

First Example of Dendrons as Topological Amplifiers

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Dedicated to the memory of our friend, the late Professor Marcial Moreno-Mañas

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A phosphorus-containing dendron was synthesized and grafted to a tetraphosphorus macrocycle. The presence of such bulky substituents allowed for the first time the amplification of topological differences in the macrocycle. These differences become detectable by ³¹P NMR spectroscopy, with

the appearance of several signals for the phosphorus atoms included in the macrocycle.

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Introduction

Dendrons,^[1] also called dendritic wedges,^[2] play an important role in dendritic macromolecular science, generally as large building blocks for the convergent synthesis of dendrimers^[3] or dendronized polymers,^[4] and for the elaboration of complex dendritic architectures.^[5] Besides these classical uses of dendrons, their very particular topological features have already found more original applications, for instance in steric protection responsible for site isolation,^[6] in new modes of self-organization,^[7] in enantiomer separation of dendronized molecular knots,^[8] as light harvesting antennae,^[9] or as rotaxane stoppers.^[10] However, to the best of our knowledge, dendrons were never used as amplifiers of local topological phenomena. We thought that such big, ramified, and conical substituents could facilitate the detection of previously undetectable phenomena, by amplifying the local difference.

Being interested since a long time in the synthesis and applications of dendrimers^[11] and dendrons,^[5,12] generally based on phosphorus,^[13,14] we decided to test this assumption by grafting dendrons to compounds in which stereoisomers must exist but were never detected. We previously reported the synthesis of a series of phosphorus macrocycles,^[15] obtained quantitatively by condensation reactions between 2 equiv. of phosphorylated dialdehydes and 2 equiv. of phosphodihydrazides.^[16] These compounds appeared as the most suitable objects to confirm or invalidate our hypothesis about the role of dendrons as topological

amplifiers. More precisely, we used macrocycle **1**,^[17] constituted of 4 tetracoordinate phosphorus atoms (P^{IV}), two of them being included in O–P–O linkages, the two others in N–P–N linkages. The four P^{IV} atoms are functionalized by an azide group as noncyclic substituent. This macrocycle possesses 4 asymmetric phosphorus centres, which can be easily functionalized through the reactivity of the azide groups (Figure 1).

Obviously, the presence of diastereoisomers in macrocycle **1** can be anticipated, and the zero value found for its optical rotation strongly suggests a 50:50 ratio for the stereoisomers on each phosphorus atom. If the macrocycle is relatively planar or if it is flexible, five diastereoisomers should be present; if the macrocycle exists in stable bent forms, as shown by the X-ray diffraction structure of a related macrocycle,^[18] nine diastereoisomers should exist. However, the existence of such diastereoisomers was never detected previously. Even ³¹P NMR spectroscopy, which is very useful for the detection of topological differences in constraint small cycles,^[19] is inefficient with unconstrained large cycles such as **1**. The ³¹P NMR spectrum of this 36-membered ring is shown in Figure 1; the 4 phosphorus atoms give two sharp singlets, one for the O–P–O linkages (P_O) and one for the N–P–N linkages (P_N).

In a first attempt to detect the presence of diastereoisomers, a small but relatively hindered compound was grafted to the macrocycle. We used a Staudinger reaction between the azide groups and the functionalized phosphane **2**.^[20] The creation of the P=N double bond occurs easily with the azide groups connected to the O–P–O linkages, and more slowly with the azide groups connected to the N–P–N linkages, as shown by ³¹P NMR spectroscopy after 1 h. Indeed, the singlet corresponding to the O–P–O linkage has

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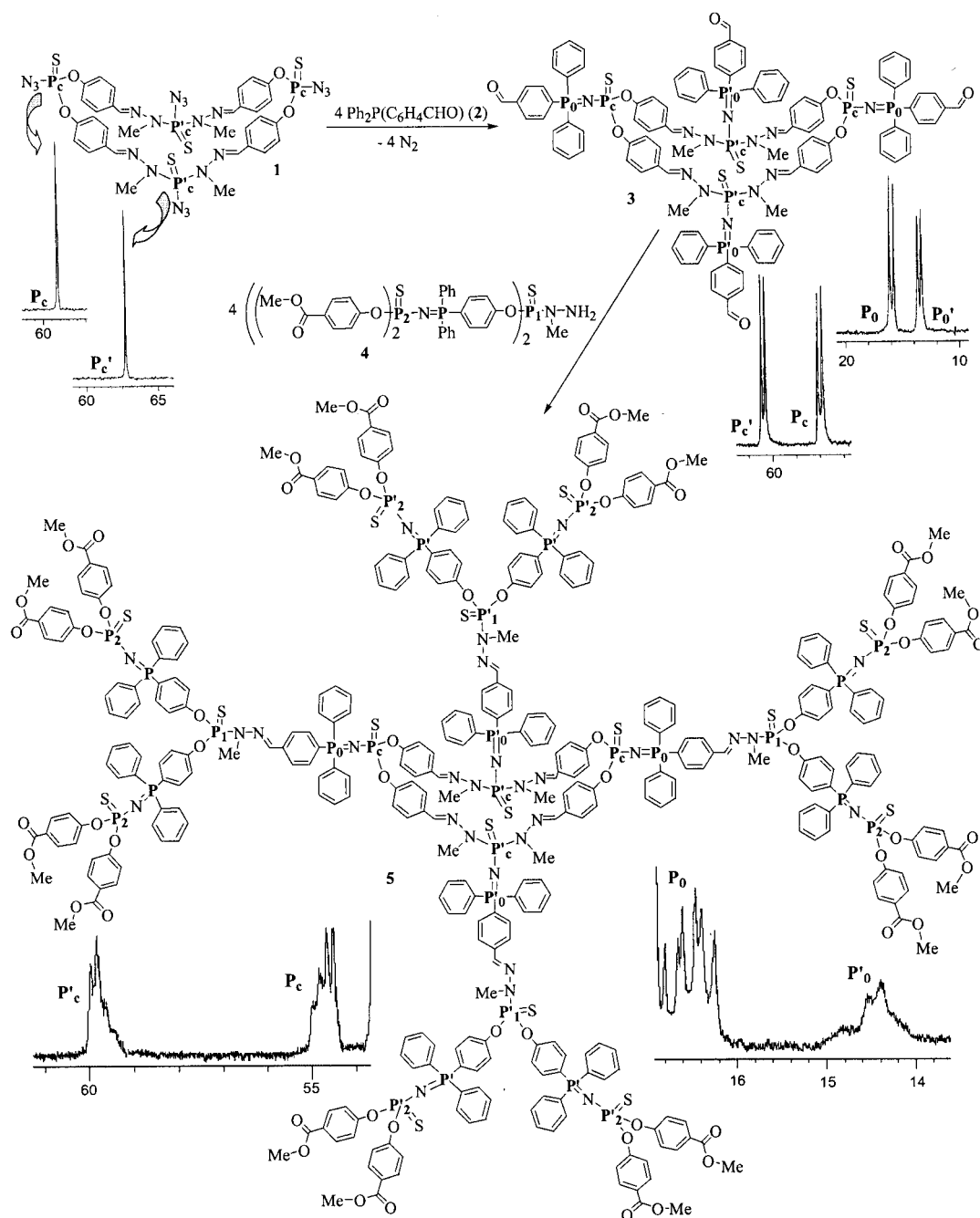


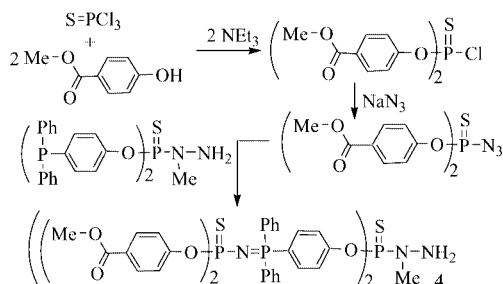
Figure 1. Synthesis of the macrocycle substituted by 4 dendrons and detection of diastereoisomers by ^{31}P NMR spectroscopy. Only the parts of the spectrum corresponding to $\text{P}_c\text{-N}=\text{P}_0$ and $\text{P}'_c\text{-N}=\text{P}'_0$ are shown for compound 5. The spectra were recorded at 25°C for 1 and 3, at 80°C for 5.

disappeared on behalf of two doublets at $\delta = 16.2$ ppm ($\text{P}=\text{N}$) and 55.7 ppm ($\text{P}=\text{S}$), whereas the singlet corresponding to the $\text{N}-\text{P}-\text{N}$ linkages remains unchanged. This difference in the reactivity of both types of azide groups could be ascribed to a higher electron-withdrawing influence of the $\text{O}-\text{Aryl}$ groups compared to the $\text{N}-\text{Me}$ substituents, favouring the reaction.^[21] However, the macrocycle 3 is finally isolated in nearly quantitative yield after reaction overnight. The ^{31}P NMR spectrum gives two sets of two sharp doublets corresponding to two types of $\text{P}=\text{N}-\text{P}=\text{S}$

linkages as expected.^[22] No trace of diastereoisomers could be detected even with these relatively bulky substituents (Figure 1).

In order to graft dendrons on the 4 aldehyde groups of 3 (one for each phosphorus atom included in the macrocycle), it was necessary to build a dendron possessing one NH_2 group at the core, preferably pertaining to an hydrazine or hydrazide linkage to ensure the stability of the future $\text{CH}=\text{N}$ bond. The size of the dendron is also of crucial importance, because it must be large enough to induce de-

tectable differences, but not too large to allow the signals of the macrocycle to be still detectable. For this purpose, we synthesized the second-generation dendron **4**, obtained by a Staudinger reaction between $\text{H}_2\text{NNMeP(S)}(\text{OC}_6\text{H}_4\text{PPh}_2)_2$ ^[23] and $\text{N}_3\text{P(S)}(\text{OC}_6\text{H}_4\text{CO}_2\text{Me})_2$, synthesized according to a method we reported previously^[24] (Scheme 1).



Scheme 1.

In the last step, 4 equiv. of the dendron **4** are condensed with the aldehyde groups of macrocycle **3**, to afford the second-generation dendrimer **5**, (Figure 1) as shown by the disappearance of the signal corresponding to the CHO group by ^1H , ^{13}C NMR, and IR spectroscopy. The ^{31}P NMR spectrum of compound **5** at room temperature gives relatively sharp signals as expected for the phosphorus atoms pertaining to the dendrons (a single singlet for P_1 and P'_1 , a single doublet for P_2 and P'_2 , and a single doublet for P and P' , not shown in Figure 1). Indeed, no particular steric hindrance or lock of bonds is foreseeable around these phosphorus atoms. However, broad signals are observed for the $\text{P}=\text{N}-\text{P}=\text{S}$ linkages in which the $\text{P}=\text{S}$ group is part of the macrocycle, in contrast to the 4 sharp doublets obtained for the same atoms in macrocycle **3**. Such behaviour is generally characteristic of a “frozen” internal structure; we have observed previously such a phenomenon for high-generation polycationic phosphorus dendrimers,^[25] but never for such small generations. Variable-temperature ^{31}P NMR experiments carried out in DMSO up to 80°C improved only slightly the definition of the signals. A slightly better resolution is observed for the $\text{P}=\text{N}$ groups linked to the macrocycle (P_0 and P'_0), compared to the $\text{P}=\text{S}$ groups included in the macrocycle (P_c and P'_c), whose degree of freedom is smaller. The better resolution observed for P_0 compared to P'_0 is presumably due to the higher degree of freedom of P_c compared to P'_c . Indeed, all the X ray structure determinations carried out up to now for $\text{P}_c\text{N}(\text{Me})\text{NC}=\text{CHC}_6\text{H}_4\text{OP}'_c$ linkages have shown that all atoms from P_c to O lie in a same plane, whereas P'_c is out of this plane.^[26] At least 3 sharp doublets can be distinguished for P_0 , which might correspond to the three main topological features expected; indeed, the dendron connected to P_0 can be surrounded with either zero, one or two dendrons, in the half space to which it belongs, defined by the average plane of the macrocycle (Figure 2). In form **A**, the dendrons linked to P_c and P'_c have two interactions, thus inducing a large modification of angles at the level of the $\text{S}=\text{P}_c-\text{N}=\text{P}_0$ and $\text{S}=\text{P}'_c-\text{N}=\text{P}'_0$ linkages. The same level of modification

of angles occurs for the $\text{S}=\text{P}'_c-\text{N}=\text{P}'_0$ linkage in form **B**, and for the $\text{S}=\text{P}_c-\text{N}=\text{P}_0$ linkage in form **C**. Dendrons having a single interaction should induce a moderate modification of angles, for the $\text{S}=\text{P}'_c-\text{N}=\text{P}'_0$ linkage in forms **C** and **D**, and for the $\text{S}=\text{P}_c-\text{N}=\text{P}_0$ linkage in forms **B** and **D**. Finally, no interaction should occur for dendrons linked to the $\text{S}=\text{P}'_c-\text{N}=\text{P}'_0$ linkage in forms **B** and **E**, and for dendrons linked to the $\text{S}=\text{P}_c-\text{N}=\text{P}_0$ linkage in forms **C** and **E**. It is known that ^{31}P NMR chemical shifts are sensitive to modification of the angles around the phosphorus atom.^[19] The minimization of interactions between the end groups of the dendrons linked to some diastereoisomers of the macrocycle necessitates modification of the angles at the level of their “root” (the $\text{P}_c-\text{N}=\text{P}_0$ and $\text{P}'_c-\text{N}=\text{P}'_0$ linkages), which is translated into variation of the chemical shift. Thus, one may attribute the phenomenon observed here by ^{31}P NMR spectroscopy to the existence of diastereoisomers. It demonstrates without any ambiguity that our assumption concerning the role of dendrons as amplifiers of local phenomena was correct, and could be usefully applied to other systems.

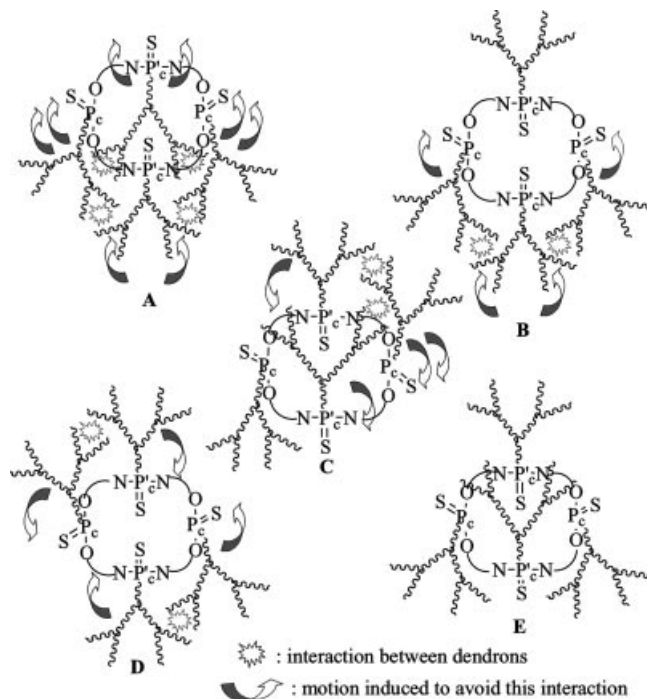
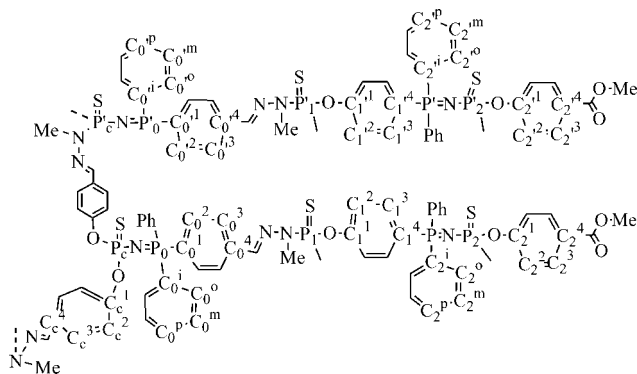


Figure 2. Schematization of the five diastereoisomers of compound **5**, showing the interactions between dendrons, and the movement to avoid these interactions, which modify the angles around the P_c (and P_0), and P'_c (and P'_0) phosphorus atoms.

Experimental Section

General: All manipulations were carried out with standard high-vacuum and dry-argon techniques. The solvents were freshly dried and distilled (THF and diethyl ether with sodium/benzophenone, pentane and CH_2Cl_2 with phosphorus pentoxide). Classical ^1H , ^{13}C , ^{31}P NMR spectra were recorded with Bruker AC 200, AC 250, DPX 300, or AMX 400 spectrometers. References for NMR chemical shifts are 85% H_3PO_4 for ^{31}P NMR, SiMe_4 for ^1H and

^{13}C NMR spectroscopy. The attribution of ^{13}C NMR signals has been done using J_{mod} , two-dimensional HMBC, and HMQC, broad-band or CW ^{31}P decoupling experiments when necessary. The numbering used for NMR assignments is depicted in Figure 3. IR analyses were recorded with Perkin–Elmer FT 1725x. Elemental analyses were performed by the Service d'Analyse du LCC, Toulouse, France. Compounds **1**,^[17] **2**,^[20] and $\text{H}_2\text{NNMeP(S)}(\text{OC}_6\text{H}_4\text{PPh}_2)_2$ ^[23] were synthesized according to methods previously reported.



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