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Reduced number of steps for the synthesis of dense and highly functionalized dendrimers

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Abstract—A series of densely functionalized dendrimers is synthesized using two branched monomers of type AB_2 and CD_2, in which the A function (NH_2) reacts with D (CHO) and the B function (Cl) reacts with C (OH). The reaction has been carried out up to the fourth generation possessing 96 end groups and has been obtained in only four steps.

The hyperbranched, perfectly defined structure of dendrimers,[1] and the easy functionalization of their end groups have induced a dramatic expansion of their potential application in various fields of nanosciences including materials[2] and biology.[3] However, the achievement of dendrimers with numerous end groups after only a small number of synthetic steps is not trivial. A few methods have been already proposed to diminish the number of steps, in particular the 'double stage method'[4] and the 'double exponential growth',[5] but these methods does not really decrease the number of steps when considering the whole synthetic process used. In fact, the most powerful strategy to date is the 'orthogonal coupling strategy',[6] which consists in using two types of branched units (AB_n and $CD_{n'}$ monomers, where n and n' are generally equal to 2). This method gives at each step a new generation of layered dendrimers, but it has been mainly used with a set of completely independent classes of protecting groups. To avoid the inconvenience of using protection/deprotection strategies, we have previously proposed for the first time AB_n and $CD_{n'}$ monomers (n, $n' = 2$ and/or 5) bearing two pairs of complementary functions able to react quantitatively and spontaneously without any activating agent.[7] In all cases, the A and D functions were phosphines and azides reacting by Staudinger reactions and creating P=N linkages, whereas the B and C functions were hydrazines and aldehydes reacting by condensation reactions and creating CH=NN linkages. These methods are particularly powerful, but imply the use of easily oxidable phosphines, which must be manipulated under a controlled atmosphere excluding oxygen. On the other hand, our main method of synthesis consists in the repetition of condensation reactions and nucleophilic substitutions;[8] it does not necessitate any drastic conditions, and allowed us to synthesize and characterize the highest generation[9] ever described for any type of dendrimer, but is relatively tedious since the number of end groups is multiplied twice only after two synthetic steps. We report in this paper a substantial improvement of this method, which allows multiplying by two the number of end groups at each step.

The method of synthesis we generally use requires a branched building block of type AB_2 ($H_2NNMeP(S)Cl_2$, with A = NH_2 and B = Cl) and a linear one of type CD (4-hydroxybenzaldehyde, with C = OH and D = CHO). In order to densify more rapidly the number of end groups, this linear building-block should be replaced by a branched one, but having the same type of functions. This is the reason as to why we have considered 5-hydroxyisophthaldehyde **1**, prepared from 5-hydroxydiethylisophthalate[10] in this study. The first step to build the dendrimer consists in grafting 6 equiv of the sodium salt of **1** to $N_3P_3Cl_6$ (Scheme 1). The reaction

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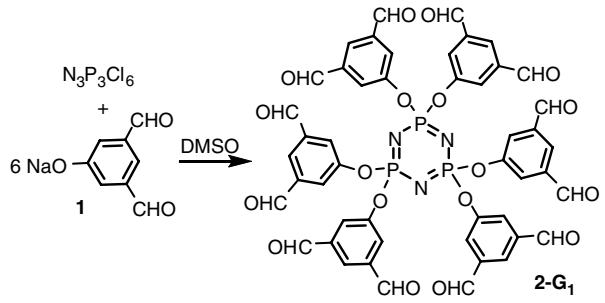


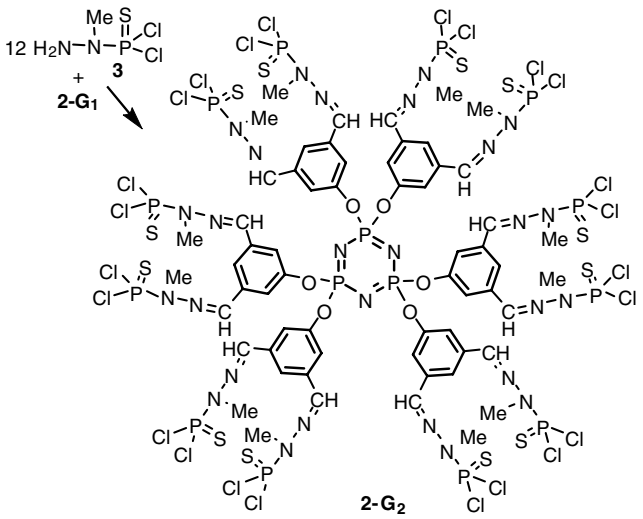
Scheme 1. Synthesis of generation 1.

is carried out in DMSO, due to the relatively poor solubility of the intermediate and resulting compounds.

The reaction is relatively slow and needs 2 days to complete, as shown by ^{31}P NMR monitoring. Indeed, all partly substituted derivatives give a complex mixture of signals, whereas the expected product **2-G$_1$** gives a singlet. This compound is the first generation, since it possesses twice the number of end groups compared to the N_3P_3 core. This dendrimer is also characterized by ^{1}H and ^{13}C NMR, as well as by mass spectrometry (FAB).[11] Figure 1 shows the numbering scheme used for the assignment of the NMR signals of all dendrimers (see references).

The next step is the condensation of **2-G$_1$** with 12 equiv of the phosphorhydrazide **3**. The completion of the reaction is monitored by ^{1}H NMR and IR, which display the total disappearance of the signals due to the aldehyde groups. This second generation (dendrimer **2-G$_2$**) possesses 24 Cl and is obtained in two steps from the hexafunctional core (Scheme 2). Dendrimer **2-G$_2$** is also characterized by mass spectrometry (Ionspray).

This second generation dendrimer is more soluble than the previous generation, thus the grafting of the dialdehyde **1** used in the next step is carried out in THF. However the reaction is relatively slow and needs 5 days to complete, as shown by ^{31}P NMR monitoring. Indeed, the singlet at $\delta = 65.16$ ppm disappears on behalf of the intermediate appearance of a singlet at 71.2 ppm, corresponding to the monosubstitution on the $P(S)Cl_2$ end groups of **2-G$_2$**. The completion of the reaction is shown by the disappearance of this signal, which transforms in the **2-G$_3$** singlet at 66.38 ppm. The third generation **2-G$_3$** possesses 48 aldehyde end groups. Besides multinuclear NMR, it is also characterized by MS (Maldi-Tof) (Scheme 3).



Scheme 2. Synthesis of generation 2.

The fourth generation is obtained by condensation of 48 equiv of the phosphorhydrazide **3** on the aldehyde end groups of dendrimers **2-G$_3$** (Scheme 4).The reaction completes after one night at room temperature, as shown by ^{1}H NMR (disappearance of the signal corresponding to aldehydes). An important broadening of the signals is observed in the ^{1}H NMR spectrum; such phenomenon denotes a 'frozen' structure, as we have already observed.[12] Dendrimer **2-G$_4$** is characterized by multinucleus NMR.[11] The molecular peak of this compound could not be observed by Maldi-Tof, due to the sensitivity of the hydrazone linkage toward the laser light used by this technique.[13]

In an attempt to obtain the fifth generation, 96 equiv of the sodium salt **1** were added to the fourth generation **2-G$_4$**. However, this reaction never went to completion even after prolonged heating, as shown by ^{31}P NMR monitoring, which is really a valued tool to ascertain the completion of reactions (with a precision better than 1%). Figure 2 displays the structure of compound **4**, which is the dendrimer obtained after the same number of steps than **2-G$_4$**, but using this 'classical' method; it allows to visualize by comparison the dramatic difference of steric hindrance between **2-G$_4$** and **4**.

Thus, it seems that steric hindrance precludes a total substitution on the end groups. The phenomenon of 'dense packing' (due to a too high number of end groups to

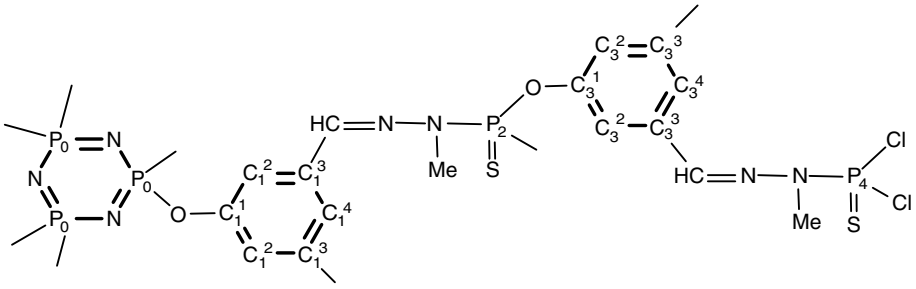
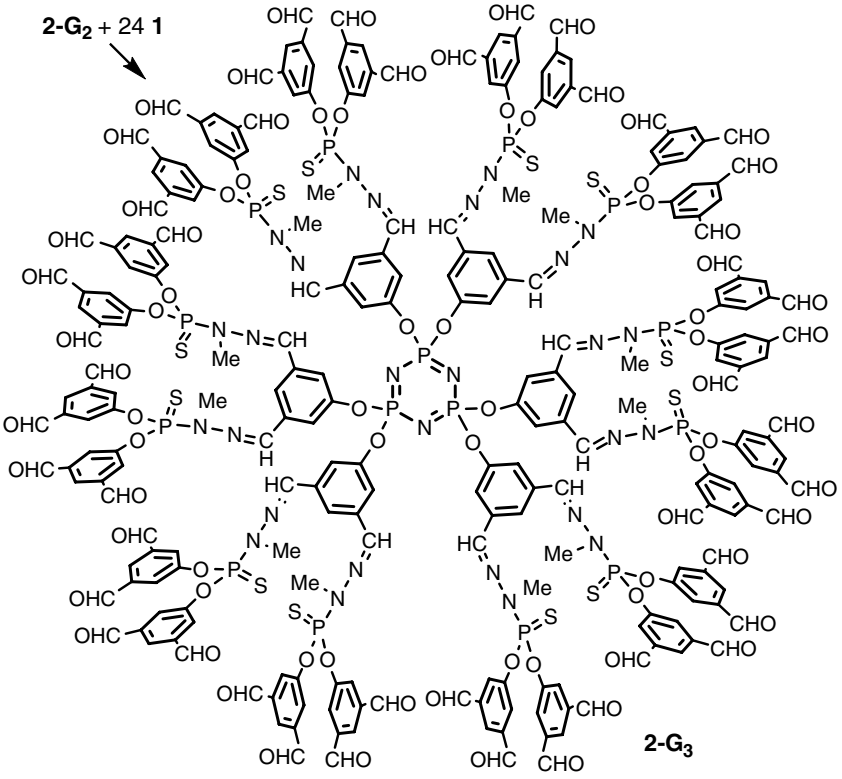
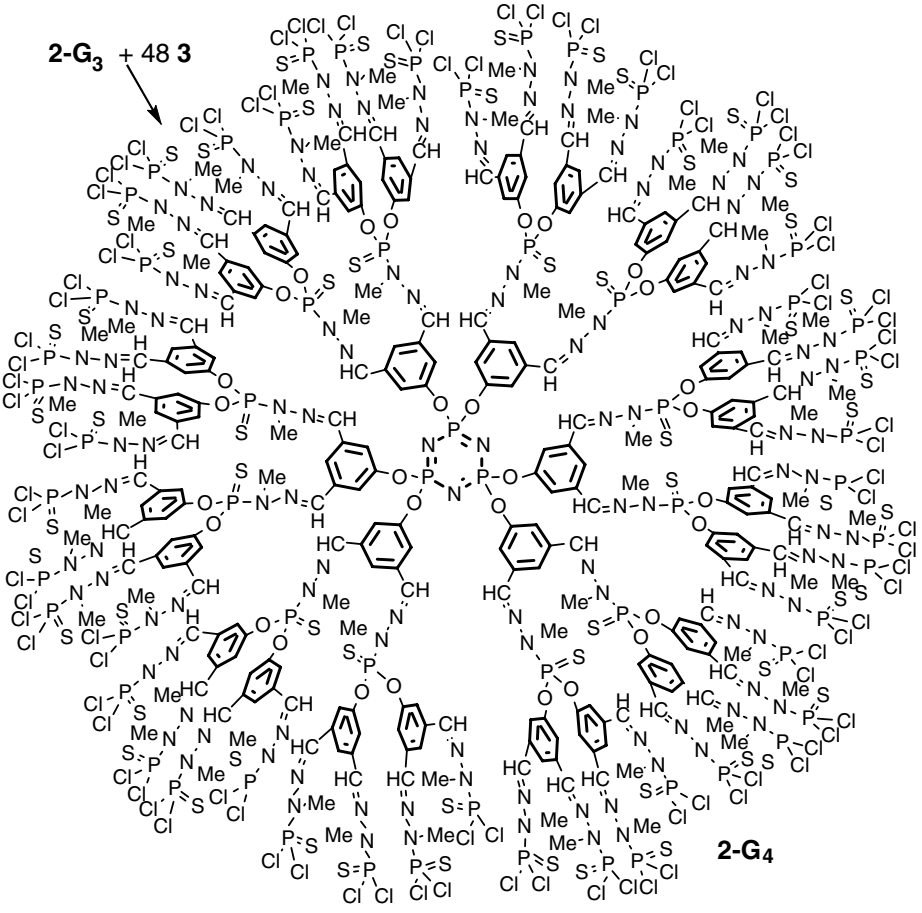


Figure 1. Numbering used for NMR assignment.



Scheme 3. Synthesis of generation 3.



Scheme 4. Synthesis of generation 4.

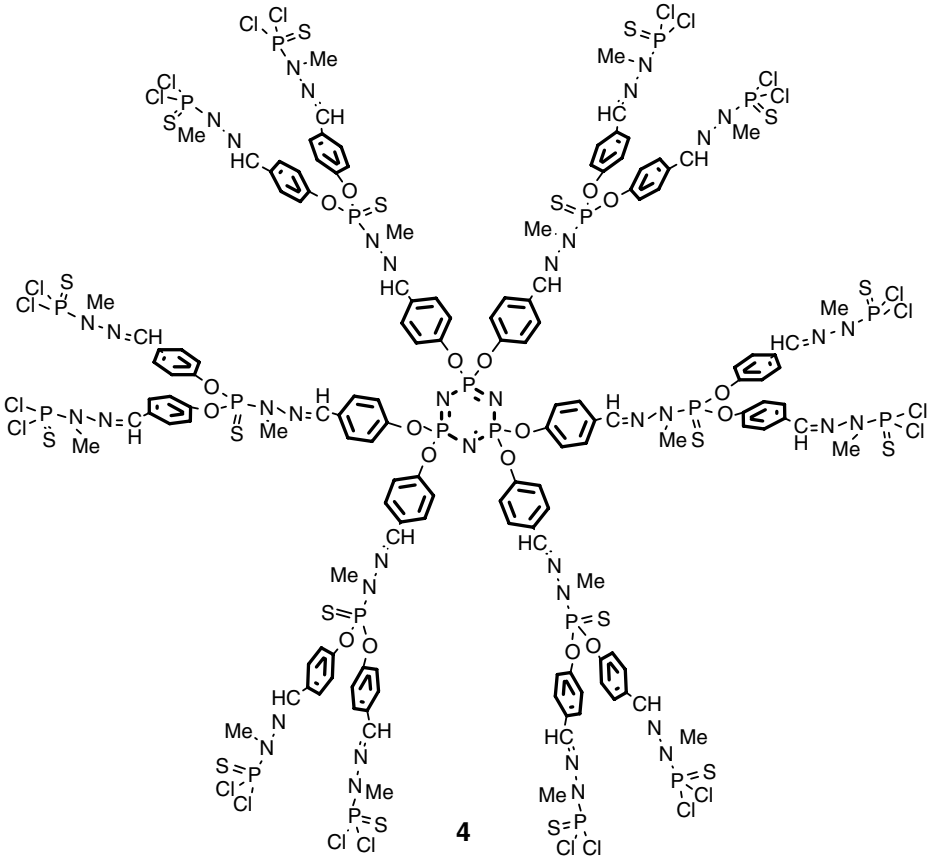


Figure 2. Dendrimer classically obtained after 4 steps (to be compared with **2-G$_4$**, Scheme 4).

be accommodated by a too small surface) has been earlier predicted by de Gennes.[14] We already experienced such phenomenon for the twelfth generation of our 'classical' dendrimers ($AB_2 + CD$ method) built from a trifunctional core,[9] but it was unexpected for a relatively small compound such as **2-G$_4$**. Thus, in addition to the crowding induced by the relatively high number of end groups, it is receivable that the geometry of compound **1** is a further important factor in precluding the total substitution of the end groups. In keeping with this hypothesis, the angle between the OH and CHO groups is 120° instead of 180° for 4-hydroxybenzaldehyde. Such bending should induce rapidly an important entanglement of the branches, which disfavors the accessibility to some end groups, and precludes a full substitution.

In conclusion, we have proposed a new method of synthesis of dendrimers, based on the alternate use of two branched monomers of type AB_2 and CD_2. A dense dendrimer possessing 96 end groups (generation 4) has been obtained in only 4 steps, by very classical and quantitative condensation and substitution reactions. Surprisingly, this compound is the highest generation obtainable in this series due to steric hindrance induced both by the high number of end groups and the geometrical entanglement of branches. Thus, this series of compounds might offer a readily available platform for studying the phenomena occurring at a crowded interface, which might be of interest in particular for explaining the catalytic behaviour of metal-decorated dendrimers.

Acknowledgments

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Supplementary data

Copy of ^{31}P, ^{1}H and ^{13}C NMR spectra for all isolated dendrimers (**2-G$_1$**–**2-G$_4$**), ^{31}P NMR spectrum of an intermediate on going from **2-G$_2$** to **2-G$_3$** as an example of the detection of incomplete substitution, and copy of mass spectra (**2-G$_1$**–**2-G$_3$**). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.112.

References and notes

1. (a) Newkome, G. R.; Vögtle, F.; Moorefield, C. N. *Dendrimers and dendrons*; John Wiley and Sons, 2001; (b) Fréchet, J. M. J.; Tomalia, D. A. *Dendrimers and other dendritic polymers*; John Wiley and Sons, 2001; (c) Majoral, J. P.; Caminade, A. M. *Chem. Rev.* **1999**, *99*, 845.
2. For recent reviews in this field, see in particular: (a) Tully, D. C.; Frechet, J. M. J. *Chem. Commun.* **2001**, 1229; (b) Caminade, A. M.; Majoral, J. P. *Acc. Chem. Res.* **2004**, *37*, 341; (c) Tomalia, D. A. *Mater. Today* **2005**, *8*, 34.
3. For recent reviews in this field, see in particular: (a) Boas, U.; Heegaard, P. M. H. *Chem. Soc. Rev.* **2004**, *33*, 43; (b) Lee, C.; MacKay, J. A.; Frechet, J. M. J.; Szoka, F. C.

Nature Biotechnol. **2005**, *23*, 1517; (c) Caminade, A. M.; Padié, C.; Laurent, R.; Maraval, A.; Majoral, J. P. *Sensors* **2006**, *6*, 901.

4. (a) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4252; (b) Miller, T. M.; Neenan, T. X.; Zayas, R.; Bair, H. E. *J. Am. Chem. Soc.* **1992**, *114*, 1018; (c) Xu, Z. F.; Kahr, M.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4537; (d) Maraval, V.; Laurent, R.; Donnadieu, B.; Mauzac, M.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 2499.
5. (a) Kawaguchi, T.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 2159; (b) Chang, H. T.; Chen, C. T.; Kondo, T.; Siuzdak, G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 182; (c) Ashton, P. R.; Anderson, D. W.; Brown, C. L.; Shipway, A. N.; Stoddart, J. F.; Tolley, M. S. *Chem. Eur. J.* **1998**, *4*, 781.
6. (a) Spindler, R.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans 1* **1993**, 913; (b) Xu, Z.; Moore, J. S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1354; (c) Zeng, F. W.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1996**, *118*, 5326; (d) Deb, S. K.; Maddux, T. M.; Yu, L. P. *J. Am. Chem. Soc.* **1997**, *119*, 9079; (e) Ishida, Y.; Jikei, M.; Kakimoto, M. *Macromolecules* **2000**, *33*, 3202.
7. (a) Brauge, L.; Magro, G.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 6698, correction: *J. Am. Chem. Soc.* **2001**, *123*, 8446.; (b) Maraval, V.; Caminade, A. M.; Majoral, J. P.; Blais, J. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1822; (c) Maraval, V.; Pyzowski, J.; Caminade, A. M.; Majoral, J. P. *J. Org. Chem.* **2003**, *68*, 6043.
8. (a) Launay, N.; Caminade, A. M.; Lahana, R.; Majoral, J. P. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1589; (b) Launay, N.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 3282; (c) Launay, N.; Caminade, A. M.; Majoral, J. P. *J. Organomet. Chem.* **1997**, *529*, 51.
9. Lartigue, M. L.; Donnadieu, B.; Galliot, C.; Caminade, A. M.; Majoral, J. P.; Fayet, J. P. *Macromolecules* **1997**, *30*, 7335.
10. This compound was synthesized in two steps from 5-hydroxydiethylisophthalate by a modification of the published procedure.[15] The first step is the reduction of the esters to the corresponding alcohols by $LiAlH_4$ as published. We modified as follows the second step. A mixture of 3,5-bis(hydroxymethyl)phenol obtained in the first step (0.250 g, 1.6 mmol) and MnO_2 (1.11 g, 12.8 mmol) in 20 mL of THF/CH_2Cl_2 (1:9) was refluxed under stirring for 2 days. The progress of the reaction was supervised by thin layer chromatography (pentane/ethyl-acetate 2:1). 5-hydroxy isophthaldehyde was isolated after column chromatography with the same solvent conditions as a white powder (yield: 62%). ^{1}H NMR (250 MHz, $CDCl_3$): 7.48 (s, 2H, C^2H), 7.78 (s, 1H, C^4H), 9.92 (s, 2H, CHO) ppm. ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$/CD_3CN): 121.04 (s, C^2), 123.23 (s, C^4), 138.53 (s, C^3), 158.38 (s, C^1), 191.33 (s, CHO) ppm. IR (KBr): 1687, 1701 (ν_{CO}) cm^{-1}. The sodium salt of this compound (**1**) was obtained by adding a solution of 5-hydroxyisophthaldehyde (1.205 g, 7.9 mmol) in THF (20 mL) to a suspension of NaH (0.187 g, 7.8 mmol) in THF (6 mL) cooled by an ice bath. The mixture was left stirring overnight, then the solvent was eliminated via a filtering canula. The crude product was washed with four portions of THF. Compound **1** was isolated as an orange powder in 73% yield. It was used for the synthesis of dendrimers without characterization, due to its very poor solubility.
11. *Synthesis of the first generation* **2-G$_1$**. Powdered sodium salt **1** (0.443 g, 2.54 mmol) was added to a solution of $N_3P_3Cl_6$ (0.11 g, 0.32 mmol) in DMSO (4.5 mL). The reaction was stirred at room temperature (rt) for 2 days, then left to evaporate in an evaporating dish. The product was washed six times with MeOH giving 0.131 g of **2-G$_1$** (yield 39.7%) as a poorly soluble white powder. ^{31}P {^{1}H} NMR (81 MHz, DMSO-d_6): 11.28 (s, P_0) ppm. ^{1}H NMR (200 MHz, DMSO-d_6): 7.85 (br s, 12H, C_1^2H), 8.27 (br s, 6H, C_1^4H), 9.96 (br s, 12H, CHO) ppm. ^{13}C {^{1}H} NMR (50 MHz, DMSO-d_6): 124.88 (s, C_1^2), 127.94 (s, C_1^4), 138.31 (s, C_1^3), 150.26 (s, C_1^1), 191.24 (s, CHO) ppm. IR (KBr): 1699 (ν_{CO}) cm^{-1}. MS (FAB): 1030 [M+H]$^+$. *Synthesis of the second generation* **2-G$_2$**. A solution of the phosphorhydrazide **3** in $CHCl_3$ (11 mL of a 0.23 M solution) was added to powdered **2-G$_1$** (0.131 g, 0.126 mmol). The resulting mixture was stirred overnight at rt then precipitated into a pentane/ether (5:1) mixture. After filtration, the resulting powder was solubilized in a minimum amount of THF then precipitated with pentane/ether; this process was repeated 3 times. Dendrimer **2-G$_2$** was isolated in 77% yield (0.288 g). ^{31}P {^{1}H} NMR (81 MHz, $CDCl_3$): 10.48 (s, P_0), 65.16 (s, P_2) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): 3.41 (d, $^3J_{HP} = 13.5$ Hz, 36H, CH_3NP_2), 7.46 (s, 12H, C_1^2H), 7.56 (s, 12H, CH=N), 7.76 (s, 6H, C_1^4H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): 32.05 (d, $^2J_{CP} = 12.8$ Hz, CH_3NP_2), 120.16 (s, C_1^2), 122.97 (s, C_1^4), 136.38 (s, C_1^3),139.74 (d, $^3J_{CP} = 9.4$ Hz, CH=N), 151.18 (s, C_1^1) ppm. MS (IS, MeOH): 2960.3 [M+H]$^+$. *Synthesis of the third generation* **2-G$_3$**. Powdered sodium salt **1** (0.239 g, 1.37 mmol) was added to a solution of the second generation dendrimer **2-G$_2$** (0.157 g, 0.528 μmol) in THF (6 mL). The reaction was left stirring for 5 days at rt while monitoring by ^{31}P NMR. This mixture was then centrifuged and the solution was evaporated to dryness. The resulting powder was solubilized in a minimum amount of THF then precipitated with pentane/ether. Dendrimer **2-G$_3$** was isolated in 46.8% yield (0.142 g). ^{31}P {^{1}H} NMR (81 MHz, DMSO-d_6): 10.42 (s, P_0), 66.38 (s, P_2) ppm. ^{1}H NMR (200 MHz, DMSO-d_6): 3.25 (br d, $^3J_{HP} = 8.9$ Hz, 36H, CH_3NP_2), 7.42 (s, 12H, C_1^2H), 7.70 (s, 12H, CH=N), 7.78 (br s, 54H, C_3^2H, C_1^4H), 8.14 (s, 24H, C_3^4H), 9.89 (s, 48H, CHO) ppm. ^{13}C {^{1}H} NMR (50 MHz, DMSO-d_6): 32.65 (d, $^2J_{CP} = 11.5$ Hz, CH_3NP_2), 119.72 (s, C_1^2), 120.73 (s, C_1^4), 126.07 (s, C_3^2), 127.67 (s, C_3^4), 136.41 (s, C_1^3), 138.00 (s, C_3^3), 140.46 (br d, $^3J_{CP} = 13.3$ Hz, CH=N), 150.64 (d, $^2J_{CP} = 7.0$ Hz, C_3^1), 150.8 (s, C_1^1), 191.09 (s, CHO) ppm. IR (KBr): 1699 (ν_{CO}) cm^{-1}. MS (Maldi-Tof): 5712 [M+Na]$^+$. *Synthesis of the fourth generation* **2-G$_4$**. A solution of the phosphorhydrazide **3** in $CHCl_3$ (3.15 mL of a 0.24 M solution) was added to powdered **2-G$_3$** (0.083 g,14.5 μmol). The resulting mixture was stirred overnight at rt then precipitated into a pentane/ether (5:1) mixture. After filtration, the resulting powder was solubilized in a minimum amount of THF then precipitated with pentane/ether; this process was repeated twice. Dendrimer **2-G$_4$** was isolated in 28.8% yield (0.056 g). ^{31}P {^{1}H} NMR (203 MHz, $CDCl_3$): 7.17 (s, P_0), 62.04 (br s, P_2, P_4) ppm. ^{1}H NMR (200 MHz, $CDCl_3$/CD_3CN): 2.8–3.4 (br m, 180H, CH_3N), 6.9–8.1 (br m, 150H, aromatics and CH=N), ppm. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$/CD_3CN): 32.23 (br s, CH_3NP_4), 33.32 (br s, CH_3NP_2), 120.87 (br s, C_1^2, C_3^2), 123.47 (s, C_1^4, C_3^4), 136.53 (br s, C_1^3, C_3^3), 140.06 (br s, CH=N), 150.96 (br s, C_1^1, C_3^1) ppm.
12. Leclaire, J.; Coppel, Y.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 2304.
13. Blais, J. C.; Turrin, C. O.; Caminade, A. M.; Majoral, J. P. *Anal. Chem.* **2000**, *72*, 5097.
14. De Gennes, P. G.; Hervet, H. *J. Phys. Lett.* **1983**, *44*, 351.
15. Star, A.; Liu, Y.; Grant, K.; Ridvan, L.; Stoddart, J. F.; Steuerman, D. W.; Diehl, M. R.; Boukai, A.; Heath, J. R. *Macromolecules* **2003**, *36*, 553.