = 4.2 Hz, 2 H, C^aH), 4.70–4.87 [m, 4 H, $CH(CH_3)_2$], 6.74–6.85 (m, 4 H, H_{ar}) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.46 MHz): δ = 23.95–24.02 [m, $CH(CH_3)$], 37.64 (t, $^1J_{CP}$ = 134.5 Hz, CH_2CH), 50.76 (s, C^a), 53.10 (s, C^b), 54.33 (s, CH_2CH), 71.17–71.49 [m, $CH(CH_3)_2$], 115.93 (s, $C_0{}^2$), 118.28 (s, $C_0{}^3$), 144.77 (s, $C_0{}^1$), 151.20 (s, $C_0{}^4$) ppm. MS (DCI): *m*/*z* = 535 $[MH]^+$. MP: 87–91 °C.

7: At 0 °C (ice bath), Boc_2O (6.54 g, 29.96 mmol) was solubilised in THF (50 mL) then 4-hydroxyaniline (2 g, 18.32 mmol) was added gently. The reaction mixture was allowed to reach room temperature and was left to react for 36 h. Solvent was removed and the residual oil was solubilised in AcOEt. Organic phase was washed three times with brine, then dried with $MgSO_4$ and filtered. After

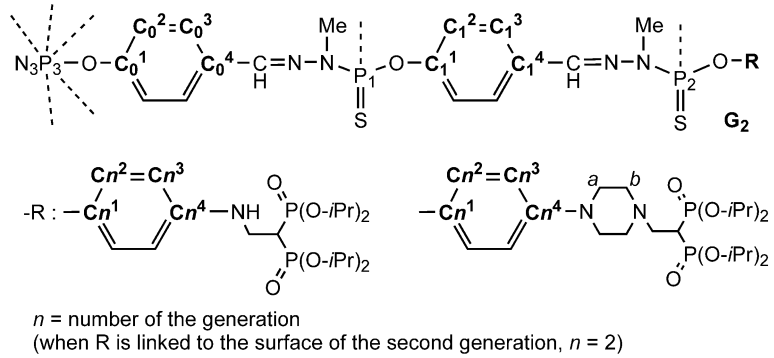

Figure 5. Numbering scheme used for NMR assignment.

removal of the residual solvents, compound **7** was obtained as a white crystalline solid in 92% yield (3.527 g). ^{1}H NMR ($CDCl_3$, 250.33 MHz): δ = 1.50 (s, 9 H, CH_3), 5.38 (s, 1 H, NH), 6.34 (s, 1 H, OH), 6.73 (d, $^3J_{HH}$ = 10.0 Hz, 2 H, C_0^2H), 7.14 (d, $^3J_{HH}$ = 10.0 Hz, 2 H, C_0^3H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 62.89 MHz): δ = 28.32 (s, CH_3), 80.45 [s, $C(CH_3)_3$], 118.52 (s, C_0^2), 122.98 (s, C_0^3), 128.93 (s, C_0^4), 138.32 (s, C_0^1), 152.7 (s, C=O) ppm. MP: 132–133 °C.

8-[G$_1$]: Dendrimer **4-[G$_1$]** (200 mg, 0.11 mmol), **7** (297 mg, 1.42 mmol) and Cs_2CO_3 (913 mg, 2.80 mmol) were left to react in THF (5 mL) at room temperature for 5 d. After reaction completion, salts were removed by centrifugation and the clear solution was concentrated under reduced pressure. The residue was then dissolved in the minimum amount of THF (ca. 1 mL) and precipitated with pentane/diethyl ether. The resulting powder was filtered off and the procedure was repeated twice to afford **8-[G$_1$]** as a brownish powder in 81% yield (348 mg). ^{31}P{^{1}H} NMR ($CDCl_3$, 121.5 MHz): δ = 8.60 (s, P=N), 63.75 (s, P=S) ppm. ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 1.48 (s, 108 H, CH_3), 3.21 (d, $^3J_{HP}$ = 10.2 Hz, 18 H, CH_3NP), 6.75 (s, 12 H, NH), 6.98 (d, $^3J_{HH}$ = 8.4 Hz, 12 H, C_0^2H), 7.08 (d, $^3J_{HH}$ = 7.8 Hz, 24 H, C_1^2H), 7.26 (d, $^3J_{HH}$ = 7.8 Hz, 24 H, C_1^3H), 7.59 (s, 6 H, CH=N), 7.63 (d, $^3J_{HH}$ = 8.4 Hz, 12 H, C_0^3H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75.46 MHz): δ = 28.34 (s, CH_3), 33.10 (d, $^2J_{CP}$ = 12.3 Hz, CH_3NP_1), 80.57 [s, $C(CH_3)_3$], 119.64 (s, C_1^3), 121.49 (br. s, C_0^2), 121.82 (d, $^2J_{CP}$ = 4.4 Hz, C_1^2), 128.30 (s, C_1^4), 132.17 (s, C_0^4), 135.83 (d, $^3J_{CP}$ = 1.7 Hz, C_1^3), 138.55 (d, $^3J_{CP}$ = 13.8 Hz, CH=N), 145.77 (d, $^2J_{CP}$ = 7.1 Hz, C_1^1), 151.21 (d, $^2J_{CP}$ = 5.0 Hz, C_0^1), 152.87 (s, C=O) ppm.

9-[G$_1$]: Dendrimer **8-[G$_1$]** (211 mg, 0.054 mmol) was solubilised at room temperature in a mixture DCM/TFA (3 mL/1 mL) for 20 min then residual solvents were removed. The procedure was repeated once. The residue obtained was solubilised in MeOH, and then solvents were removed under reduced pressure to eliminate the excess of TFA by co-evaporation. The procedure was repeated twice. Final compound **9-[G$_1$]** was obtained as yellowish powder in 100% yield (218 mg). ^{31}P{^{1}H} NMR (CD_3OD, 121.49 MHz): δ = 8.63 (s, P=N), 62.93 (s, P=S) ppm. ^{1}H NMR (CD_3OD, 300.13 MHz): δ = 3.32 (m, 18 H, CH_3NP), 7.03 (d, $^3J_{HH}$ = 8.4 Hz, 12 H, C_0^2H), 7.31 (s, 48 H, C_1^2H, C_1^3H), 7.65 (d, $^3J_{HH}$ = 8.4 Hz, 12 H, C_0^3H), 7.82 (s, 6 H, CH=N) ppm. ^{13}C{^{1}H} NMR (CD_3OD, 75.46 MHz): δ = 32.11 (d, $^2J_{CP}$ = 12.1 Hz, CH_3NP), 121.00 (s, C_0^2), 122.62 (d, $^3J_{CP}$ = 4.5 Hz, C_1^2), 123.42 (s, C_1^3), 128.13 (s, C_0^3), 129.82 (s, C_0^4), 132.32 (s, C_1^4), 140.11 (d, $^3J_{CP}$ = 14.3 Hz, CH=N), 149.81 (d, $^2J_{CP}$ = 6.8 Hz, C_1^1), 151.20 (s, C_0^1) ppm.

5-[G$_1$]: Dendrimer **9-[G$_1$]** (108 mg, 0.027 mmol) and Cs_2CO_3 (215 mg, 0.66 mmol) were mixed in CH_3CN (1 mL) for 30 min at room temperature. Compound **1** (491 mg, 1.377 mmol) was dropped in and the reaction mixture was left to react for 3 d. After reaction completion (^{1}H and ^{31}P monitoring), 20 mL of DCM were added and the organic phase was washed with water (20 mL) twice. Residue was dried with $MgSO_4$, filtered, concentrated and precipitated with pentane. The resulting powder was filtered off and the procedure was repeated twice to afford **5-[G$_1$]** as a white powder in 64% yield (121 mg). ^{31}P{^{1}H} NMR ($CDCl_3$, 81.015 MHz): δ = 8.09 (s, P=N), 19.91 (s, P=O), 65.17 (s, P=S) ppm. ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 1.31–1.40 [m, 288 H, CH(CH_3)], 2.52 (tt, $^3J_{HH}$ = 5.4, $^2J_{HP}$ = 23.4 Hz, 12 H, CH_2CH), 3.27 (d, $^3J_{HP}$ = 9.9 Hz, 18 H, CH_3NP), 3.62 (td, $^3J_{HH}$ = 5.4, $^3J_{HP}$ = 15.6 Hz, 12 H, CH_2CH), 4.77 [m, 48 H, $CH(CH_3)$], 6.57 (d, $^3J_{HH}$ = 8.1 Hz, 24 H, C_1^2H), 7.00–7.09 (m, 36 H, C_0^2H, C_1^3H), 7.61–7.65 (m, 18 H, C_0^3H, CH=N) ppm. ^{13}C{^{1}H} NMR (CD_3CN, 125.80 MHz): δ = 23.28 [m, CH(CH_3)], 32.85 (d, $^2J_{CP}$ = 11.3 Hz, CH_3NP), 37.76 (t, $^1J_{CP}$ = 132.1 Hz, CH_2CH), 40.82 (s, CH_2CH), 70.54–71.42 [m, $CH(CH_3)$], 113.53 (s, C_1^3), 121.19 (s, C_0^2), 122.06 (s, C_1^2), 128.23 (s, C_0^3), 132.73 (s, C_0^4), 139.05 (d, $^3J_{CP}$ = 13.8 Hz, CH=N), 142.02 (d, $^2J_{CP}$ = 6.3 Hz, C_1^1), 145.10 (s, C_1^4), 150.95 (s, C_0^1) ppm.

10: At 0 °C (ice bath), Boc_2O (4.40 g, 20.16 mmol) was solubilised in THF (50 mL) then 4-hydroxypiperazine (3.08 g, 17.28 mmol) was added gently. The reaction mixture was allowed to reach room temperature and was left to react during 4 h. Solvent was removed and the residual oil was solubilised in AcOEt (150 mL). Organic phase was washed once with a saturated solution of $NaHCO_3$, twice with brine, then dried with $MgSO_4$ and filtered. After removal of the residual solvents, compound **10** was obtained as a brownish crystalline solid in 98% yield (4.714 g). ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 1.50 (s, 9 H, CH_3), 2.98 (t, $^3J_{HH}$ = 5.1 Hz, 2 H, C^aH), 3.58 (t, $^3J_{HH}$ = 5.1 Hz, 2 H, C^bH), 6.55 (br. s, 1 H, OH), 6.77–6.86 (m, 4 H, C_0^2H, C_0^3H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 62.89 MHz): δ = 28.46 (s, CH_3), 43.50 (s, C^b), 51.17 (s, C^a), 80.28 [s, $C(CH_3)_3$], 116.00 (s, C_0^2), 129.23 (s, C_0^3), 145.03 (s, C_0^1), 150.95 (s, C_0^4), 154.98 (s, C=O) ppm. MP: 170–173 °C.

11-[G$_1$]: Dendrimer **4-[G$_1$]** (0.635 g, 0.347 mmol), **10** (1.2 g, 4.31 mmol) and Cs_2CO_3 (2.81 g, 8.62 mmol) were left to react in THF (5 mL) at room temperature overnight. After reaction completion, salts were removed by centrifugation and the clear solution was concentrated under reduced pressure. The residue was then dissolved in the minimum amount of THF (ca. 3 mL) and precipitated with pentane/diethyl ether. The resulting powder was filtered off and the procedure was repeated twice to afford **11-[G$_1$]** as a brownish powder in 87% yield (1.428 g). ^{31}P{^{1}H} NMR ($CDCl_3$, 81.015 MHz): δ = 12.16 (s, P=N), 67.81 (s, P=S) ppm. ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ = 1.45 (s, 108 H, CH_3), 2.98 (t, $^3J_{HH}$ = 4.8 Hz, 48 H, C^bH_2), 3.20 (d, $^3J_{HP}$ = 10 Hz, 18 H, CH_3NP_1), 3.49 (t, $^3J_{HH}$ = 4.8 Hz, 48 H, C^aH_2), 6.74 (d, $^3J_{HH}$ = 9 Hz, 24 H, C_1^3H), 6.93 (d, $^3J_{HH}$ = 8.4 Hz, 12 H, C_0^2H), 7.04 (dd, $^3J_{HH}$ = 9 Hz, 24 H, C_1^2H), 7.56–7.64 (m, 18 H, CH=N, C_0^3H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 62.89 MHz): δ = 28.42 (s, CH_3), 33.13 (d, $^2J_{CP}$ = 11.7 Hz, CH_3NP_1), 43.53 (br. s, C^b), 49.55 (s, C^a), 79.89 [s, $C(CH_3)_3$], 117.39 (s, C_1^3), 121.42 (s, C_0^2), 121.94 (s, C_1^2), 128.24 (s, C_0^3), 132.40 (s, C_0^4), 138.6 (d, $^3J_{CP}$ = 14.1 Hz, CH=N), 143.88 (d, $^2J_{CP}$ = 7.0 Hz, C_1^1), 148.84 (s, C_1^4), 151.10 (s, C_0^1), 154.65 (s, C=O) ppm.

11-[G$_2$]: Dendrimer **4-[G$_2$]** (0.250 g, 0.052 mmol), **1** (0.36 g, 1.29 mmol) and Cs_2CO_3 (0.850 g, 2.60 mmol) were left to react in THF (2 mL) at room temperature overnight. After reaction completion, salts were removed by centrifugation and the clear solution was concentrated under reduced pressure. The residue was then dissolved in the minimum amount of THF (ca. 1 mL) and precipitated with pentane/diethyl ether. The resulting powder was filtered off and the procedure was repeated twice to afford **11-[G$_2$]** as a brownish powder in 79% yield (435 mg). ^{31}P{^{1}H} NMR ($CDCl_3$, 121.49 MHz): δ = 8.61 (s, P=N), 62.50 (s, P_1=S), 64.55 (s, P_2=S) ppm. ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 1.46 [s, 216 H, C(CH_3)], 3.00 (br. s, 96 H, C^bH_2), 3.17 (d, $^3J_{HP}$ = 10.5 Hz, 18 H, CH_3NP_1), 3.20 (d, $^3J_{HP}$ = 9.9 Hz, 18 H, CH_3NP_2), 3.50 (br. s, 96 H, C^aH_2), 6.70–6.81 (m, 48 H, C_2^3H), 6.86 (d, $^3J_{HH}$ = 8.1 Hz, 12 H, C_0^2H), 7.05 (d, $^3J_{HH}$ = 7.8 Hz, 48 H, C_2^2H), 7.16 (d, $^3J_{HH}$ = 8.1 Hz, 24 H, C_1^2H), 7.54 (s, 12 H, CH=NNP_1), 7.62 (d, $^3J_{HH}$ = 7.8 Hz, 48 H, C_1^3H, CH=NNP_2) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75.46 MHz): δ = 28.44 [s, CH(CH_3)], 32.85–33.17 (m, CH_3NP_1, CH_3NP_2), 43.52 (br. s, C^b), 49.56 (s, C^a), 79.88 [s, $C(CH_3)_3$], 117.39 (s, C_2^3), 121.48 (s, C_0^2), 121.83 (s, C_1^2), 122.07 (s, C_1^3), 128.27 (s, $C_0^3$and C_1^3), 132.18 (s, C_0^4), 132.55 (s, C_1^4), 138.29 (d, $^3J_{CP}$ = 13.8 Hz, CH=NNP_2), 139.17 (d, $^3J_{CP}$ = 14 Hz, CH=NNP_1), 143.82 (d, $^2J_{CP}$ = 7.0 Hz, C_2^1), 148.84 (s, C_2^4), 151.09 (d, $^2J_{CP}$ = 7.2 Hz, C_0^1, C_1^1), 154.65 (s, C=O) ppm.

11-[G_3]: Dendrimer **4-[G_3]** (0.180 g, 0.016 mmol), **10** (0.250 g, 0.897 mmol) and Cs_2CO_3 (0.575 g, 1.764 mmol) were left to react in THF (2 mL) at room temperature overnight. After reaction completion, salts were removed by centrifugation and the clear solution was concentrated under reduced pressure. The residue was then dissolved in the minimum amount of THF (ca. 1 mL) and precipitated with pentane/diethyl ether. The resulting powder was filtered off and the procedure was repeated twice to afford **11-[G_3]** as a brownish powder in 82% yield (293 mg). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121.49 MHz): δ = 8.17 (s, P=N), 62.56 (s, P_2=S), 63.62 (s, P_1=S), 64.27 (s, P_3=S) ppm. ^1H NMR ($CDCl_3$, 300.13 MHz): δ = 1.46 [br. s, 432 H, C(CH_3)], 2.99 (br. s, 192 H, C^bH_2), 3.23 (m, 126 H, CH_3NP_1, CH_3NP_2, CH_3NP_3), 3.50 (br. s, 192 H, C^aH_2), 6.60–6.85 (m, 96 H, $C_3{}^3H$), 6.85–7.25 (m, 180 H, $C_0{}^2H$, $C_1{}^2H$, $C_2{}^2H$, $C_3{}^2H$), 7.50–7.80 (m, 126 H, CH=N, $C_0{}^3H$, $C_1{}^3H$, $C_2{}^3H$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.46 MHz): δ = 28.44 [s, CH(CH_3)], 32.85–33.2 (m, CH_3NP), 43.41 (br. s, C^b), 49.56 (s, C^a), 79.86 [s, $C(CH_3)_3$], 117.39 (s, $C_3{}^3$), 121.98 (m, $C_0{}^2$, $C_1{}^2$, $C_2{}^2$, $C_3{}^2$), 128.26 (m, $C_0{}^3$, $C_1{}^3$, $C_2{}^3$), 132.50 (m, $C_0{}^4$,$C_1{}^4$, $C_2{}^4$), 138.33 (d, $^3J_{CP}$ = 15.4 Hz, $CH{=}NNP_3$), 139.01 (m, $CH{=}NNP_1$, $CH{=}NNP_2$), 143.91 (d, $^2J_{CP}$ = 7.1 Hz, $C_3{}^1$), 148.81 (s, $C_3{}^4$), 151.09 (m, $C_0{}^1$, $C_1{}^1$, $C_2{}^1$), 154.65 (s, C=O) ppm.

12-[G_1]: Dendrimer **11-[G_1]** (0.6 mg, 0.126 mmol) was solubilised at room temperature in a mixture TFA/DCM (2 mL/ 8 mL) for 20 min then residual solvents were removed. The procedure was repeated twice. Residue obtained was solubilised in MeOH, and then solvents were removed under reduced pressure to eliminate the excess of TFA by co-evaporation. The procedure was repeated twice. Final compound **12-[G_1]** was obtained as a yellowish powder in 95% yield (586 mg). $^{31}P\{^1H\}$ NMR (CD_3OD, 121.49 MHz): δ = 9.34 (s, P=N), 63.93 (s, P=S) ppm. ^1H NMR (CD_3OD, 200.13 MHz): δ = 3.30 (m, 18 H, C^aH_2, C^bH_2, CH_3NP_1), 6.87 (d, $^3J_{HH}$ = 9 Hz, 36 H, $^3J_{HH}$ = 8.7 Hz, $C_0{}^2H$, $C_1{}^2$-H), 7.08 (d, $^3J_{HH}$ = 9 Hz, 24 H, $C_1{}^3H$), 7.75 (s, 6 H, CH=N) ppm. $^{13}C\{^1H\}$ NMR (CD_3OD, 75.46 MHz): δ = 32.42 (d, $^2J_{CP}$ = 11.5 Hz, CH_3NP), 43.28 (s, $CH_2NH_2{}^+$), 46.68 (s, CH_2NAr), 117.74 (s, $C_1{}^3$), 121.19 (s, $C_0{}^2$), 121.74 (d, $^3J_{CP}$ = 4.5 Hz, $C_1{}^2$), 128.12 (s, $C_0{}^3$), 132.74 (s, $C_0{}^4$), 138.83 (d, $^3J_{CP}$ = 14.4 Hz, CH=N), 144.68 (d, $^2J_{CP}$ = 7.1 Hz, $C_1{}^1$), 147.89 (s, $C_1{}^4$), 150.89 (s, $C_0{}^1$), 161.40 (d, $^3J_{CP}$ = 34.5 Hz, CF_3-*C*=O) ppm. (CF_3 could not be attributed).

12-[G_2]: Dendrimer **11-[G_2]** (0.391 mg, 0.036 mmol) was solubilised at room temperature in a mixture TFA/DCM (2 mL/ 8 mL) for 20 min then residual solvents were removed. The procedure was repeated twice. Residue obtained was solubilised in MeOH, and then solvents were removed under reduced pressure to eliminate the excess of TFA by co-evaporation. The procedure was repeated twice. Final compound **12-[G_2]** was obtained as yellowish powder in 97% yield (382 mg). $^{31}P\{^1H\}$ NMR [CD_3COD_3 + D_2O (4:1), 121.49 MHz]: δ = 9.02 (s, P=N), 62.36 (br. s, P_1=S), 64.46 (br. s, P_2=S) ppm. ^1H NMR (CD_3COD_3 + D_2O, 200.13 MHz): δ = 3.10–3.50 (br. s, 236 H, C^aH_2, C^bH_2, CH_3NP_1, CH_3NP_2), 6.88–7.25 (m, 132 H, $C_0{}^2H$, $C_1{}^2H$, $C_2{}^2H$, $C_2{}^3H$), 7.55–7.80 (m, 54 H, $C_0{}^3H$, $C_1{}^3H$, $CH{=}NNP_1$, $CH{=}NNP_2$) ppm. $^{13}C\{^1H\}$ NMR (CD_3COD_3 + D_2O, 75.46 MHz): δ = 32.55–32.84 (m, CH_3NP_1, CH_3NP_2), 43.27 (s, $CH_2NH_2{}^+$), 46.47 (s, CH_2NAr), 116.26 (q, $^1J_{CF}$ = 291 Hz, CF_3), 118.02 (s, $C_2{}^3$), 121.05 (s, $C_0{}^2$), 121.14 (s, $C_1{}^2$), 121.27 (s, $C_2{}^2$), 128.41 (br. s, $C_0{}^3$, $C_1{}^3$), 132.50 (s, $C_0{}^4$), 132.80 (s, $C_1{}^4$), 139.50–139.80 (m, $CH{=}NNP_1$, $CH{=}NNP_2$), 144.27 (d, $^2J_{CP}$ = 4.5 Hz, $C_2{}^1$), 147.96 (s, $C_2{}^4$), 150.91 (m, $C_0{}^1$, $C_1{}^1$), 161.40 (d, $^3J_{CP}$ = 36.2 Hz, CF_3C=O) ppm.

12-[G_3]: Dendrimer **11-[G_3]** (0.399 mg, 0.0168 mmol) was solubilised at room temperature in a mixture TFA/DCM (2.5 mL/ 7.5 mL) for 20 min then residual solvents were removed. The procedure was repeated twice. Residue obtained was solubilised in MeOH, and then solvents were removed under reduced pressure to eliminate the excess of TFA by co-evaporation. The procedure was repeated twice. Final compound **12-[G_3]** was obtained as yellowish powder in 97% yield (375 mg). $^{31}P\{^1H\}$ NMR (CD_3COD_3 + D_2O, 121.49 MHz): δ = 8.62 (s, P=N), 62.71 (br. s, P_1=S, P_2=S), 64.27 (s, P_3=S) ppm. ^1H NMR (CD_3COD_3 + D_2O, 200.13 MHz): δ = 2.90–3.70 (br. s, 498 H, C^aH_2, C^bH_2, CH_3N), 6.80–8.00 (m, 402 H, H_{ar}, CH=N) ppm. $^{13}C\{^1H\}$ NMR (CD_3COD_3 + D_2O, 75.46 MHz): δ = 32.00 (m, CH_3-N), 43.28 (br. s, $CH_2NH_2{}^+$), 46.47 (s, CH_2NAr), 116.26 (q, $^1J_{CF}$ = 291 Hz, CF_3), 117.82 (s, $C_3{}^3$), 121.89 (s, $C_0{}^2$, $C_1{}^2$, $C_2{}^2$, $C_3{}^2$), 128.32 (br. s, $C_0{}^3$, $C_1{}^3$, $C_2{}^3$), 132.50 (s, $C_0{}^4$, $C_1{}^4$, $C_2{}^4$), 139.50–134.00 (m, CH=N), 144.50 (br. s, $C_3{}^1$), 147.97 (br. s, $C_3{}^4$), 151.00 (m, $C_0{}^1$, $C_1{}^1$, $C_2{}^1$), 161.00 (q, $^3J_{CP}$ = 36.0 Hz, CF_3C=O) ppm.

6-[G_1]: Dendrimer **12-[G_1]** (220 mg, 0.044 mmol) and Cs_2CO_3 (350 mg, 1.074 mmol) were mixed in CH_3CN (1 mL) for 30 min at room temperature. Compound **1** (800 mg, 2.24 mmol) was dropped in and the reaction mixture was left to react for 3 d. After reaction completion (^{31}P monitoring), 20 mL of DCM were added and the organic phase was washed with water (20 mL) twice. The residue was dried with $MgSO_4$, filtered and the solvents evaporated. It was then solubilised in ether and precipitated with pentane. The resulting powder was filtered off and the procedure was repeated twice to afford **6-[G_1]** as a brownish powder in 65% yield (223 mg). $^{31}P\{^1H\}$ NMR (CD_3CN, 121.50 MHz): δ = 9.19 (s, P=N), 20.54 (s, P=O), 64.29 (s, P=S) ppm. ^1H NMR (CD_3CN, 300.13 MHz): δ = 1.28–1.34 [m, 288 H, CH(CH_3)], 2.46 (tt, $^3J_{HH}$ = 5.4, $^2J_{HP}$ = 24.0 Hz, 12 H, CH_2CH), 2.54 (br. s, 48 H, C^bH_2), 2.81 (td, $^3J_{HH}$ = 5.4, $^3J_{HP}$ = 15.0 Hz, 24 H, CH_2CH), 3.00 (br. s, 48 H, C^aH_2), 3.20 (d, $^3J_{HP}$ = 9.6 Hz, 18 H, CH_3NP_1), 4.65–4.78 [m, $CH(CH_3)$], 6.74 (d, $^3J_{HH}$ = 8.4 Hz, 24 H, $C_1{}^3H$), 6.91 (s, 12 H, $C_0{}^2H$), 7.00 (d, $^3J_{HH}$ = 8.4 Hz, 24 H, $C_1{}^2H$), 7.59 (d, $^3J_{HH}$ = 7.8 Hz, 12 H, $C_0{}^3H$), 7.67 (s, 6 H, $CH{=}NNP_1$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.80 MHz): δ = 23.13–23.67 [m, CH(CH_3)], 32.96 (d, $^2J_{CP}$ = 11.3 Hz, CH_3NP_1), 37.67 (t, $^2J_{CP}$ = 133.3 Hz, CH_2CH), 48.86 (s, C^a), 52.87 (s, C^b), 54.47 (s, CH_2CH), 70.52–71.20 [m, $CH(CH_3)$], 116.37 (s, $C_1{}^3$), 121.37 (s, $C_0{}^2$), 121.67 (s, $C_1{}^2$), 128.25 (s, $C_0{}^3$), 132.74 (s, $C_0{}^4$), 139.00 (m, CH=N), 143.10 (d, $^2J_{CP}$ = 7.0 Hz, $C_1{}^1$), 149.12 (s, $C_1{}^4$), 150.91 (s, $C_0{}^1$) ppm.

6-[G_2]: Dendrimer **12-[G_2]** (226 mg, 0.021 mmol) and Cs_2CO_3 (328 mg, 1.006 mmol) were mixed in CH_3CN (1 mL) for 30 min at room temperature. Compound **1** (600 mg, 1.68 mmol) was dropped in and the reaction mixture was left to react for 3 d. After reaction completion (^{31}P monitoring), 20 mL of DCM were added and the organic phase was washed with water (20 mL) twice. Residue was dried with $MgSO_4$, filtered and the solvents evaporated. It was then solubilised in ether and precipitated with pentane. The resulting powder was filtered off and the procedure was repeated twice to afford **6-[G_2]** as a brownish powder in 56% yield (197 mg). $^{31}P\{^1H\}$ NMR (CD_3CN, 121.50 MHz): δ = 9.11 (s, P=N), 20.54 (s, P=O), 62.27 (s, P_1=S), 64.80 (br. s, P_2=S) ppm. ^1H NMR (CD_3CN, 300.13 MHz): δ = 1.25–1.40 [m, 576 H, CH(CH_3)], 2.46 (br. t, $^3J_{HP}$ = 24.0 Hz, 24 H, CH_2CH), 2.63 (br. s, 96 H, C^bH_2), 2.91 (br. t, $^3J_{HP}$ = 14.4 Hz, 48 H, CH_2CH), 3.09 (br. s, 96 H, C^aH_2), 3.28 (m, 54 H, CH_3N), 4.78 [br. s, 96 H, $CH(CH_3)$], 6.70–6.85 (m, 48 H, $C_2{}^3H$), 6.95–7.30 (m, 84 H, $C_0{}^2H$, $C_1{}^2H$, $C_2{}^2H$), 7.55–7.70 (m, 54 H, CH=N, $C_0{}^3H$, $C_1{}^3H$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.46 MHz): δ = 23.80–24.30 [m, CH(CH_3)], 33.14 (m, CH_3-N), 37.80 (t, $^2J_{CP}$ = 133.9 Hz, CH_2CH), 49.32 (s, C^a), 52.93 (s, C^b), 54.36 (s, CH_2CH), 70.52–71.25 [m, $CH(CH_3)$], 116.70 (s, $C_1{}^3$), 121.41 (m, $C_0{}^2$), 121.92 (br. s, $C_1{}^2$, $C_2{}^2$), 128.26 (s, $C_0{}^3$, $C_1{}^3$), 132.18

(s, C_0^4), 132.62 (s, C_1^4), 138.24 (m, CH=NNP$_2$), 139.06 (m, CH=NNP$_2$), 143.53 (m, C_2^1), 148.90 (s, C_2^4), 150.22 (s, C_0^1, C_1^1) ppm.

6-[G$_3$]: Dendrimer **12-[G$_3$]** (410 mg, 0.0155 mmol) and Cs_2CO_3 (483 mg, 1.48 mmol) were mixed in CH_3CN (1 mL) for 30 min at room temperature. Compound **1** (883 mg, 2.48 mmol) was dropped in and the reaction mixture was left to react for 2 d. After reaction completion (^{31}P monitoring), 20 mL of DCM were added and the organic phase was washed with water (20 mL) twice. Residue was dried with $MgSO_4$, filtered and the solvents evaporated. It was then solubilised in ether and precipitated with pentane. The resulting powder was filtered off and the procedure was repeated twice to afford **6-[G$_3$]** as a brownish powder in 61% yield (327 mg). ^{31}P{^{1}H} NMR (CD_3CN, 121.50 MHz): δ = 20.57 (s, P=O), 62.69 (s, P$_1$=S, P$_2$=S), 64.58 (s, P$_3$=S) ppm (P=N could not be attributed). ^{1}H NMR (CD_3CN, 300.13 MHz): δ = 1.34 [br. s, 1152 H, CH(CH_3)], 2.41 (br. t, $^3J_{HP}$ = 24.0 Hz, 48 H, CH_2CH), 2.63 (br. s, 192 H, C^{b}H$_2$), 2.91 (br. t, $^3J_{HP}$ = 14.4 Hz, 96 H, CH_2CH), 3.09 (br. s, 192 H, C^{a}H$_2$), 3.28 (m, 126 H, CH_3N), 4.78 [br. s, 192 H, CH(CH_3)], 6.80 (br. s, 96 H, C_3^3H), 6.95–7.30 (m, 180 H, C_0^2H, C_1^2H, C_2^2H, C_3^2H), 7.55–7.70 (m, 126 H, CH=N, C_0^3H, C_1^3H, C_2^3-H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75.46 MHz): δ = 23.8–24.31 [m, CH(CH_3)], 32.97 (m, CH_3N), 37.80 (t, $^2J_{CP}$ = 133.9 Hz, CH_2CH), 49.32 (s, C^a), 52.92 (s, C^b), 54.34 (s, CH_2CH), 70.52–71.35 [m, CH(CH_3)], 116.70 (s, C_3^3), 121.90 (m, C_0^2, C_1^2, C_2^2, C_3^2), 128.26 (s, C_0^3, C_1^3, C_1^3), 132.54 (s, C_0^4, C_1^4, C_2^4), 138.26 (m, CH=NNP$_3$), 139.06 (m, CH=NNP$_2$, CH=NNP$_1$), 143.50 (m, C_3^1), 148.8 (s, C_3^4), 151.22 (s, C_0^1, C_1^1, C_2^1) ppm.

6-[G$_1$] Gd$_{12}$: To a solution of **6-[G$_1$]** (20.3 mg, 2.6×10^{-6} mol) in CH_3CN (3 mL) was added dropwise a solution containing a slight excess of Gd(trifl)$_3$·6H$_2$O (**13**) (25 mg, 3.5×10^{-5} mol). The resulting solution was stirred at room temperature for 48 h. Then the solvent was removed and the solid was washed with CH_2Cl_2 (5 mL) to eliminate the excess of gadolinium triflate. Addition of diethyl ether to the solid yielded a powder product that was filtered off and dried. Yield 12.7 mg, 31.5%. The same procedure was applied to obtain **6-[G$_2$] Gd$_{24}$** and **6-[G$_3$] Gd$_{48}$**.

6-[G$_2$] Gd$_{24}$, 6-[G$_2$]: (25.0 mg, 1.5×10^{-6} mol), Gd(trifl)$_3$·6H$_2$O (**13**) (34 mg, 4.8×10^{-5} mol). Yield 19.2 mg, 40%.

6-[G$_3$] Gd$_{48}$, 6-[G$_3$]: (30.5 mg, 8.8×10^{-7} mol), Gd(trifl)$_3$·6H$_2$O (**13**) (41 mg, 5.7×10^{-5} mol). Yield 21.7 mg, 38%.

14: Phenylpiperazine (136 mg, 0.841 mmol) and **1** (302 mg, 0.855 mmol) were left to react in THF (4 mL) at 50 °C during 5 h. After reaction completion (^{31}P NMR monitoring), the solution was filtered through celite to remove any residual insoluble starting material. After removal of the residual solvent, solid obtained was washed 2 times with pentane (5 mL) and then crystallized with a mixture *n*-pentane/diethyl ether (3:1, with the minimum amount of ether) 3 times to afford **14** as a crystalline powder in 84% yield (366 mg). ^{31}P{^{1}H} NMR ($CDCl_3$, 121.5 MHz): δ = 20.45 (s, P=O) ppm. ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 1.11–1.25 [m, 24 H, CH(CH_3)$_2$], 2.36 (tt, $^3J_{HH}$ = 6.0, $^2J_{HP}$ = 274.3 Hz, 1 H, CH_2CH), 2.49 (t, $^3J_{HH}$ = 4.8 Hz, 2 H, C^{b}H), 2.78 (dt, $^3J_{HH}$ = 6.1, $^3J_{HP}$ = 15.0 Hz, 2 H, CH_2CH), 2.99 (t, $^3J_{HH}$ = 4.6 Hz, 2 H, C^{a}H), 4.57–4.69 [m, 4 H, CH(CH_3)$_2$], 6.64 (t, $^3J_{HH}$ = 7.2 Hz, 1 H, C_0^1-H), 6.72 (d, $^3J_{HH}$ = 8.1 Hz, 2 H, C_0^3-H), 7.06 (dd, $^3J_{HH}$ = $^3J_{HH}$ = 8.4 Hz, 2 H, C_0^2-H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75.47 MHz): δ = 23.47–24.17 [m, CH(CH_3)], 37.68 (t, $^1J_{CP}$ = 133.5 Hz, CH_2CH), 48.86 (s, C^a), 52.80 (s, C^b), 54.25 (s, CH_2CH), 70.58–71.01 [m, CH(CH_3)$_2$], 115.75 (s, C_0^2), 119.36 (s, C_0^1), 128.86 (s, C_0^3), 151.17 (s, C_0^4) ppm. MS (DCI): m/z = 519 [MH]$^+$.

Complex 15: Addition of Gd(CH_3COO)$_3$ (0.007 g, 0.20 10^{-4} mol) and Gd(hfa)$_3$·2H$_2$O (0.077 g, 0.95 10^{-4} mol) to a stirred solution of ligand **14** (0.06 g, 1.15 10^{-4} mol) in diethyl ether (5 mL) yielded a yellow oil 48 h later, after solvent evaporation. Pentane addition induced precipitation of a colorless powder, which was dissolved in dichloromethane and saturated by pentane vapors to give colorless crystals suitable for X-ray analysis.

Crystal Structure Determination: CCDC-727232 (for **15**) contains the supplementary crystallographic data for the complex reported in this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data for 15: $C_{66}H_{100.5}F_{13.5}Gd_2N_4O_{24}P_4$, M = 2028.88, triclinic, a = 12.1180(6), b = 19.9790(10), c = 22.1570(12) Å, α = 114.825(2), β = 92.508(3), γ = 101.168(2)°, V = 4729.1(4) Å^3, T = 180 K, space group $P\bar{1}$, Z = 2, μ (Mo-K_α) = 1.549 mm^{-1}, 166117 reflections collected, 23318 independent (R_{int} = 0.027). The final R values were $R(F)$ = 0.0321 for 20169 reflections with $I > 2\sigma I$ and $wR(F^2)$ = 0.1098 for all data.

Supporting Information (see also the footnote on the first page of this article): Crystallographic data collection and structure determination for **15**, temperature dependence of the magnetic moment μ for **6-[G$_2$]** and **6-[G$_3$]**.

Acknowledgments

We thank the European Community for a PhD grant to G. F. (Fond Social Européen). E. C. thanks the Fundacion Ramon Areces for financial support.

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Received: April 28, 2009
Published Online: July 22, 2009

