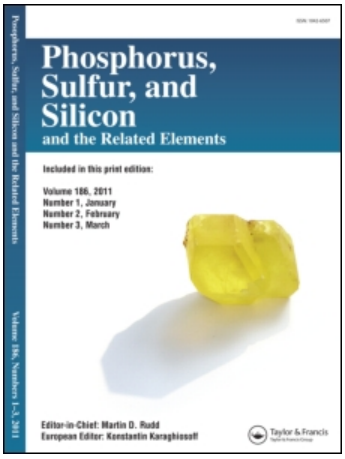

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On the Scent of Dandelion Dendrimers. Part I. Cyclophosphazenic Hexapodanes as New Cores

François Sournies[a]; Laurence Labrousse[a]; Marcel Graffeuil[a]; François Crasnier[a]; Jean-Paul Faucher[a]; Marie-Christine Labarre[a]; Jean-François Labarre[a]

[a] Institut de Chimie Moléculaire Paul Sabatier, Laboratoire Structure et Vie, Université Paul Sabatier, Toulouse Cedex, France

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ON THE SCENT OF DANDELION DENDRIMERS. PART I. CYCLOPHOSPHAZENIC HEXAPODANES AS NEW CORES

FRANÇOIS SOURNIES, LAURENCE LABROUSSE, MARCEL GRAFFEUIL, FRANÇOIS CRASNIER, JEAN-PAUL FAUCHER, MARIE-CHRISTINE LABARRE and JEAN-FRANÇOIS LABARRE*

Institut de Chimie Moléculaire Paul Sabatier, Laboratoire Structure et Vie, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex, France

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Aminolysis of $N_3P_3Cl_6$ by long-chain diamines, $H_2N—(CH_2)_n—NH_2$ ($n \geq 6$), leads regiospecifically to hexadangling (or hexapodanes) monomeric species provided it was achieved on alumina impregnated with potassium hydroxide. These reactions run instantaneously at room temperature. Such hexapodanes constitute starting materials (cores) for future design of spherical (i.e. aesthetically similar to dry dandelion flowers) cyclophosphazenic dendrimers.

Key words: Cyclophosphazene; regiospecific aminolysis; dry media; alumina supported reaction; dendrimers; dandelion flowers.

INTRODUCTION

Biogenic polyamines-linked cyclophosphazenes[1] were developed in our group during the last decade with the aim of producing more selective antitumour and immuno-modulating drugs, biogenic polyamines (namely 1,3-Diaminopropane, putrescine, cadaverine, spermidine and spermine) being used as tumor finders.[2,3]

The reactions of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, with biogenic polyamines give unique products the structure of which depends drastically on the nature of the polyamine and on the reactional medium. 1,3-Diaminopropane (DAP) and 1,4-Diaminobutane (putrescine) lead commonly to spiro configurations (in which the diamino ligand is grafted as a spiro loop onto one phosphorus atom of one N_3P_3 ring) whereas 1,5-Diaminopentane (cadaverine) and higher cousins yield bino structures (in which the diamino ligand bridges two different N_3P_3 rings). Moreover, the bis-(2-aminoethyl)-ether, $H_2N—(CH_2)_2—O—(CH_2)_2—NH_2$, an oxygenated isologous of cadaverine, yields neat cis-ansa derivatives (in which the diamino ligand is grafted on one side of one N_3P_3 ring as an ansa arch onto two different phosphorus atoms).[4–7] On the other hand, spermidine and spermine generate exotic structures, coded as spiransa[1,8,9] and dispiransa,[1,9,10] which are merged configurations from the pure spiro and cis-ansa ones (Figure 1). Thus, there exists a sort of molecular additivity within the field of polyamine-linked cyclophosphazene chemistry, any molecule containing several spiro loops, bino bridges and/or ansa arches being synthesized at demand. This "box of bricks" chemical game was labelled as B.A.S.I.C. (Bino-Ansa-Spiro In Cyclophosphazenes) "Molecular

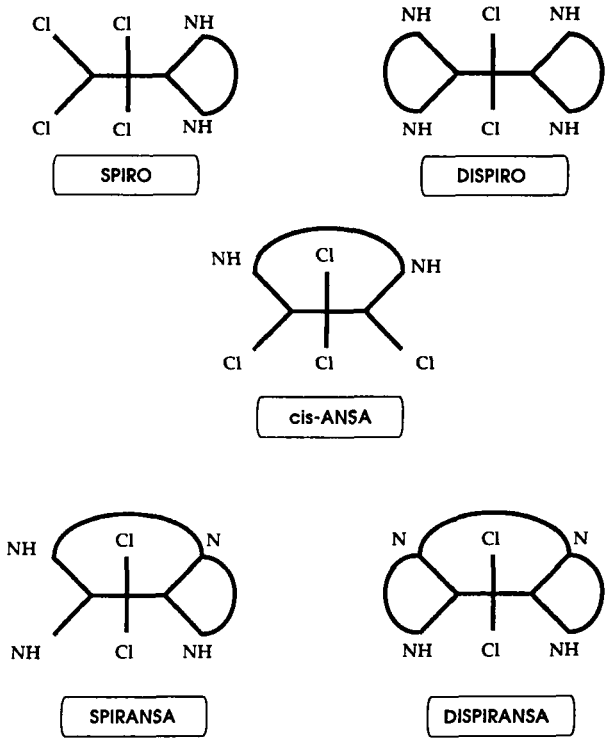

FIGURE 1 Some configurations obtained upon aminolysis of $N_3P_3Cl_6$ by aliphatic polyamines.

Lego."[1,11] Incidentally, the way the three basic bricks, namely bino, ansa and spiro, of the B.A.S.I.C. game are built was elucidated by 121.5 MHz ^{31}P NMR kinetic studies.[12]

In the same way, reactions of oxadiamines, $H_2N—(CH_2)_m—O—(CH_2)_n—O—(CH_2)_m—NH_2$, on hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, yield regioselectively macrocycle-bearing cyclophosphazenic architectures, i.e., cyclophosphazenic cryptands the configuration (spiro, bino, cis-ansa and trans-ansa[13]), the conformation, the cavity size and the number of coordination sites of which may be designed at demand for any "bird-caging" request.[14] The same kind of chemistry could be achieved also with thiadiamines, $H_2N—(CH_2)_m—S—(CH_2)_n—S—(CH_2)_m—NH_2$, leading to monomeric and polymeric cryptates endowed with exotic properties.[15-17]

Thus, it may be concluded that nucleophilic attack of $N_3P_3Cl_6$ by difunctional reagents such as diamines [or amino-alcohols][18] generates macrocycles which are linked to the cyclophosphazenic ring through a double covalent linkage. Moreover, the 121.5 MHz ^{31}P NMR kinetic study of aminolysis of $N_3P_3Cl_6$ by $H_2N—(CH_2)_2—O—(CH_2)_2—NH_2$ we performed at 280 K[12] revealed that such a reaction occurs according to a two-step mechanism, the reaction intermediate being the dangling (or podane) moiety in which only one function of the diamine is grafted on the N_3P_3 ring whereas the second one remains as it was in the genuine reagent, i.e., free for further linkage either to the same N_3P_3 ring (leading so to spiro or

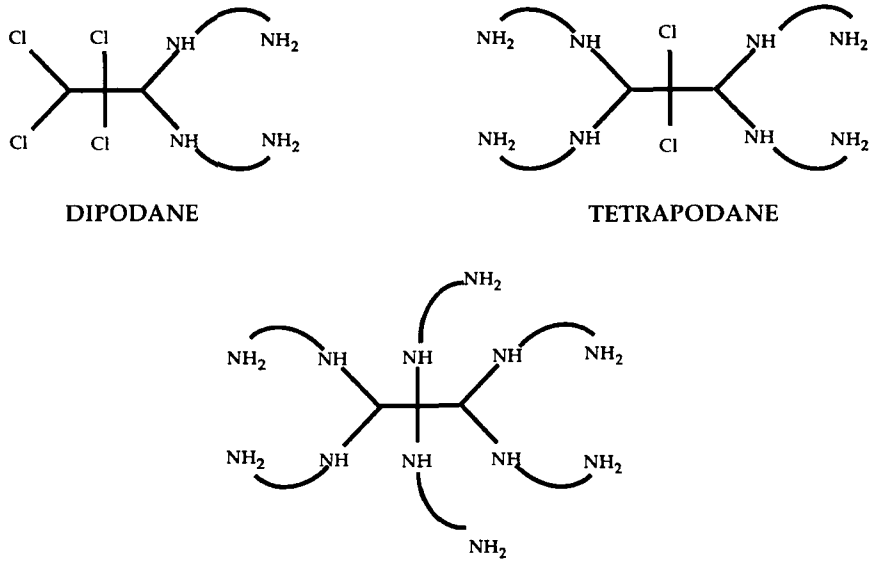

FIGURE 2 Some dangling cyclophosphazenic architectures.

ansa configurations) or to another N_3P_3 ring (leading so to bino configurations). Incidentally, this first step of the aminolysis is so fast that it could not be evidenced at room temperature. In other words, dangling compounds with [—NH—$(CH_2)_n$—NH_2] groups as tentacles (Figure 2) could not be prepared up-to-now as stable entities at room temperature, in common experimental conditions at least.

Actually, the neat obtention of such pure chemicals in a time-and-money non-consuming way was recently required for new developments within the field of cyclophosphazenic dendrimers, arborols and/or cascade molecules[19–26] which constitute a definite breakthrough into generations of new materials. It is well-known indeed that the whole story of such shell molecules is based on skillful choices of the starting materials which will be suitable for generating controlled molecular architectures along two or three topologically well-defined directions. Then, hexadangling cyclophosphazenes of Figure 2 [coded as hexapodanes according to References 27 and 28 or as sexapus by reference to octopus with only six tentacles] would constitute exciting 3-dimensional 6-functional cores capable of generating cyclophosphazenic spherical (i.e., analogous to the structure of a dry dandelion flower and not of a Tomalia's cauliflower) dendrimers.

The present contribution reports on an efficient technique for the fast regio-specific synthesis of such sexapus cores.

FAST SYNTHESIS OF PURE SEXAPUS CORES

It is well-known that a wide variety of chemical reactions can be promoted in heterogeneous media thanks to the acidic and/or basic sites located on the surface

of suitable solids such as alumina, clay, silica gel, talc and others.[29] The significant advantages of such "solid support" reactions relatively to the coresponding homogeneous reactions are the milder conditions, the more specific (chemospecific, regiospecific and/or stereospecific) transformations, the extremely high rate of reaction and the easier isolation of final pure products.

Within this frame of mind, we recently demonstrated that aminolysis of $N_3P_3Cl_6$ by lipophilic long-chain monoamines runs regiospecifically when achieved on some solid supports constituted from alumina impregnated with potassium hydroxide.[30] In the same way, aminolysis of $N_3P_3Cl_6$ by the oxodiamines $H_2N—(CH_2)_3—O—(CH_2)_2—O—(CH_2)_3—NH_2$ and $H_2N—(CH_2)_3—O—(CH_2)_6—O—(CH_2)_3—NH_2$ occurs immediately and regiospecifically when performed on the same solid supports leading to the corresponding spiro cryptands.[31] Thus, these "dry media processes" are actual improvements (time, selectivity and workup) on the standard reactions.

What happens now when the same dry media process is applied to aminolysis of $N_3P_3Cl_6$ by non-oxygenated diamines, $H_2N—(CH_2)_n—NH_2$? Will the final products be the spiro, bino and/or ansa moieties we evoked above or shall we reveal some exotic architectures?

The alumina-supported potassium hydroxide we used [coded as ALPOT (50:11)] was prepared according to References 30 and 31. Then, a typical experiment of aminolysis of $N_3P_3Cl_6$ by a diamine was achieved as follows (Figure 3). ALPOT (50:11) was firstly impregnated with a toluene solution of $N_3P_3Cl_6$ and the solvent was immediately removed in vacuo, fixing so $N_3P_3Cl_6$ to the alumina surface. Secondly, this system was impregnated with a toluene solution of the 1,6 Diaminohexane and the solvent was immediately removed in vacuo as previously. A simple washing of the solid support with toluene leads to the final product which is the pure $N_3P_3[HN—(CH_2)_6—NH_2]_6$ (coded as sexapus 6) chemical. Thus, aminolysis of $N_3P_3Cl_6$ by 1,6-Diaminohexane on ALPOT (50:11) yields instantaneously the pure hexadangling (or hexapodane or sexapus) entity. Remember that the same reaction in standard conditions leads regioselectively (and not regiospecifically) after 48 h at room temperature (and not in few minutes) to a mixture of conformations with the bino one as the major product and that no dangling moiety was ever observed in such standard conditions.

The same synthesis may be repeated with homologues of 1,6-Diaminohexane such as 1,7-Diaminoheptane. Sexapus 7 is then observed neat.

Conversely, more intricate features are observed for shorter diamines such as 1,4-Diaminobutane (putrescine) and 1,5-Diaminopentane (cadaverine), a certain amount of diamino ligands being grafted through both their ends leading so to partially spiro-like chemicals. In other words, sexapus *n* with $n \leq 5$ cannot be obtained in a pure state on ALPOT (50:11).

Then, sexapus *n* with $n \geq 6$ may be synthesized in a pure state (and rapidly) on ALPOT (50:11). These amazing architectures constitute cores for further design of dendrimers according to their 6 free amino functions located by pair in a set of three directions of space belonging to the D_{3h} symmetry. These sexapus are then capable of generating cascade molecules[32] through Tomalia's chemical pathways[19,22] but also of being starting materials for something which is more specifically proper to our Field of Research, that is the synthesis of spherical cyclophosphazenic den-

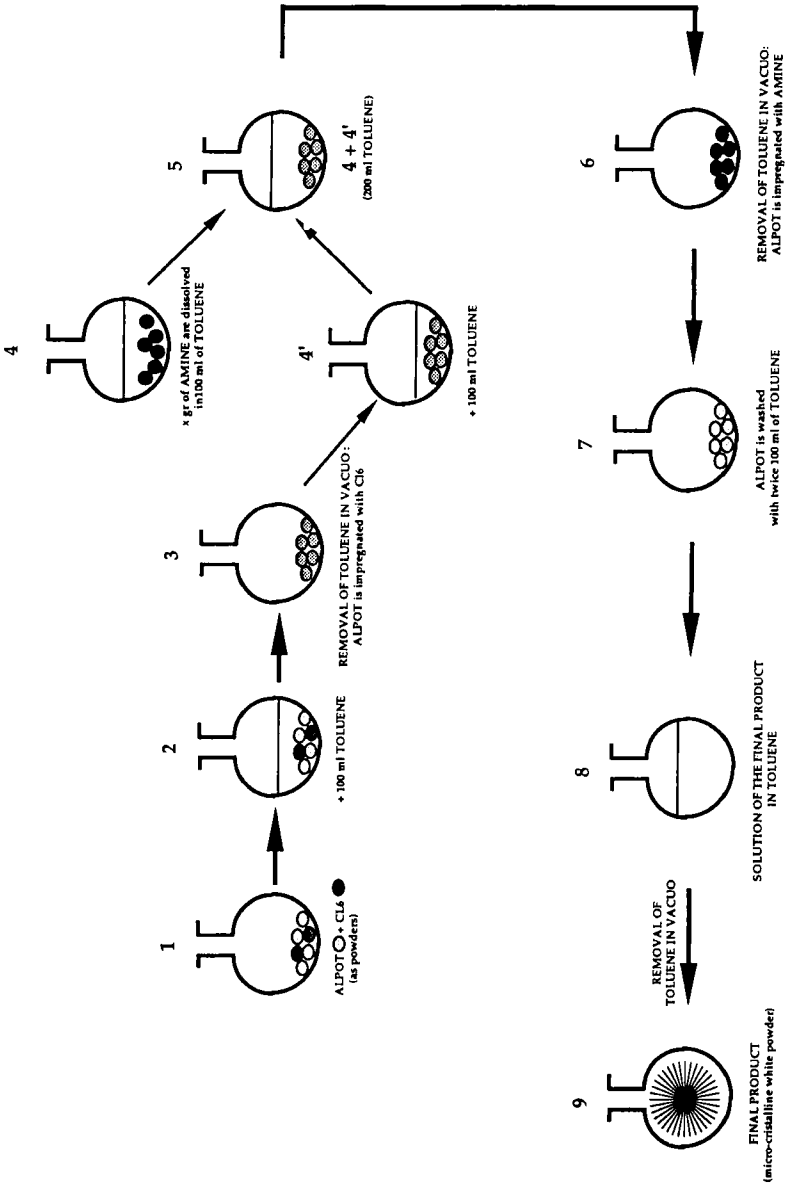

FIGURE 3 A typical experiment of aminolysis on ALPOT (50:11).

drimers (coded as dandelion dendrimers according to their aesthitical similarity with the dry flower of a dandelion) through the chain of reactions we shall evoke briefly now.

THE FIRST STEP OF THE SYNTHESIS OF CYCLOPHOSPHAZENIC DENDRIMERS

What happens indeed when sexapus is allowed to react with six new molecules of $N_3P_3Cl_6$? According to our previous results about the synthesis of polybino derivatives,[33] polar solvents are required for linking $N_3P_3Cl_5$ to each tentacle, leading so to architectures of Figure 4. In other words, toluene is no more the right solvent for such syntheses and ethyl ether has to be used here. The reaction

$$N_3P_3[HN—(CH_2)_6—NH_2]_6 + 6\ N_3P_3Cl_6 \rightarrow N_3P_3[HN—(CH_2)_6—NHN_3P_3Cl_5]_6 + 6\ HCl$$

was then achieved in ethyl ether either with ALPOT (50:11) or with Et_3N for scavenging hydrogen chloride. Actually, it does not work at all on ALPOT (50:11) whatever the solvent is (final product remaining definitely glued on the solid support

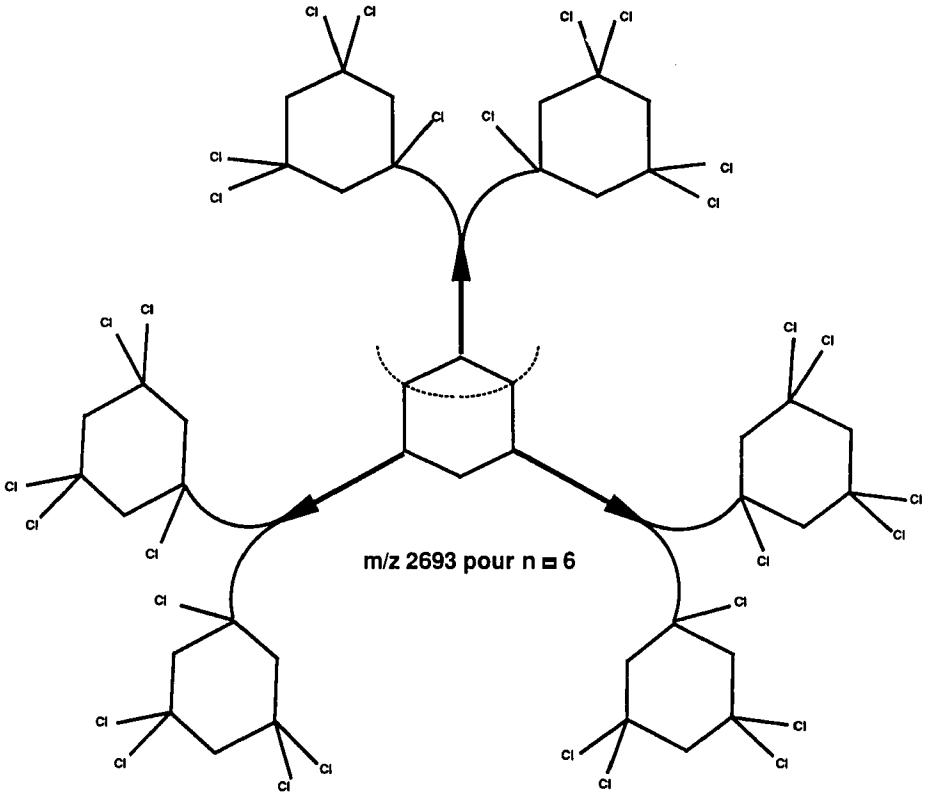

FIGURE 4 The molecular pattern of STEP 1 in the synthesis of cyclophosphazenic dendrimers.

whatever the eluent is) and it yields the expected primary step of cyclophosphazenic dendrimers only when Et_3N is used for scavenging hydrogen chloride. The FAB mass spectrum of the final product reveals the molecular peak at the m/z 2693 expected value. In other words, the final product corresponds actually to the polybino structure of Figure 4.

Now, we are in the position to go on, the next step of the dendrimers design being the further linkage of 30 diamino ligands as dangling tentacles on the 30 chlorine atoms of $N_3P_3[HN—(CH_2)_6—NHN_3P_3Cl_5]_6$.

THE SECOND STEP OF THE SYNTHESIS OF CYCLOPHOSPHAZENIC DENDRIMERS

Figure 5 shows the molecular pattern of the expected "step 2" architecture. This chemical was prepared through the peraminolysis of the polybino configuration of Figure 4. Reaction was achieved once more with Et_3N for scavenging hydrogen chloride in ethyl ether as the solvent. Electrospray mass spectrometry of the "step 2" architecture with $n = 6$ gave the molecular peak at the m/z 5085 expected value.

CONCLUSIVE REMARKS

Synthesis of hexadangling cyclophosphazenic architectures (coded as sexapus) runs regiospecifically when achieved on a peculiar solid support [ALPOT (50:11)] con-

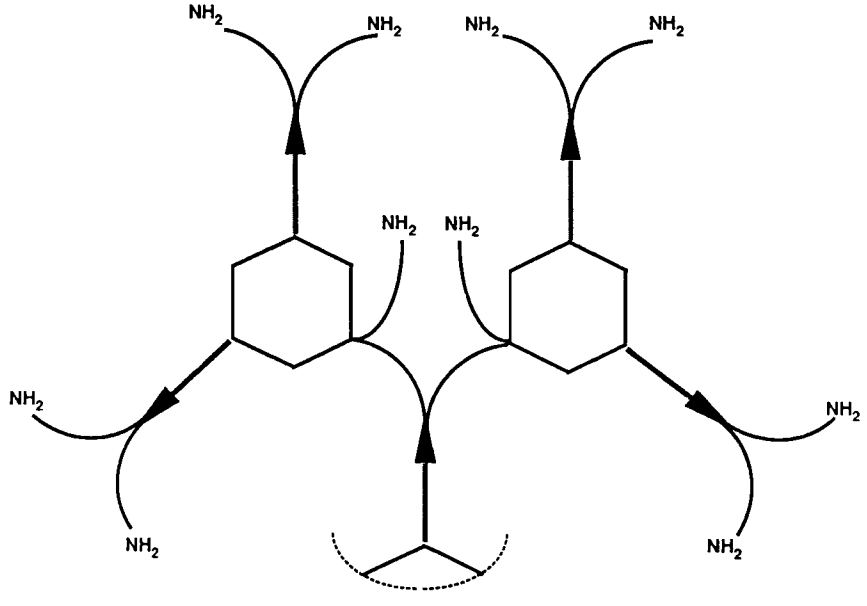

FIGURE 5 The molecular pattern (actually one third) of STEP 2 in the synthesis of cyclophosphazenic dendrimers.

stituted from alumina impregnated with potassium hydroxide. These sexapus are exotic cores for the design of spherical (dandelion) dendrimers through alternate additions of $N_3P_3Cl_5$ flagstones ("step 1" architectures) and of diamino tentacles as linkers ("step 2" architectures). Identification of architectures obtained in the further steps will require not only FAB and/or Electrospray mass spectrometry as matrices and ^{31}P NMR spectroscopy at 202.46 and even 242.95 MHz but also non-conventional physico-chemical techniques such as LALLS (Low-Angle Laser Light Scattering) and the capability of these approaches to reach the actual molecular weights of the chemicals in a plus or minus accurate manner with probably constitute the unique limitation for the design of large cyclophosphazenic dandelion dendrimers.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker AC 200 spectrometer with H_3PO_4 85% as external reference.

Molecular modelings were achieved by using functionalities of the MAD (Molecular Advanced Design) software developed by Lahana (Oxford Molecular SA, X-Pole, Ecole Polytechnique, 91128 Palaiseau Cedex, France).

Hexachlorocyclotriphosphazene was generously provided to us (degree of purity ≥99.8%) by SHIN NISSO KAKO Co., subsidiary company of NIPPON SODA Co. FLUKA supplied us with the primary diamines (degree of purity ≥98%).

Alumina-supported potassium hydroxide: Potassium hydroxide (Prolabo Rectapur, 11 g) in H_2O (250 ml) was mixed with neutral chromatographic alumina (Fluka, type 207 C, 90–110 μ, 50 g). After stirring for 5 min, the water was removed under reduced pressure. The resulting powder was further dried at 70°C for 24 h in oven. This reagent [coded as ALPOT (50:11)] may be kept in a dessicator without loss of activity during several months.

General pattern for the synthesis of sexapus: 150 g of ALPOT (50:11) were firstly impregnated with a toluene solution of $N_3P_3Cl_6$ (11.96 g in 400 ml) and the solvent was immediately removed in vacuo at 25°C, fixing so $N_3P_3Cl_6$ to the alumina surface. Secondly, this system was impregnated with a toluene (200 ml) solution of the 1,6 diaminohexane (6 diamines, i.e., 24.16 g, for 1 $N_3P_3Cl_6$) and the solvent was immediately removed in vacuo as previously. A simple washing of the solid support twice with 200 ml of toluene as the eluent leads to the final product (15.75 g, 55.5% yield) which is the pure $N_3P_3[HN—(CH_2)_6—NH_2]_6$ (coded as sexapus 6) chemical. Indeed, (i) the ^{31}P NMR spectrum at 81.015 MHz reveals a singlet at 18.3 ppm and (ii) the DCI/NH_3 mass spectrum (Ribermag R1010-H Quadrupole Mass Spectrometer) reveals the molecular ion MH^+ at m/z 826 (with a major side-peak at m/z 710 which corresponds to the "sexapus 6 minus one tentacle" fragment, $N_3P_3[HN—(CH_2)_6—NH_2]_5$, and a minor one at m/z 594 which corresponds to the "sexapus 6 minus two tentacles" fragment, $N_3P_3[HN—(CH_2)_6—NH_2]_4$). Thus, aminolysis of $N_3P_3Cl_6$ by 1,6-diaminohexane on ALPOT (50:11) yields instantaneously the pure hexadangling (or hexapodane or sexapus) entity as an hygroscopic microcrystalline white powder (m.p. = 39°C). Incidentally, the FAB mass spectrum with a mixture of glycerol/thioglycerol (80/20) as the matrix reveals also the molecular ion at m/z 826 but together with 3 side-peaks at m/z 710, 594 and 498, respectively, the latter corresponding to the loss of 3 tentacles, i.e., to the fragment $N_3P_3[HN—(CH_2)_6—NH_2]_3$. Moreover, the persubstitution of the 6 Cl atoms of $N_3P_3Cl_6$ by tentacles goes together with a vanishing of both ν_s(P—Cl) and ν_{as}(P—Cl) strong vibrational bands of $N_3P_3Cl_6$ at 600 and 520 cm^{-1} and with an emergence of ν(N—H) bands at 3382 and 3319 cm^{-1}.

General pattern for the synthesis of STEP 1: The reaction

$$N_3P_3[HN—(CH_2)_6—NH_2]_6 + 6\ N_3P_3Cl_6 \rightarrow N_3P_3[HN—(CH_2)_6—NHN_3P_3Cl_5]_6 + 6\ HCl$$

was achieved in ethyl ether with Et_3N for scavenging hydrogen chloride. The reaction in ethyl ether takes 48 h and is considered as complete when the singlet of $N_3P_3[HN—(CH_2)_6—NH_2]_6$ at 18.3 ppm has disappeared. Final product (which appeared to be soluble in $CDCl_3$) is characterized by a 81.015 MHz ^{31}P NMR A_2B system (triplet PClNH centered at 18.7 ppm, doublet PCl_2 centered at 21.3 ppm), the singlet of the core being shifted at 22.0 ppm. The FAB mass spectrum of the final product (recorded

TABLE I

Micro-analytical data of some chemicals described in the present study

CODE	FORMULA	M.W.	MICRO-ANALYTICAL DATA (%) [Theor. (first line) *versus* exp. (second line)]				
SEXAPUS 6	$N_3P_3[HN\text{-}(CH_2)_6\text{-}NH_2]_6$ $C_{36}H_{90}N_{15}P_3$	826	C 52.3 52,7	H 11.0 11,2	N 25.4 25,0	P 11.2 10.8	
STEP 1 from SEXAPUS 6	(SEXAPUS 6 - 6H) + $6(N_3P_3Cl_5)$ $C_{36}H_{84}N_{33}P_{21}Cl_{30}$	2693	C 16.0 16,3	H 3.1 3,1	N 17.2 16.9	P 24.1 23.8	Cl 39.5 39,0
STEP 2 from STEP 1 of SEXAPUS 6	(STEP 1 - 30Cl) + $30[HN\text{-}(CH_2)_6\text{-}NH_2]$ $C_{216}H_{534}N_{93}P_{21}$	5085	C 51.0 50,4	H 10.6 10,4	N 25.6 25,2	P 12.8 12,4	
SEXAPUS 7	$N_3P_3[HN\text{-}(CH_2)_7\text{-}NH_2]_6$ $C_{42}H_{102}N_{15}P_3$	910	C 55.4 54.9	H 11.3 11.0	N 23.1 22.8	P. 10.2 9.9	
STEP 1 from SEXAPUS 7	(SEXAPUS 7 - 6H) + $6(N_3P_3Cl_5)$ $C_{42}H_{96}N_{33}P_{21}Cl_{30}$	2777	C 18.2 18.0	H 3.5 3.5	N 16.6 16.3	P 23.4 22.9	Cl 38.3 38.6
STEP 2 from STEP 1 of SEXAPUS 7	(STEP 1 - 30Cl) + $30[HN\text{-}(CH_2)_7\text{-}NH_2]$ $C_{252}H_{606}N_{93}P_{21}$	5591	C 54.1 54,4	H 10.9 10,4	N 23.3 23.8	P 11.6 12,1	

with MNBE as the matrix) reveals the molecular peak at m/z 2693. We had to use MNBE, i.e., an ester, instead of the more common glycerol/thioglycerol mixture as the matrix, because the 30 chlorine atoms of $N_3P_3[HN—(CH_2)_6—NHN_3P_3Cl_5]_6$ are substituted in situ by glyceryl and thioglyceryl groups, leading so to molecular moieties with masses much larger than 2000, that is outer of the threshold of response of the detector. The IR spectrum reveals an emergence of one ν(N—H) band at 3234 cm^{-1} and no (P—Cl) band was observed anymore in the 400–600 cm^{-1} range.

General Remark: In our case, infra-red spectroscopy is a powerful tool for testing the purity of every step of the chain leading to cyclophosphazenic dendrimers. Indeed, IR spectra of odd steps such as STEP 1 must reveal strong (P—Cl) vibrational bands within the 500–600 cm^{-1} range whereas such bands have to disappear in even steps such as STEP 2.

Micro-analytical data: They are reported in Table I for some of the chemicals described here. Notice the huge variations of C% and Cl% when passing from each step to the next one, making identification of each step unambiguous.

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