Grafting of Tetraazamacrocycles on the Surface of Phosphorus-Containing Dendrimers

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Three types of tetraazamacrocycles (1,4,8,11-tetraazacyclotetradecane, 1,4,8,12-tetraazacyclopentadecane, and 1,4,8,11-tetraazacyclotetradecane-5,7-dione) are grafted on the surface of phosphorus-containing dendrimers possessing $P(S)Cl_2$ end groups (for generations 1 and 3: this corresponds to three and twelve macrocycles, respectively) and on the model compound $PhCH=NN(Me)P(S)Cl_2$. Depending on the nature of the macrocycle, the reaction induces the formation of five-membered rings (diazaphospholanes) or of six-membered rings (diazaphosphorinanes). The structure of the adducts is deduced from ^{13}C NMR spectra and from X-ray diffraction studies of the reaction products (**8**, **9**, **10**) of the model compound.

Introduction

Macrocyclic tetraamine derivatives are useful substrates in various fields of chemistry, including heteropolycyclic chemistry, inorganic coordination chemistry, or medicinal chemistry (contrast agents). In most cases, these derivatives contain only one macrocyclic unit; however, recent work shows that bis(tetraazamacrocycle)s constitute a novel class of antiviral agents against HIV replication.[1] Increasing more the number of tetraazamacrocycles should modify or enhance the properties of the monomeric unit. In this perspective, dendrimers[2] appear as promising supports for a large number of tetraazamacrocycles. Indeed, polyamidoamine (PAMAM)[2a,2b] dendrimers have been coated with DOTA chelators of yttrium (1,4,7,10-tetraazacyclododecanetetraacetic acid) and coupled with a monoclonal antibody for use in radioimmunotherapy.[3] PAMAM dendrimers have also been linked to acetic acid derivatives of cyclen (1,4,7,10-tetrazacyclododecane), and their gadolinium complexes can be used as magnetic resonance imaging agents.[4][5]

We have already shown that phosphorus-containing dendrimers react easily with a large variety of functional groups that can be linked to the surface of the dendrimer,[6] or even to the internal layers.[7] It appeared interesting to us to try to graft tetraazamacrocycles on these phosphorus-containing dendrimers having $P(S)Cl_2$ end groups.

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Results and Discussion

Each site on the surface of the dendrimer possesses two reactive functions (two chlorine), and each tetraazamacrocycle used in this work possesses four NH groups, thus many types of reactions may occur. In order to facilitate the characterization of the resulting products, all experiments with tetraazamacrocycles have been conducted first with a model compound possessing only one $P(S)Cl_2$ group, then applied to the first and third generations of the dendrimer.

Reactions on the Model Compound 2

The phosphorhydrazone **2** is a model compound for one arm of the dendrimer; it is obtained by condensation of benzaldehyde with phosphorhydrazide dichloride **1**. Derivative **2** is treated with three types of tetraazamacrocycles: 1,4,8,11-tetraazacyclotetradecane **3** (cyclam), 1,4,8,12-tetraazacyclopentadecane **4**, and 1,4,8,11-tetraazacyclotetradecane-5,7-dione **5**, in the presence of K_2CO_3 in all cases. First experiments were carried out with one equivalent of macrocycle for each chlorine terminal atom; however, the integration of ^1H-NMR spectra of the resulting products indicated that only one macrocycle per $P(S)Cl_2$ unit was grafted. Thus, the ratio of one macrocycle per $P(S)Cl_2$ group has been used throughout (Scheme 1).

The reaction of macrocycles **3**, **4**, or **5** is monitored by ^{31}P NMR, which indicates the disappearance of the signal at $\delta = 63.6$, corresponding to **2**, in favor of a singlet at $\delta =$ 74.5 (compound **6**), or 72.9 (compound **7**), or 75.9 (compound **8**). ^1H-NMR and mass spectra confirm the quantitative formation of the 1:1 adducts **6**, **7**, and **8** (1 macrocycle per 1 phosphorhydrazone) and the reaction of both chlorine atoms, but do not give any indication of the structure of

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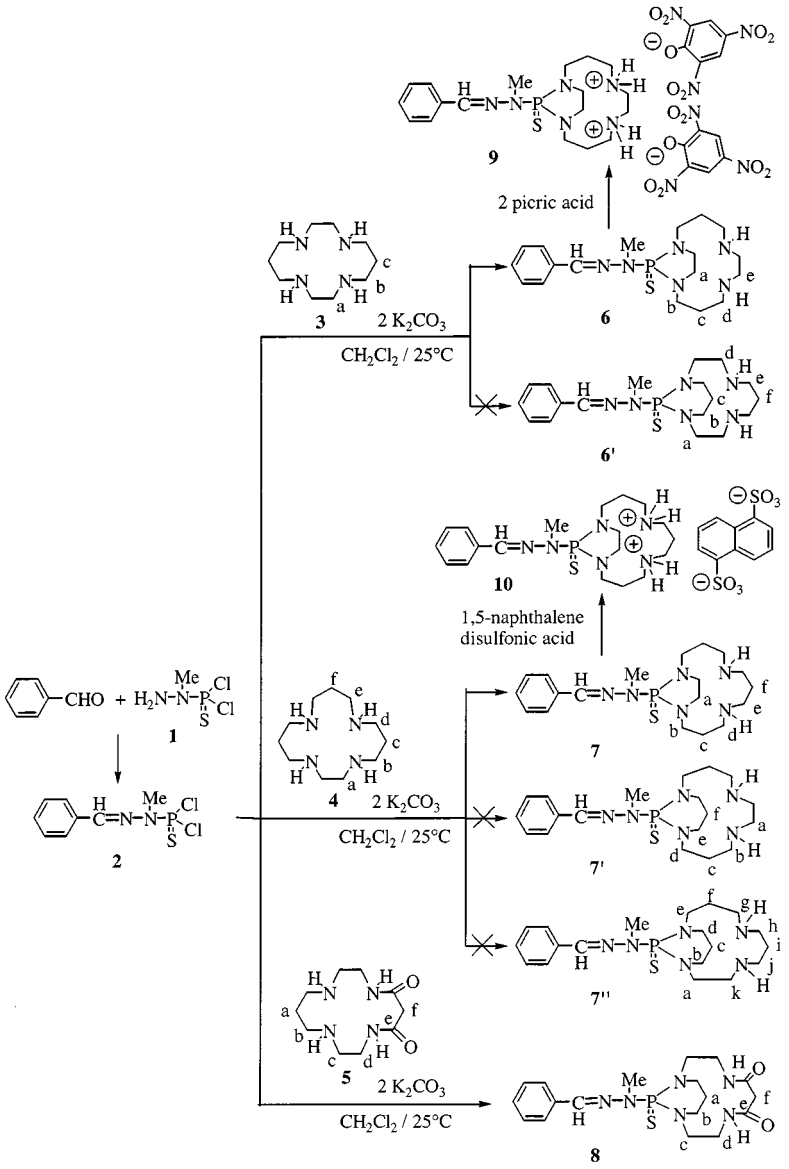


Scheme 1. Reaction of various tetraazamacrocycles with the dichlorothiophosphorhydrazone **2**

the sole regioisomer formed. Indeed, the reaction may theoretically occur across the macrocycle (1,8 position, transannular reaction), or between two adjacent nitrogen atoms. The reaction across the macrocycle would lead to the formation of nine- or ten-membered rings, which are generally thermodynamically unfavorable; this option can thus be rejected. However, the reaction at the two adjacent nitrogen atoms can lead either to the formation of five-membered rings (compounds **6** and **7**: 1,4 position) or six-membered rings (compounds **6′** and **7′′**: 4,8 position; compound **7′**: 8,12 position; compound **8**: 1,11 position) (Scheme 1). Both types of rings are well-known in phosphorus chemistry; for instance, previous work concerning the reaction of $P(NMe_2)_3$ with macrocycles such as cyclam **3** leads to the formation of both diazaphospholane (five-membered ring) and diazaphosphorinane (six-membered ring).[8−10]

Only one type of compound (the diazaphosphorinane **8**) can be obtained from macrocycle **5**, since the reaction of the amide groups is unlikely. The structure is confirmed by an X-ray diffraction determination (Table 1); the CAMERON drawing is depicted in Figure 1. This picture confirms the formation of the diazaphosphorinane **8**, with a chair conformation. The formation of the six-membered ring induces a large deformation of the 14-membered macroring, which is folded. Selected bond lengths and bond angles are gathered in Tables 2 and 3, respectively. All P−N bonds lie in the range expected for such type of bonds.

Two types of compounds could be obtained starting from cyclam **3**, either the diazaphospholane **6** or the diazaphosphorinane **6′** (Scheme 1). The structure actually obtained can be deduced from ^{13}C-NMR spectra; indeed, the formation of the diazaphospholane should give five signals for the CH_2 groups (labeled a−e), whereas the formation of the diazaphosphorinane should give six signals for the CH_2 groups (labeled a−f). The ^{13}C NMR spectrum displays only five different signals for the CH_2 groups, all located in areas

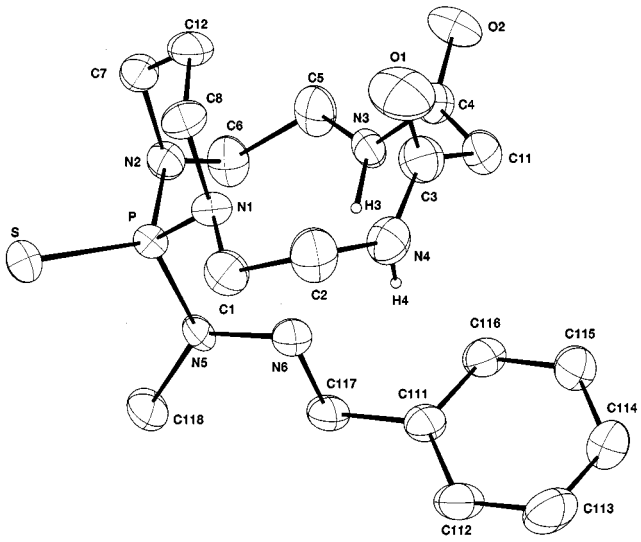


Figure 1. CAMERON drawing of compound **8**

Table 3. Selected bond angles for compounds **8**, **9**, and **10**

Compound	**8**	**9**	**10**
S−P−N(1)	113.72(13)	117.01(7)	118.60(16)
S−P−N(2)	112.91(13)	112.65(7)	115.48(14)
S−P−N(5)	111.96(12)	111.13(7)	109.49(13)
N(1)−P−N(2)	103.00(16)	92.14(9)	93.23(19)
N(1)−P−N(5)	106.48(16)	110.74(9)	110.87(18)
N(2)−P−N(5)	108.15(17)	111.92(9)	107.98(19)
P−N(1)−C(8)	111.7(3)	113.44(14)	114.8(3)
N(1)−C(8)−C(12)	112.0(3)		
N(1)−C(8)−C(7)		106.70(17)	107.0(4)
C(8)−C(12)−C(7)	113.5(3)		
C(12)−C(7)−N(2)	112.0(3)		
C(8)−C(7)−N(2)		106.17(18)	107.0(4)
C(7)−N(2)−P	112.7(3)	114.41(14)	109.5(3)

close to those observed for **3**: three doublets corresponding to the carbon atoms close to phosphorus [C(a), C(b), C(c)], and two singlets corresponding to C(d) and C(e). These data indicate the formation of the diazaphospholane **6**.

Table 1. Crystal data and data-collection information for compounds **8**, **9**, and **10**

Compound	**8**	**9**	**10**
Asymmetric unit	$C_{18}H_{27}N_6O_2PS$	$[C_{18}H_{33}N_6PS][C_6H_2N_3O_7]_2$	$[C_{19}H_{35}N_6PS][C_{10}H_6O_6S_2].[C_3H_7NO]$
Molecular mass	422.49	852.73	769.93
ρ_{calcd} [g·cm^{-3}]	1.38	1.54	1.38
μ [cm^{-1}]	2.55	2.07	2.90
*F*000	896.90	888.64	800.99
Crystal System	Monoclinic	Triclinic	Triclinic
Space group	$P2_1/n$	$P\bar{1}$	$P\bar{1}$
a [Å]	8.884(2)	12.133(3)	7.2307(9)
b [Å]	24.227(3)	13.536(2)	13.972(2)
c [Å]	9.627(2)	14.029(3)	19.003(3)
α [deg]		97.84(2)	79.33(2)
β [deg]	100.74(2)	114.88(2)	79.56(2)
γ [deg]		110.74(2)	78.37(2)
Z	4	2	2
crystal size	0.20×0.12×0.05	0.20×0.10×0.07	0.30×0.15×0.05
2Θ range [°]	2.9−48.4	2.9−48.4	2.9−48.4
reflections measured	8770	14457	12472
symmetry-independent reflections	2127	5402	5437
R	0.042	0.048	0.066
R_w	0.044	0.056	0.074

Table 2. Selected bond lengths for compounds **8**, **9**, and **10**

Compound	**8**	**9**	**10**
P−S	1.9453(14)	1.9414(6)	1.9272(14)
P−N(1)	1.661(3)	1.6403(18)	1.634(4)
P−N(2)	1.647(3)	1.6694(18)	1.665(3)
P−N(5)	1.665(3)	1.6751(18)	1.681(4)
N(5)−N(6)	1.393(4)	1.391(3)	1.375(5)
N(5)−C(118)	1.461(5)	1.460(3)	1.454(5)
N(6)−C(117)	1.278(5)	1.272(3)	1.279(6)
N(1)−C(1)	1.475(5)	1.459(3)	1.528(7)
N(1)−C(8)	1.486(5)	1.467(3)	1.454(6)
N(2)−C(6)	1.456(5)	1.472(3)	1.450(6)
N(2)−C(7)	1.471(6)	1.484(3)	1.490(6)
N(3)−C(4)	1.335(5)	1.498(3)	1.494(8)
N(3)−C(5)	1.452(5)	1.510(3)	1.498(8)
N(4)−C(2)	1.453(6)	1.508(3)	1.468(7)
N(4)−C(3)	1.344(6)	1.489(3)	1.483(8)

However, in order to confirm the formation of **6**, it was highly desirable to obtain single crystals suitable for X-ray structure determination. We did not succeeded with compound **6**, but with its bis(ammonium) salt **9**. For this purpose, two equivalents of picric acid are added to **6**, leading to the quantitative formation of the salt **9** as crude product (Scheme 1). Single crystals are grown by the slow diffusion of ether in a DMF solution of **9**. The X-ray structure determination of salt **9** confirms the formation of the five-membered ring (Figure 2). Two protons are linked to both nitrogen atoms that are not bonded to phosphorus, as could be expected. The bond lengths and bond angles compare well with the values found for compound **8**. The carbon and nitrogen atoms of the five-membered ring almost define a plane; the phosphorus atom lies above this plane. The $C_6H_5CH{=}NN(Me)P{=}S$ moieties are almost flat, a tend-

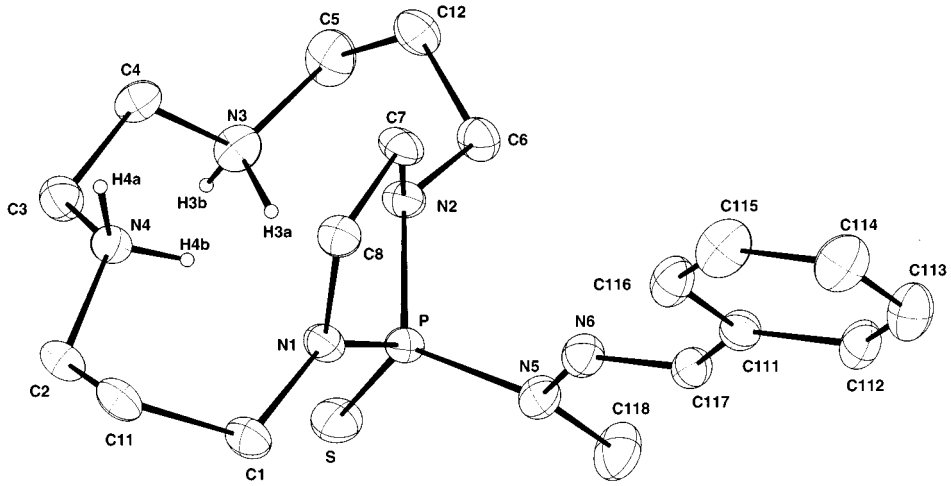


Figure 2. CAMERON drawing of the cationic moieties of compound **9**

ency which was already observed for dendrimers including this type of linkage.[6n]

The less symmetrical macrocycle **4** could lead to the formation of three types of compounds, either the diazaphospholane **7** or the diazaphosphorinanes **7′** or **7′′** (Scheme 1). In this case also, only one regioisomer is obtained, whose structure could be deduced from ^{13}C-NMR spectra. Indeed, all CH_2 groups are nonequivalent for compound **7′′**; they would give 11 signals (labeled a−k), whereas 6 signals are expected for both compounds **7** and **7′**. As the ^{13}C-NMR spectrum displays only 5 signals (one of them is more intense than the others, indicating the overlap of two singlets), structure **7′′** can be ruled out. The choice between structures **7** and **7′** is more difficult. A comparison between the chemical shifts of compound **4** and those obtained for **7** (or **7′**) favors the formation of compound **7**: for instance, the signal identified as C(a) in compound **4** is actually a doublet in compound **7**, whereas it would remain a singlet in compound **7′**. However, it is highly desirable to ascertain the structure of **7**. For this purpose, the bis(ammonium) salt **10** was obtained by adding 1,5-naphthalene disulfonic acid, and crystallized. As for compound **9**, an X-ray structure determination of salt **10** confirms the formation of the five-membered ring (Figure 3). All the data concerning the cationic part of the molecule compares well with that obtained for compound **9**.

Reactions with the First and Third Generations of the Dendrimer

As seen above, the reaction of the model compound with tetraazamacrocycles leads cleanly to the formation of only one product in each case, in spite of the presence of two functional groups on one compound and four on the other one. A question arises when applying this type of reaction to dendrimers: will the regiospecificity observed on a "small" compound be maintained with dendrimers? The experiments are carried out with the first generation of the dendrimer **2-G**$_1$, which possesses three P(S)Cl_2 groups. The reaction with three equivalents of macrocycle leads to the formation of only one type of compound in all cases (Scheme 2), as shown by the presence of only two signals in ^{31}P NMR: one singlet corresponding to the core (δ ca. 53) and another singlet corresponding to the phosphorus linked to the macrocycle [δ = 74.6 (**6-G**$_1$), or 72.9 (**7-G**$_1$), or

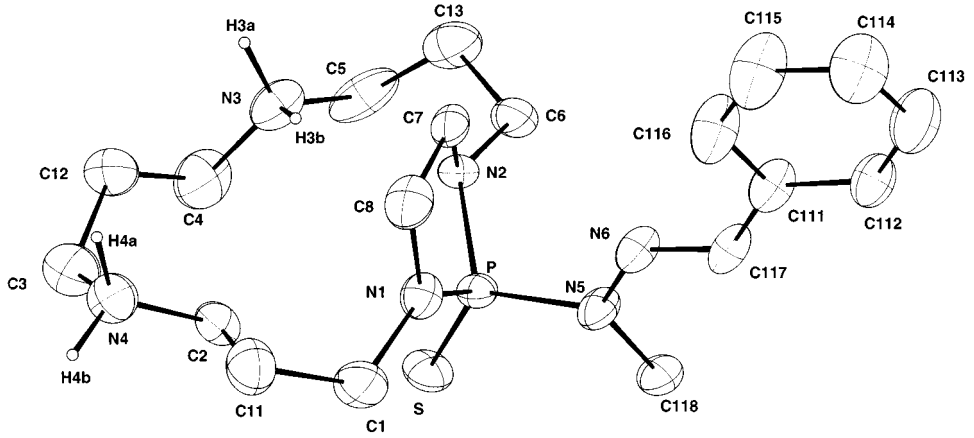
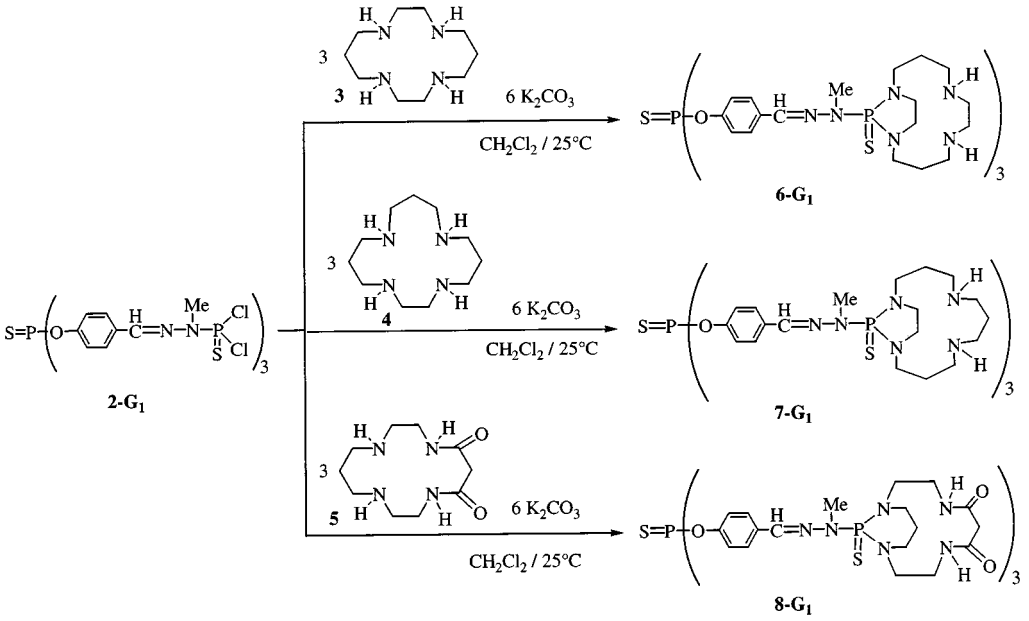


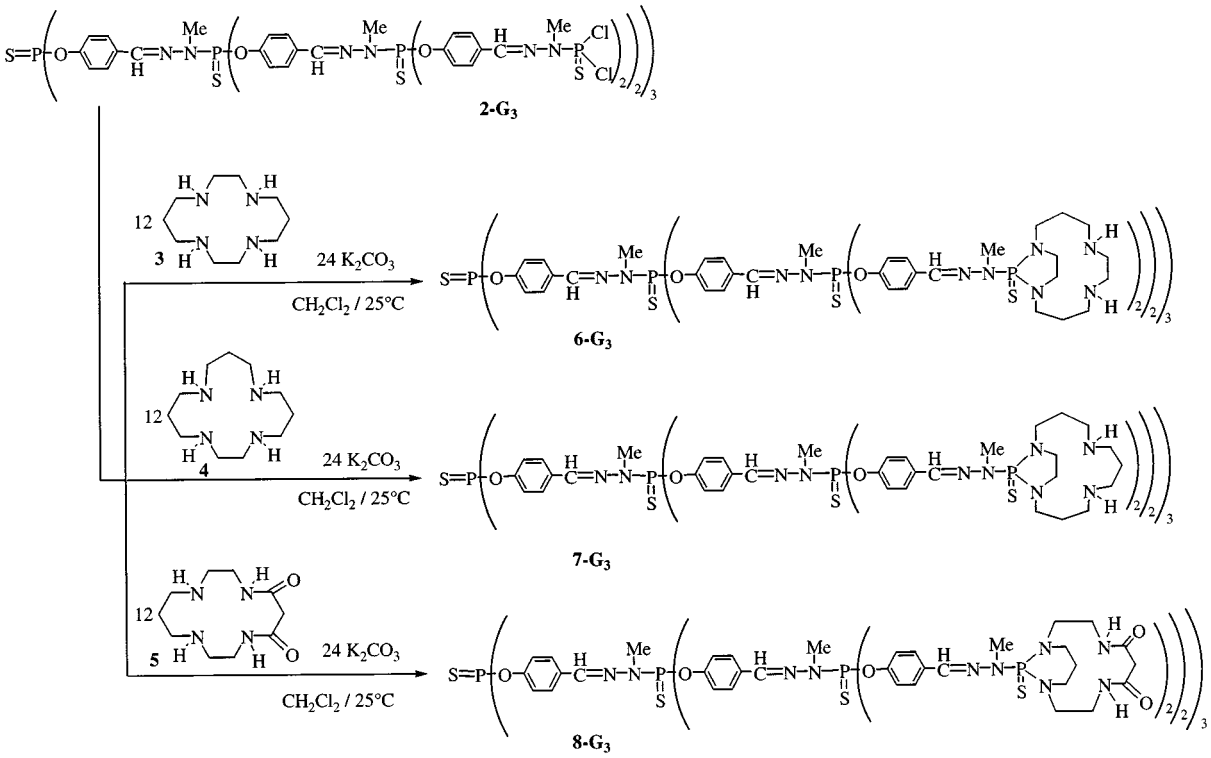
Figure 3. CAMERON drawing of the cationic moieties of compound **10**



Scheme 2. Reaction of various tetraazamacrocycles with the first generation of the dendrimer

75.8 (**8-G**$_1$)]. Mass spectrometry confirms that each P(S)Cl$_2$ group reacted with one macrocycle. Furthermore, the signals corresponding to the CH$_2$ groups on ^{13}C-NMR spectra are absolutely analogous to those obtained for the model compounds **6**, **7**, and **8**. Therefore, one can conclude that macrocycles **3** and **4** react to form five-membered rings, leading to dendrimers **6-G**$_1$ and **7-G**$_1$, respectively, whereas macrocyle **5** forms six-membered rings, leading to dendrimer **8-G**$_1$.

Analogous reactions are carried out with the third generation of the dendrimer **2-G**$_3$, and occur in the same conditions (Scheme 3). These reactions lead to the grafting of 12 macrocycles on the surface of the dendrimer. In all cases, a deshielding of the signal corresponding to the phosphorus of the surface is observed from $\delta = 63$ for **2-G**$_3$ to $\delta = 74.5$, 72.9, or 75.7 for **6-G**$_3$, **7-G**$_3$, and **8-G**$_3$, respectively. ^{13}C-NMR spectra allow to draw analogous conclusions concerning the type of phosphorus heterocycles formed: diaza-



Scheme 3. Reaction of various tetraazamacrocycles with the third generation of the dendrimer

phospholane for **6-G$_3$** and **7-G$_3$**, and diazaphosphorinane for **8-G$_3$**.

We tried to carry out the same type of reaction with the fifth generation of the dendrimer. However in this case, beside the expected signals, small additional peaks are observed, which were not detected for the previous generations. These additional signals may correspond to the formation of a small amount of diazaphosphorinanes (when macrocycles **3** and **4** are used) or to the grafting of some macrocycles between two arms or even between two dendrimers. Thus, in the case of the fifth generation, it has been impossible to purify the expected products by washing or by chromatography.

Conclusion

The reaction of tetraazamacrocycles with RP(S)Cl$_2$ derivatives leads to the formation of five- or six-membered heterocycles, depending on the type of the macrocycle used. X-ray structure determinations show that this reaction induces the selective difunctionalization of the basic macrocyclic skeleton, a type of reaction which is not frequent for tetraazamacrocycles.[11−13] Furthermore, it is well-known that some phosphorus derivatives can act as stable protecting groups for nitrogen.[14] Thus, one can expect that both NH groups of compounds such as **6** or **7** may undergo an *N*-alkylation with electrophiles which possess additional reactive groups, thus leading to 1,4-difunctionalized tetraazamacrocycles after deprotection. Work is also in progress to test the coordination ability of the macrocycles linked to the dendrimers.

Experimental Section

General Remarks: All manipulations were carried out with standard high-vacuum techniques under a dry argon atmosphere. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AC200 or a AMX400 spectrometer. ^{31}P NMR chemical shifts were reported in ppm relative to 85% H_3PO_4. The numbering used for NMR is depicted in Figure 4 for the skeleton of the dendrimer and in Scheme 1 for the macrocyclic moieties. Mass spectra were recorded on a Nermag 1010 spectrometer.

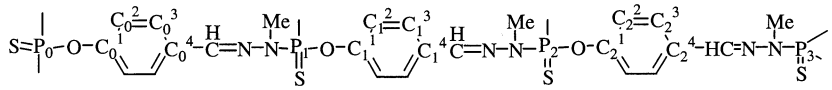


Figure 4. Numbering scheme used for NMR

Synthesis of Compound (2): To a solution of 6.4 mmol of dichlorophosphorhydrazide **1** in chloroform (20 mL) was added 6.4 mmol of benzaldehyde (0.65 mL). The resulting mixture was stirred for 3 h at room temperature and then evaporated to dryness. The residue was washed twice with pentane/ether (1:1) to yield compound **2** as a white powder (47% yield). − ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 63.6 (s). − ^{1}H NMR ($CDCl_3$): δ = 3.50 (d, $^3J_{HP}$ = 14.0 Hz, 3 H, $PNCH_3$), 7.25 (s, 1 H, CH=N), 7.40−7.80 (m, 5 H, C_6H_5). − ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 31.8 (d, $^2J_{CP}$ = 13.7 Hz, $PNCH_3$), 127.4 (s, C_0^2), 128.8 (s, C_0^3), 130.2 (s, C_0^1), 134.1 (s, C_0^4), 141.9 (d, $^3J_{CP}$ = 17.7 Hz, CH=N). − $C_8H_9Cl_2N_2PS$ (267.12): calcd. C 35.97, H 3.40, N 10.49; found: C 35.95, H 3.35, N 10.38.

General Procedure for the Synthesis of Compounds 6, 7, and 8: To a solution of 0.56 mmol of compound **2** in CH_2Cl_2 (10 mL) was added 0.56 mmol of tetraazamacrocycle **3**, **4**, or **5** and 1.12 mmol of potassium carbonate. The resulting suspension was stirred for 3 days at room temperature. The suspension was centrifuged, then filtered, and the solution was evaporated to dryness to yield compounds **6**, **7**, or **8** as white powders.

Compound (6): 55% yield. − ^{31}P{^{1}H} NMR (CH_2Cl_2): δ = 74.5 (s). − ^{1}H NMR (CD_2Cl_2): δ = 2.75−3.53 [m, 12 H, CH_2(c,d,e)], 3.23 (d, $^3J_{HP}$ = 9.25 Hz, 3 H, $PNCH_3$), 3.76−3.87 [m, 8 H, $PNCH_2$(a,b)], 6.50 (br s, 2 H, NH), 7.24−7.60 (m, 6 H, C_6H_5, CH=N). − ^{13}C{^{1}H} NMR (CD_2Cl_2): δ = 24.4 [d, $^3J_{CP}$ = 4.3 Hz, CH_2(c)], 33.1 (d, $^2J_{CP}$ = 10.3 Hz, $PNCH_3$), 43.2 [d, $^2J_{CP}$ = 7.0 Hz, $PNCH_2$(b)], 43.5 [d, $^2J_{CP}$ = 7.2 Hz, $PNCH_2$(a)], 45.7 [s, CH_2(e)], 47.3 [s, CH_2(d)], 126.3 (s, C_0^2), 128.5 (s, C_0^1), 128.6 (s, C_0^3), 135.2 (s, C_0^4), 136.9 (d, $^3J_{CP}$ = 13.0 Hz, CH=N). − $C_{18}H_{31}N_6PS$ (394.52): calcd. C 54.80, H 7.92, N 21.30; found: C 54.67, H 7.85, N 21.18.

Compound (7): 52% yield. − ^{31}P{^{1}H} NMR (CH_2Cl_2): δ = 72.9 (s). − ^{1}H NMR (CD_2Cl_2): δ = 1.53−3.07 [m, 14 H, CH_2(c,d,e,f)], 3.34 (d, $^3J_{HP}$ = 13.9 Hz, 3 H, P-N-CH_3), 3.92−4.00 [m, 8 H, $PNCH_2$(a, b)], 6.06 (br s, 2 H, NH), 7.30−7.57 (m, 6 H, C_6H_5, CH=N). − ^{13}C{^{1}H} NMR (CD_2Cl_2): δ = 24.7 [d, $^3J_{CP}$ = 3.2 Hz, CH_2(c)], 26.1 [s, CH_2(f)], 33.0 (d, $^2J_{CP}$ = 11.1 Hz, $PNCH_3$), 43.9 [d, $^2J_{CP}$ = 7.0 Hz, $PNCH_2$(a)], 44.6 [d, $^2J_{CP}$ = 7.3 Hz, $PNCH_2$(b)], 51.3 [br s, CH_2(d,e)], 126.5 (s, C_0^2), 128.7 (s, C_0^1), 128.8 (s, C_0^3), 135.8 (s, C_0^4), 137.2 (d, $^3J_{CP}$ = 13.1 Hz, CH=N). − IR (KBr): 3400 cm^{-1} ($\tilde{\nu}_{NH}$). − $C_{19}H_{33}N_6PS$ (408.55): calcd. C 55.86, H 8.14, N 20.57; found: C 55.74, H 7.99, N 20.43.

Compound (8): 55% yield. − ^{31}P{^{1}H} NMR (CH_2Cl_2): δ = 75.9 (s). − ^{1}H NMR ($CDCl_3$): δ = 1.70 [br s, 4 H, CH_2(d)], 2.84 (d, $^3J_{HP}$ = 9.40 Hz, 3 H, $PNCH_3$), 2.97−3.45 [m, 4 H, CH_2(a,e)], 3.70−3.85 [m, 4 H, CH_2(c)], 4.20−4.40 [m, 4 H, CH_2(b)], 6.65 (br s, 2 H, NH), 7.25−7.56 (m, 6 H, C_6H_5, CH=N). − ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 26.8 [s, CH_2(a)], 30.3 (d, $^2J_{CP}$ = 7.3 Hz, $PNCH_3$), 37.2 [d, $^3J_{CP}$ = 2.1 Hz, $PNCH_2$(d)], 45.9 [br s, CH_2(b)], 46.2 [s, CH_2(e)], 48.5 [d, $^2J_{CP}$ = 5.2 Hz, $PNCH_2$(c)], 126.1 (s, C_0^2), 128.4 (s, C_0^1), 128.5 (s, C_0^3), 135.5 (s, C_0^4), 138.0 (d, $^3J_{CP}$ = 14.4 Hz, CH=N), 167.1 (s, C=O). − IR (KBr): 3322 cm^{-1} ($\tilde{\nu}_{NH}$). − $C_{18}H_{27}N_6O_2PS$ (422.49): C 51.17, H 6.44, N 19.89; found: C 51.03, H 6.41, N 19.73.

General Procedure for the Synthesis of Dendrimers (6-G$_1$), (6-G$_3$), (7-G$_1$), (7-G$_3$), (8-G$_1$), and (8-G$_3$): To a solution of dendrimer **2-G$_n$** (n = 1, 0.220 mmol; n = 3, 0.0186 mmol) in CH_2Cl_2 (10 mL) was added the tetraazamacrocycle **3**, **4**, or **5** (n = 1, 0.660 mmol; n = 3, 0.224 mmol) and potassium carbonate (n = 1, 1.320 mmol; n = 3, 0.448 mmol). The resulting suspension was stirred for 4 days at room temperature, and then centrifuged. The solution was evaporated to dryness to yield compounds **6-G$_n$**, **7-G$_n$** or **8-G$_n$** (n = 1,3) as white powders.

Dendrimer (6-G$_1$): 70% yield. − ^{31}P{^{1}H} NMR (CH_2Cl_2): δ = 52.9 (s, P_0), 74.6 (s, P_1). − ^{1}H NMR ($CDCl_3$): δ = 1.60−3.50 [m, 36 H, CH_2(c,d,e)], 3.25 (d, $^3J_{HP}$ = 8.7 Hz, 9 H, P_1NCH_3), 3.77−3.84 [m,

24 H, P_1NCH_2(a,b)], 5.51 (br s, 6 H, NH), 7.24−7.52 (m, 15 H, C_6H_4, CH=N). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 24.4 [d, $^3J_{CP}$ = 4.0 Hz, P_1NCH_2(c)], 33.2 (d, $^2J_{CP}$ = 10.5 Hz, P_1NCH_3), 43.1 [d, $^2J_{CP}$ = 7.1 Hz, P_1NCH_2(b)], 43.4 [d, $^2J_{CP}$ = 6.0 Hz, P_1NCH_2(a)], 45.6 [s, CH_2(e)], 47.2 [s, CH_2(d)], 121.0 (d, $^3J_{CP}$ = 4.3 Hz, C_0^2), 127.5 (s, C_0^3), 133.0 (br s, C_0^4), 135.6 (br s, CH=N), 150.3 (br s, C_0^1). − IR (KBr): 3404 cm^{-1} ($\tilde{\nu}_{NH}$). − MS: *m/z*: 1291 $[M + 1]^+$. − $C_{54}H_{90}N_{18}O_3P_4S_4$ (1291.57): calcd. C 50.22, H 7.02, N 19.52; found: C 50.07, H 6.89, N 19.32.

Dendrimer (6-G_3): 58% yield. − $^{31}P\{^1H\}$ NMR (CH_2Cl_2): δ = 52.3 (br s, P_0), 62.4 (br s, P_1, P_2), 74.5 (s, P_3). − ^1H NMR ($CDCl_3$): δ = 1.57−3.06 [m, 144 H, CH_2(c,d,e)], 3.25 (d, $^3J_{HP}$ = 12.5 Hz, 63 H, $P_{1,2,3}NCH_3$), 3.67−3.83 [m, 96 H, P_3NCH_2(a,b)], 5.54 (br s, 24 H, NH), 7.18−7.66 (m, 105 H, C_6H_4, CH=N). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 24.9 [br s, CH_2(c)], 33.4 (d, $^2J_{CP}$ = 11.8 Hz, $P_{1,2,3}NCH_3$), 43.4 [d, $^2J_{CP}$ = 4.0 Hz, P_3NCH_2(b)], 43.6 [d, $^2J_{CP}$ = 6.0 Hz, P_3NCH_2(a)], 46.7 [br s, CH_2(e)], 49.3 [br s, CH_2(d)], 121.5 (br s, C_0^2, C_1^2), 121.8 (s, C_2^2), 127.5 (s, C_2^3), 128.3 (br s, C_0^3, C_1^3), 132.2 (s, C_2^4), 132.9 (br s, C_0^4, C_1^4), 135.7−136.2 [m, $(CH=N)_{0,1}$], 138.6−139.4 [m, $(CH=N)_2$], 150.6−151.2 (m, C_0^1, C_1^1, C_2^1). − IR (KBr): 3400 cm^{-1} ($\tilde{\nu}_{NH}$).· − $C_{288}H_{432}N_{90}O_{21}P_{22}S_{22}$ (6877.98): calcd. C 50.29, H 6.33, N 18.33; found: C 49.93, H 6.21, N 18.09.

Dendrimer (7-G_1): 64% yield. − $^{31}P\{^1H\}$ NMR (CH_2Cl_2): δ = 53.0 (s, P_0), 72.9 (s, P_1). − ^1H NMR (CD_2Cl_2): δ = 1.55−3.07 [m, 42 H, CH_2(c,d,e,f)], 3.34 (d, $^3J_{HP}$ = 9.15 Hz, 9 H, P_1NCH_3), 3.92−3.98 [m, 24 H, P_1NCH_2(a,b)], 6.72 (br s, 6 H, NH), 7.20−7.63 (m, 15 H, C_6H_4, CH=N). − $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 24.7 [br s, CH_2(c)], 26.0 [br s, CH_2(f)], 33.2 (d, $^2J_{CP}$ = 10.8 Hz, P_1NCH_3), 43.9 [d, $^2J_{CP}$ = 6.5 Hz, P_1NCH_2(a)], 44.6 [d, $^2J_{CP}$ = 7.2 Hz, P_1NCH_2(b)], 51.3 [br s, CH_2(d,e)], 121.5 (d, $^3J_{CP}$ = 4.3 Hz, C_0^2), 127.8 (s, C_0^3), 133.8 (s, C_0^4), 135.7 (d, $^3J_{CP}$ = 13.0 Hz, CH=N), 150.5 (d, $^2J_{CP}$ = 7.3 Hz, C_0^1). − IR (KBr): 3400 cm^{-1} ($\tilde{\nu}_{NH}$). − MS: *m/z*: 1333 $[M + 1]^+$. − $C_{57}H_{96}N_{18}O_3P_4S_4$ (1333.65): C 51.33, H 7.26, N: 18.90; found: C 51.22, H 5.14, N 18.83.

Dendrimer (7-G_3): 30% yield. − $^{31}P\{^1H\}$ NMR (CH_2Cl_2): δ = 52.4 (s, P_0), 62.4 (br s, P_1, P_2), 72.9 (s, P_3). − ^1H NMR (CD_2Cl_2): δ = 0.80−3.05 [m, 168 H, CH_2(c,d,e,f)], 3.27 (d, $^3J_{HP}$ = 8.80 Hz, 63 H, $P_{1,2,3}NCH_3$), 3.84−3.90 [m, 96 H, P_3NCH_2(a,b)], 6.00 (br s, 24 H, NH), 7.13−7.67 (m, 105 H, C_6H_4, CH=N). − $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 22.5 [br s, CH_2(c)], 24.6 [br s, CH_2(f)], 33.0 (d, $^2J_{CP}$ = 10.9 Hz, $P_{1,2,3}NCH_3$), 43.7 [br s, P_3NCH_2(a)], 44.4 [d, $^2J_{CP}$ = 7.3 Hz, P_3NCH_2(b)], 51.2 [br s, CH_2(e)], 51.6 [br s, CH_2(d)], 121.6 (br s, C_0^2, C_1^2, C_2^2), 127.4 (s, C_2^3), 128.2 (br s, C_0^3, C_1^3), 132.0 (br s, C_0^4, C_1^4), 132.8 (s, C_2^4), 135.7 [d, $^3J_{CP}$ = 11.4 Hz, $(CH=N)_2$], 138.8−139.4 [m, $(CH=N\text{-})_{0,1}$], 150.5 (d, $^2J_{CP}$ = 6.7 Hz, C_2^1), 151.1 (d, $^2J_{CP}$ = 7.3 Hz, C_0^1, C_1^1). − IR (KBr): 3435 cm^{-1} ($\tilde{\nu}_{NH}$). − $C_{300}H_{456}N_{90}O_{21}P_{22}S_{22}$ (7046.30): calcd. C 51.14, H 6.52, N 17.89; found: C 50.84, H 6.40, N 17.63.

Dendrimer (8-G_1): 75% yield. − $^{31}P\{^1H\}$ NMR (CH_2Cl_2): δ = 52.7 (s, P_0), 75.8 (s, P_1). − ^1H NMR ($CDCl_3$): δ = 0.82−3.41 [m, 24 H, CH_2(a,d,e)], 2.81 (d, $^3J_{HP}$ = 9.3 Hz, 9 H, P_1NCH_3), 3.65−3.76 [m, 12 H, P_1-N-CH_2(c)], 4.18−4.25 [m, 12 H, P_1-N-CH_2(b)], 6.68 (br s, 6 H, NH), 7.16−7.63 (m, 15 H, C_6H_4, CH=N). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 27.0 [br s, CH_2(a)], 30.6 (d, $^2J_{CP}$ = 7.3 Hz, P_1NCH_3), 37.4 [br s, P_1NCH_2(d)], 45.9 [br s, CH_2(b)], 46.0 [br s, CH_2(e)], 48.7 [d, $^2J_{CP}$ = 4.0 Hz, P_1NCH_2(c)], 121.5 (d, $^3J_{CP}$ = 4.6 Hz, C_0^2), 127.6 (s, C_0^3), 134.0 (s, C_0^4), 136.6 (d, $^3J_{CP}$ = 14.4 Hz, CH=N), 150.5 (d, $^2J_{CP}$ = 8.0 Hz, C_0^1), 167.3 (s, C=O). − IR (KBr): 3322 ($\tilde{\nu}_{NH}$), 1677 cm^{-1} ($\tilde{\nu}_{C=O}$). − MS: *m/z*: 1375 $[M + 1]^+$. − $C_{54}H_{78}N_{18}O_9P_4S_4$ (1375.47): calcd. C 47.15, H 5.72, N 18.33; found: C 47.01, H 5.61, N 18.24.

Dendrimer (8-G_3): 25% yield. − $^{31}P\{^1H\}$ NMR (CH_2Cl_2): δ = 52.5 (s, P_0), 62.2 (br s, P_1, P_2), 75.7 (s, P_3). − ^1H NMR ($CDCl_3$): δ = 1.64−3.43 [m, 96 H, CH_2(a,d,e)], 3.30 (d, $^3J_{HP}$ = 10.2 Hz, 63 H, $P_{1,2,3}NCH_3$), 3.71−4.24 [m, 96 H, P_3NCH_2(c,b)], 6.71 (br s, 24 H, NH), 7.13−7.70 (m, 105 H, C_6H_4, CH=N). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 26.8 [br s, CH_2(a)], 30.6 (d, $^2J_{CP}$ = 6.0 Hz, P_3NCH_3), 33.0 (br s, $P_{1,2}NCH_3$), 37.3 [br s, CH_2(d)], 45.9 [br s, CH_2(b)], 46.4 [br s, CH_2(e)], 48.6 [d, $^2J_{CP}$ = 3.6 Hz, P_3NCH_2(c)], 121.7 (d, $^3J_{CP}$ = 4.5 Hz, C_0^2, C_1^2, C_2^2), 127.4 (s, C_2^3), 128.4 (br s, C_0^3, C_1^3), 133.2 (br s, C_0^4, C_1^4, C_2^4), 136.9−137.3 [m, $(CH=N)_2$], 138.8−139.0 [m, $(CH=N)_{0,1}$], 150.6−151.2 (m, C_0^1, C_1^1, C_2^1), 167.4 (s, C=O). − IR (KBr): 3293 ($\tilde{\nu}_{NH}$), 1677 cm^{-1} ($\tilde{\nu}_{C=O}$). − $C_{288}H_{384}N_{90}O_{45}P_{22}S_{22}$ (7213.58): calcd. C 47.95, H 5.37, N 17.47; found: C 47.79, H 5.21, N 17.32.

Synthesis of Compound (9): To a solution of 0.25 mmol of compound **6** in methanol (10 mL) was added a solution of 0.5 mmol of 2,4,6-trinitrophenol in methanol (10 mL). A yellow precipitate was obtained and separated by filtration. The precipitate was dissolved in a minimum amount of DMF and crystallized by the slow diffusion of ether into DMF.

9: Yellow crystals, 21% yield. − $^{31}P\{^1H\}$ NMR (DMF): δ = 74.5 (s). − ^1H NMR ([D_6] DMSO): δ = 3.13−3.46 [m, 12 H, CH_2(c,d,e)], 3.23 (d, $^3J_{HP}$ = 10.0 Hz, 3 H, $PNCH_3$), 3.73−3.81 [m, 8 H, $PNCH_2$(a,b)], 7.4−7.76 (m, 6 H, C_6H_5, CH=N), 8.73 (s, 4 H, C_6H_2). − $^{13}C\{^1H\}$ NMR ([D_6] DMSO): δ = 22.6 [d, $^3J_{CP}$ = 5.0 Hz, CH_2(c)], 32.7 (d, $^2J_{CP}$ = 9.2 Hz, $PNCH_3$), 42.7 [d, $^2J_{CP}$ = 4.7 Hz, $PNCH_2$(b)], 43.5 [d, $^2J_{CP}$ = 6.1 Hz, $PNCH_2$(a)], 42.4 [s, CH_2(e)], 44.8 [s, CH_2(d)], 124.6 (s, C^o), 125.4 (s, C^m), 126.5 (s, C_0^2), 128.8 (br s, C_0^1, C_0^3), 135.5 (s, C_0^4), 138.6 (d, $^3J_{CP}$ = 13.0 Hz, CH=N), 141.8 (s, C^p), 161.0 (s, C^i). − $C_{30}H_{37}N_{12}O_{14}PS$ (852.73): C 42.26, H 4.37, N 19.71; found: C 42.21, H 4.33, N 19.63

Synthesis of Compound (10): To a solution of 0.25 mmol of compound **7** in ethanol (10 mL)) was added a solution of 0.25 mmol of 1,6-naphthalene disulfonic acid in ethanol (5 mL). A white precipitate was obtained and separated by filtration. The precipitate was dissolved in a minimum amount of DMF and crystallized by the slow diffusion of ether into DMF. Compound **10** crystallized with one molecule of DMF.

10: Pale yellow crystals, 8% yield. − $^{31}P\{^1H\}$ NMR (DMF): δ = 72.9 (s). − $C_{29}H_{41}N_6O_6PS_3$,C_3H_7NO (769.99): C 48.22, H 6.28, N 12.73; found: C 48.31, H 6.20, N 12.69

X-ray Crystallographic Study of 8, 9, and 10: The X-Ray diffraction analyses were carried out on a STOE I.P.D.S for all compounds and with a Mo-K_α radiation (λ = 0.71073 Å) at room temperature for **8** and at low temperature (T = 160 K) for **9** and **10**. Crystal decay was monitored by measuring 200 reflections by image, and the final unit cells were obtained by the least-squares refinement. Only statistical fluctuations were observed in the intensity monitors over the course of the data collection; no absorption corrections were applied on the data.

The three structures were solved by using direct methods (SIR92)[15] and refined by least-squares procedures on Fobs. The hydrogen atoms were located on difference Fourier maps, but they were introduced in the calculation in idealized positions (d_{C-H} = 0.98 Å) with isotropic thermal parameters fixed at 20% higher than those of the carbon to which they were connected, and their atomic coordinates were recalculated after each cycle of refinement. However, the specific H atoms of the amine functions have been isotropically refined.

For the structure **10** a molecule of dimethylformamide was located; this molecule is statistically distributed on two sites with a ratio

(0.60\0.40). Refinement of this model gave a convergence at R (Rw) = 0.066 (0.074).

For all models, refinements were carried out by minimizing the function $\Sigma w(||F_o| - |F_c||)^2$, where F_o and F_c are respectively the observed and calculated structure factors. In the last cycles of refinement a scheme of ponderation was used,[16] and the models reached convergence with the formula:

$$R = \Sigma(||F_o|-|F_c||)/\Sigma|F_o| \quad Rw = [\Sigma w(||F_o|-|F_c||)^2/\Sigma w(|F_o|)^2]^{1/2}$$

The calculations were performed with the aid of CRYSTALS programs[17] running on a PC, and the drawing of molecules were realized with CAMERON[18] with thermal ellipsoids fixed at 50% probability level. The atomic scattering factors were taken from International Tables for X-Ray Crystallography.[19]

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-114170 (**8**), CCDC-114171 (**9**), and CCDC-114172 (**10**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. Code +44 (1223) 336-033; E-mail: deposit@ccdc.cam.ac.uk]

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