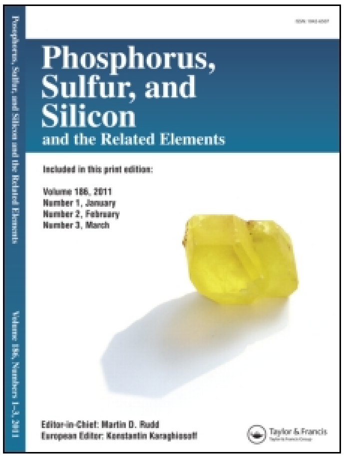


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

THE B.A.S.I.C. (BINO-ANSA-SPIRO-IN-CYCLOPHOSPHAZENES) SYSTEM. PART I: NEW DERIVATIVES OF THE BIS-(TETRACHLORO-CYCLOTRIPHOSPHAZENYL)-SPERMINE

Michèle Willson[a]; Louis Lafaille[a]; Lionel Vidaud[b]; Jean-François Labarre[b]
[a] Laboratoire des Hétérocycles du Phosphore et de l'Azote, Université Paul Sabatier, Toulouse Cedex, France [b] Laboratoire Structure et Vie, Université Paul Sabatier, Toulouse Cedex, France

To cite this Article Willson, Michèle , Lafaille, Louis , Vidaud, Lionel and Labarre, Jean-François(1987) 'THE B.A.S.I.C. (BINO-ANSA-SPIRO-IN-CYCLOPHOSPHAZENES) SYSTEM. PART I: NEW DERIVATIVES OF THE BIS-(TETRACHLORO-CYCLOTRIPHOSPHAZENYL)-SPERMINE', Phosphorus, Sulfur, and Silicon and the Related Elements, 29: 2, 147 — 157

To link to this Article: DOI: 10.1080/03086648708080497

URL: http://dx.doi.org/10.1080/03086648708080497

Phosphorus and Sulfur, 1987, Vol. 29, pp. 147–157
Photocopying permitted by license only

THE B.A.S.I.C. (BINO-ANSA-SPIRO-IN-CYCLOPHOSPHAZENES) SYSTEM. PART I: NEW DERIVATIVES OF THE BIS-(TETRACHLORO-CYCLOTRIPHOSPHAZENYL)-SPERMINE

MICHÈLE WILLSON,* LOUIS LAFAILLE,* LIONEL VIDAUD**
and JEAN-FRANÇOIS LABARRE**†

**Laboratoire des Hétérocycles du Phosphore et de l'Azote, Université Paul Sabatier, 118, Route de Narbonne, 31062 Toulouse Cedex, France*

***Laboratoire Structure et Vie, Université Paul Sabatier, 118, Route de Narbonne, 31062 Toulouse Cedex, France*

(*Received November 5, 1985; in final form March 6, 1986*)

The synthesis of new derivatives of bis-(tetrachlorocyclotriphosphazenyl)-spermine was achieved upon reaction of some MONOSPIRO-$N_3P_3Cl_4[HN—(CH_2)_n—NH]$ ($n = 2, 3, 4$) derivatives and of the gem-$N_3P_3Az_2Cl_4$ with spermine. All compounds were obtained in the monomeric state. ^{31}P and ^{13}C high-resolution NMR were used, together with IR spectroscopy and mass spectrometry, to assign molecular structures and to reveal conformational equilibria, if any.

INTRODUCTION

The reaction of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, with natural (biogenic) polyamines as tumor finders has been widely investigated recently, with the aim of designing more selective antitumorals.[1] The main conclusion from this work is that such a reaction leads to well-defined configurations depending on the nature of the polyamine: (i) MONOSPIRO for 1,2-diaminoethane,[2] 1,3-diaminopropane[3,4] and 1,4-diaminobutane (putrescine);[5] (ii) DISPIRO (symmetrical or fused) for 1,2-diaminoethane, 1,3-diaminopropane and putrescine;[2,6] (iii) TRISPIRO for 1,3-diaminopropane and putrescine;[6] (iv) BINO for 1,5-diaminopentane (cadaverine) and higher analogs;[7] (v) SPIRO–BINO for spermidine and DISPIRO–BINO for spermine;[8] (vi) ANSA for 3-amino 1-propanol with $N_3P_3Cl_5(CH_3)$,[1,9] and in some SPIRO–ANSA and DISPIRO–DIANSA–BINO relatives.[10]

Thus, any cyclophosphazene containing several SPIRO and/or ANSA and/or BINO moieties may be synthesized in a quantitative manner from now on. This new "box of bricks" chemical game was recently labelled as "B.A.S.I.C.", i.e., *B*INO-*A*NSA-*S*PIRO-*I*n-*C*yclophosphazenes.[1,11]

All these chemicals are obtained in a quite neat way and the SPIRO and BINO configurations just described can be combined within the same molecule only. Several such mixed structures have recently been reported upon reaction of 1,3-

---

[†] Author to whom all correspondence should be addressed.

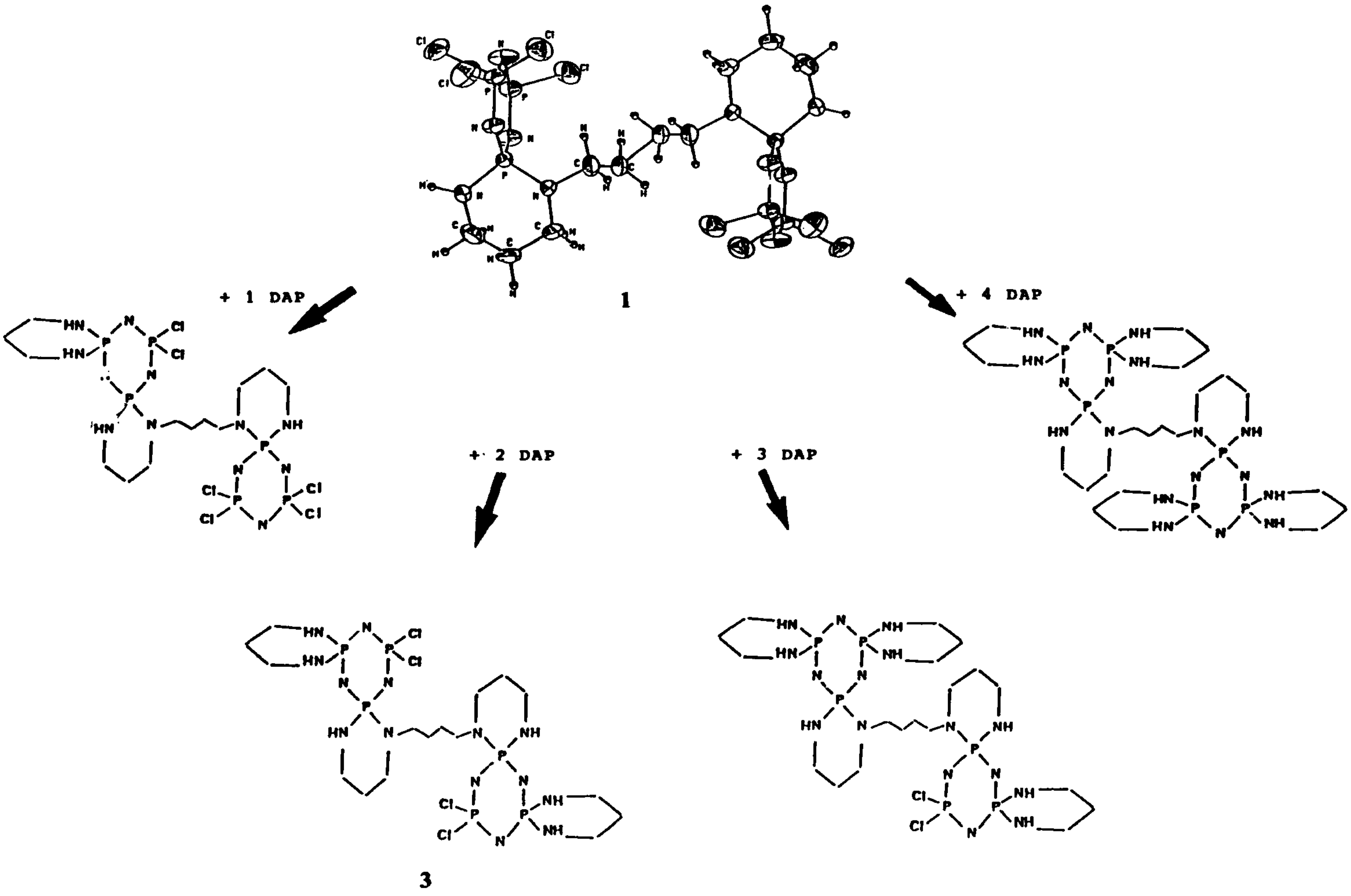


FIGURE 1 Products of the reaction of 1,3-diaminopropane (DAP) with the DISPIRO–BINO derivative from spermine.

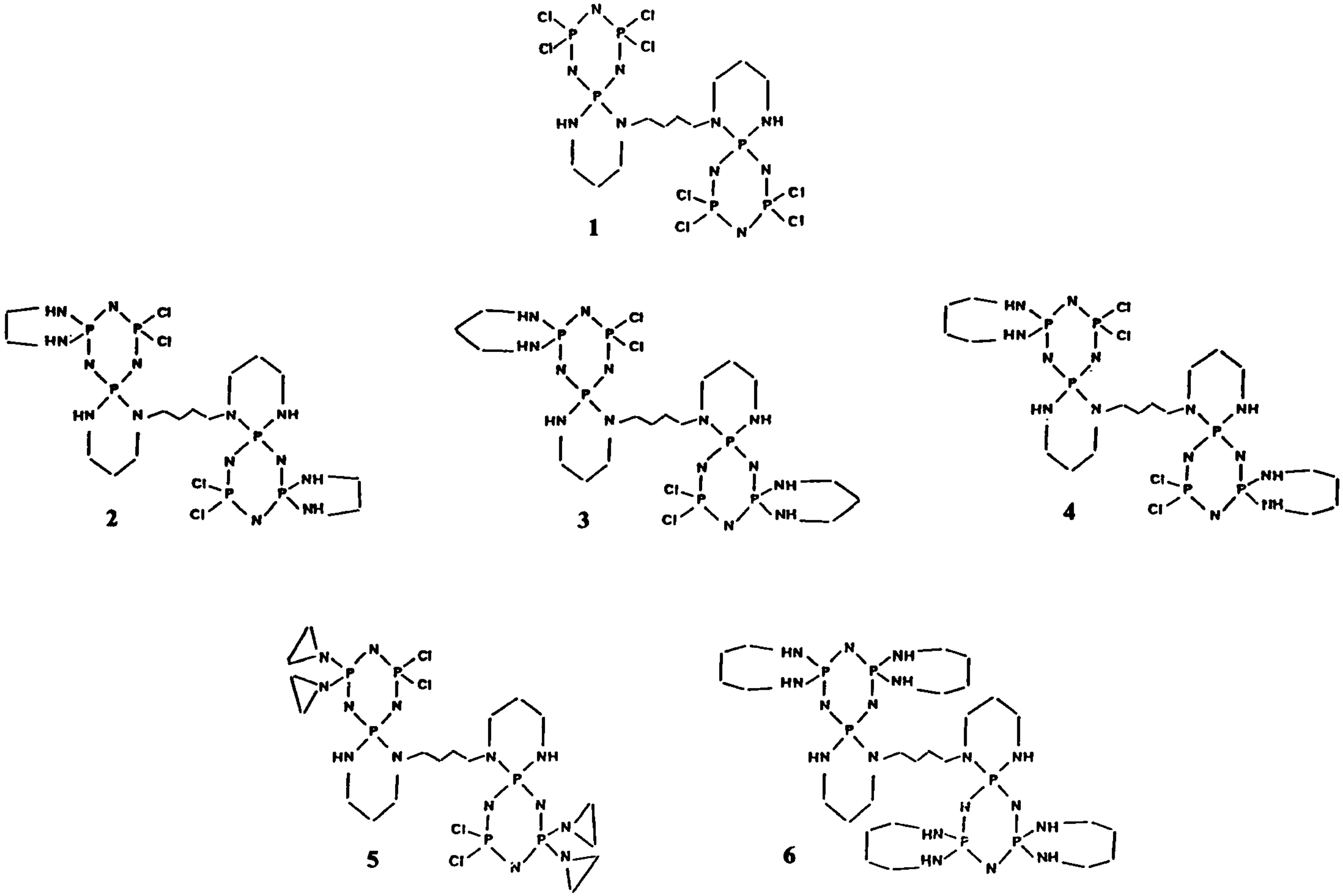


FIGURE 2 New B.A.S.I.C. derivatives of SPM reported here.

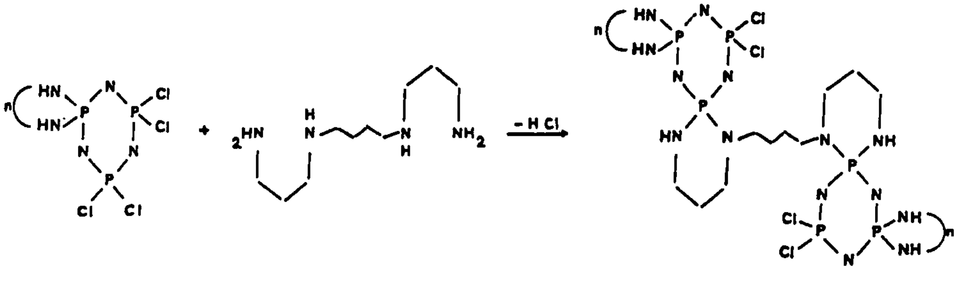
diaminopropane (DAP) with the DISPIRO–BINO compound from spermine, **1**[11] (Figure 1).

In order to emphasize the regio-selective character of the B.A.S.I.C. system, we have attempted the preparation of new derivatives of this DISPIRO–BINO compound, the X-ray structure of this starting material, **1** hereinafter coded as SPM, being presented in Figure 1.

The present contribution describes the synthesis and the physical identity (^{31}P and ^{13}C high-resolution NMR, mass spectra and IR spectra) of new B.A.S.I.C. derivatives of SPM, as depicted in Figure 2.

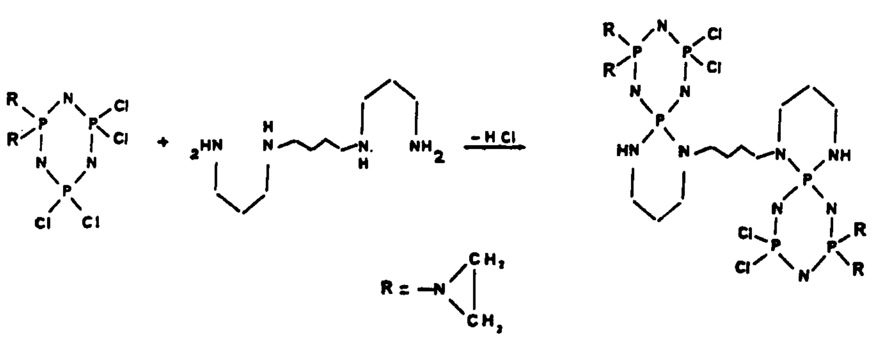
SYNTHESIS

The synthetic process for compounds **2** to **4** of Figure 2 is suggested to occur via the following pathway:



where n = —CH_2—CH_2— for **2**,
n = —CH_2—CH_2—CH_2— for **3**,
n = —CH_2—CH_2—CH_2—CH_2— for **4**.

The same procedure is used for the synthesis of **5**:



The nomenclature is the following: a SPIRO loop such as [HN—$(CH_2)_n$—NH] will be labelled as D_n, the corresponding DISPIRO symmetrical derivative of **1** is then labelled as $[N_3P_3Cl_2D_n]_2$SPM. Compound **5** will be labelled as $[N_3P_3Cl_2Az_2]_2$SPM.

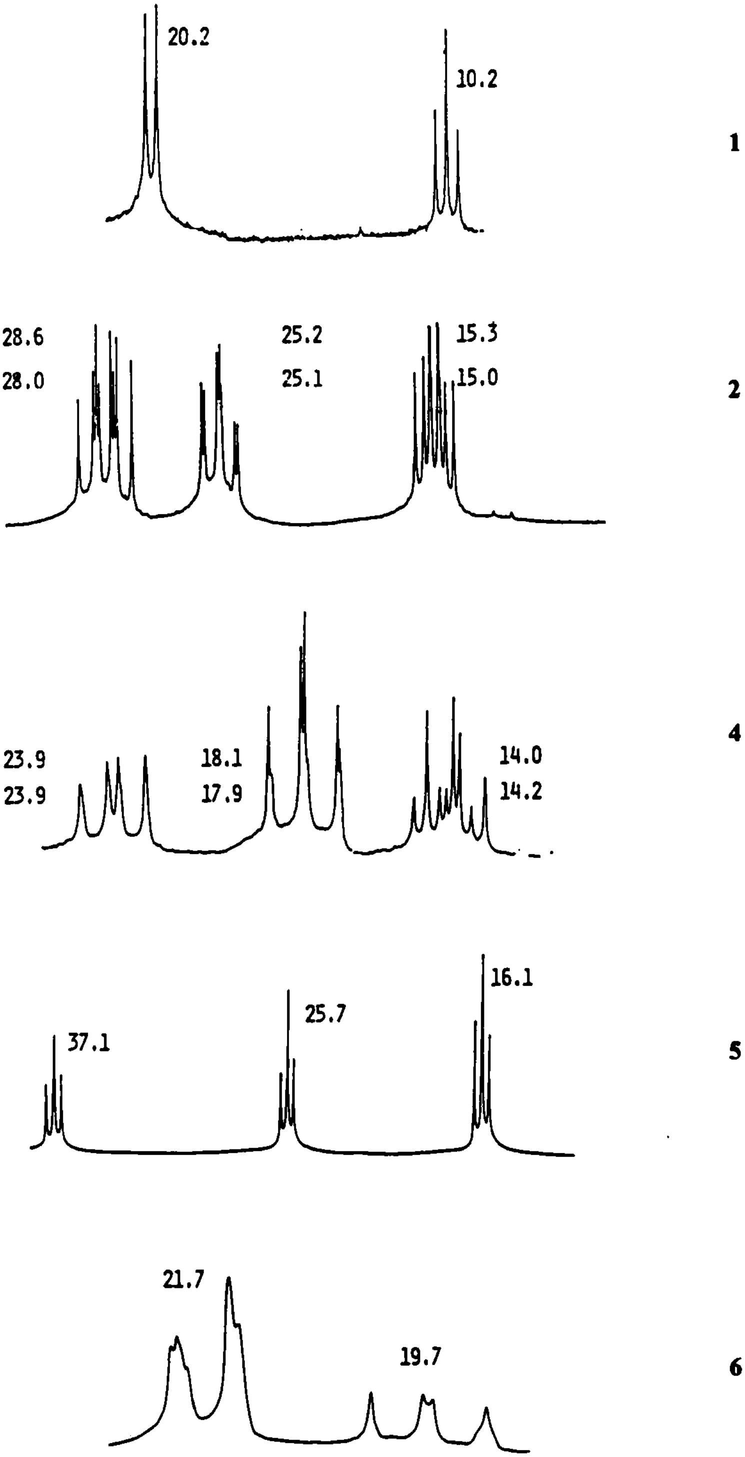


FIGURE 3 ^{31}P NMR spectra (101.27 MHz) of compounds **1**, **2**, **4**, **5**, and **6**.

RESULTS AND DISCUSSION

^{31}P NMR spectra of compounds **1**, **2**, **4**, **5** and **6** are shown in Figure 3. First order A_2B and ABC spectra are obtained for **1**, **5** and **6** when the 3 components of the expected ABC spectra for **2** to **4** show fine structure.

Chemical shifts and coupling constants J, are listed in Table I. The δ ($\underline{P}Cl_2$), δ ($\underline{P}D_2$) and δ ($\underline{P}D_4$) values are within the ranges 22–26 ppm, 28–29 ppm and around 18 ppm, respectively. The δ ($\underline{P}D_3$) chemical shifts for the spermine-bearing phosphorus atoms are about 15 ppm, to be compared with the 10.2 ppm value in **1**: attaching the D2 or D4 loops in **1** induces a low-field shift of about 5 ppm for δ ($\underline{P}D_3$), in agreement with previously reported data[2] for fused DISPIRO cyclotriphosphazenes.

Concerning the values of the J coupling constants in Table I, we may notice that:

(i) the smallest values for $^2J_{PP}$ (around 33–38 ppm) are observed for the couplings between ($\underline{P}Cl_2$) and ($\underline{P}D_3$) in **4** and **5**, for the couplings between ($\underline{P}Cl_2$) and ($\underline{P}Az_2$), together with the coupling between ($\underline{P}Az_2$) and ($\underline{P}D_3$) in **5**. However, $^2J_{PP}$ between ($\underline{P}Cl_2$) and ($\underline{P}D_3$) in **2** (46 Hz) is noticeably outside this 33–38 Hz range;

(ii) in the middle δ range, $^2J_{PP}$ is about 40–44 Hz for couplings between ($\underline{P}D_2$) and ($\underline{P}D_3$), together with ($\underline{P}D_3$) and ($\underline{P}D_4$) moieties;

(iii) the largest values for $^2J_{PP}$ (around 50–51 Hz) correspond to couplings between ($\underline{P}Cl_2$) and ($\underline{P}D_2$), together with couplings between ($\underline{P}Cl_2$) and ($\underline{P}D_4$).

These δ and $^2J_{PP}$ data could, actually, have been foreseen from the B.A.S.I.C. rules we reported recently:[2] there exists indeed a linear relationship between δ values for the loop-bearing atoms in cyclotriphosphazenes and NPN endocyclic angles θ at such atoms, the equation describing this straight line being $\theta = 109.619 \pm 0.262\delta$ ($R = 0.992$).

Incidentally, parameters of compound **1**, i.e., $\delta = 10.2$ ppm and $\theta = 113.0°$,[8] fit this equation well. ^{31}P δ values for spermino loop-bearing P atoms in compounds **2** to **4** being within the 14–16 ppm range, corresponding NPN endocyclic θ angles may be predicted to fall within the 113–114° range, whatever the two other loops

TABLE I

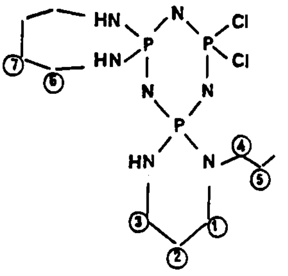
^{31}P chemical shifts, δ (ppm), and coupling constants, $^2J_{PP}$ (Hz), in $CDCl_3$ (101.27 MHz), for compounds **1** to **6**

Compound	$\delta(\underline{P}Cl_2)$	$\delta(\underline{P}D_3)$	$\delta(\underline{P}D_n)$	$J(\underline{P}Cl_2)(\underline{P}D_3)$	$J(\underline{P}Cl_2)(\underline{P}D_n)$	$J(\underline{P}D_n)(\underline{P}D_3)$
1	20.2	10.2	—	41.1	—	—
2	25.2	15.3	28.6	46	50	40
	25.1	15.0	28.0	46	50	40
3	22.6	16.0	13.9	36	39	45
	22.4	15.7	13.8	36	39	45
4	23.9	14.0	18.1	36	51	44
	23.9	14.2	17.9	35	51	44
5	25.7	16.1	37.1*	34	33**	38***
6	—	19.7	21.7	—	—	40

*i.e. $\delta(\underline{P}Az_2)$.
**i.e. $J(\underline{P}Cl_2)(\underline{P}Az_2)$.
***i.e. $J(\underline{P}Az_2)(\underline{P}D_3)$.

TABLE II

^{13}C NMR chemical shifts, δ (ppm), in $CDCl_3$ (62.9 MHz)
for compounds **1**, **2**, **4**, **5** and **7**



Compound	C_1	C_2	C_3	C_4	C_5	C_6	C_7
1	46.7	26.7	40.8	47.6	25.2		
2	46.5	26.8	40.4	47.7	24.9	42.0	
4	46.7	27.0	40.9	47.8	25.0	40.3	31.8
5	46.7	27.4	41.0	47.6	25.1	23.8	23.9
7	46.7	27.0	40.3	47.6	24.9	40.3	31.8

$^3J_{PC_2}$ = 5.5 Hz; $^2J_{PC_3}$ = 3.7 Hz; $^3J_{PC_5}$ = 5.5 Hz.

(D_2, D_3 or D_4) attached to adjacent P atoms are. Thus, the nature of these D_n loops does not modify noticeably the skeleton of **1** at the level of spermino-linked P atoms, in contrast to what happens in $N_3P_3Cl_4D_n$ MONOSPIRO derivatives where the graft of the D_n loop distorts the N_3P_3 ring far from its D_{3h} symmetry.[1]

Let us come back to the complex ^{31}P NMR patterns for compounds **2** and **4**, as shown in Figure 3 and Table I. It is noteworthy that the splitting of multiplets for **2** and **4** is not observed for compound **5**.

Such a splitting cannot be attributed to a mixture of compounds, as demonstrated by NMR and mass spectrometry: (i) ^{13}C NMR spectra are indeed straightforward for **2** and **4**, as they are for **1** and **5** (Table II): no questionable splittings of the various carbon chemical shifts of uncertain origin were ever observed, in contrast to what happens in the ^{31}P NMR: (ii) DCI mass spectrometry reveals only one MH^+ and/or MNH_4^+ molecular peak for every term of the series, including **2** and **4** (in agreement with unique spots in t.l.c. whatever the eluant was); (iii) ^{31}P NMR VTP experiments within the 300–400 K range (experiments could not be performed at higher temperature because of decomposition) do not reveal any coalescence: (iv) finally, the BINO bridge does not induce any splitting by itself, as proved by the ^{31}P NMR spectrum of compound **7**, i.e.,

$$N_3P_3Cl_2[HN{-}(CH_2)_4{-}NH][HN{-}(CH_2)_3{-}N{-}C_2H_5]$$

(Figure 4), which is undoubtedly an ABC-type spectrum, and by ^{13}C NMR (Table II) and IR data (Table IV).

On the other hand, ^{31}P NMR measurements in solution (Table III) and IR spectroscopy (Table IV) reveal that compounds **2** and **4** are capable of giving associations; (i) when recording ^{31}P NMR spectra of **2** and **4** from solutions in various protic and aprotic, polar and nonpolar solvents, their three multiplets are

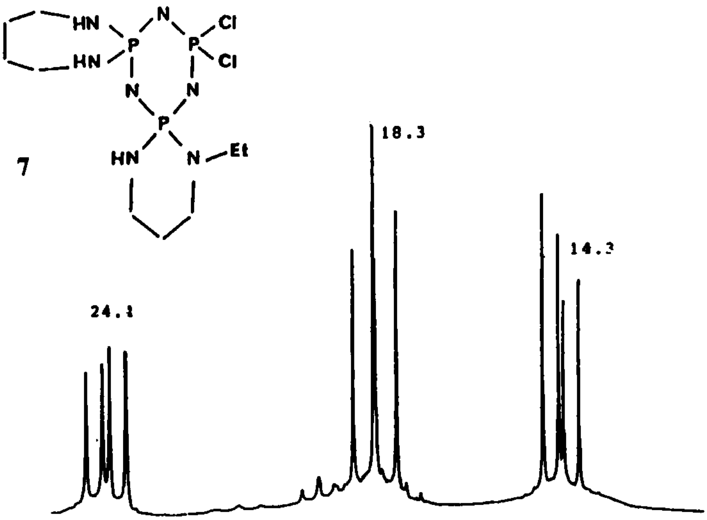


FIGURE 4 ^{31}P NMR spectrum (101.27 MHz) of compound 7.

shifted *jointly, without any changes in the relative magnitude of their components* (Table III); (ii) IR spectra of CCl_4 solutions (Table IV) make two (N—H) stretching frequencies conspicuous at 3437 (free) and 3355 (associated) cm^{-1} for **2**, 3440 (free) and 3380 (associated) cm^{-1} for **4**; the gap between the two bands (82 and 60 cm^{-1}, respectively) suggests that associations are weak, i.e., intramolecular, the differences in the case of intermolecular interactions (which are normally stronger) being much larger, i.e., about 150 cm^{-1} at least.

These results provide a comprehensive description of the complexity of the ^{31}P NMR spectra for **2** and **4**: the splitting of the expected ABC-type spectra in two ABC + A′B′C′ sets of multiplets seems to be due to a magnetic non-equivalence of the two sets of P atoms belonging to the two N_3P_3 rings. In other words, the ABC system would correspond to a conformation similar to the one existing in compound **1**, the A′B′C′ system being attributed to another conformation where some intramolecular hydrogen bonding could exist between NH groups of the D_2 and/or D_4 loop on one N_3P_3 ring and the chlorine atoms on the other. This assump-

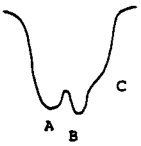
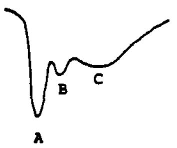
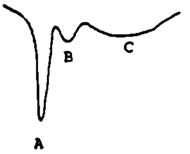
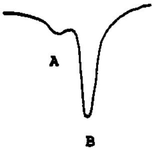
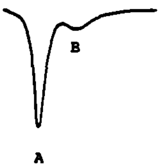
TABLE III

Effect of the solvent on ^{31}P chemical shifts, (ppm) of compound 4

Solvent	$\delta(\underline{P}Cl_2)$	$\delta(\underline{P}D_4)$	$\delta(\underline{P}D_3)$
$CDCl_3$	23.9 23.9	18.1 17.9	14.0 14.2
CD_2Cl_2	27.1 27.2	22.0 21.8	18.7 18.8
$C_6D_5CD_3$	29.9 29.8	25.4 25.5	23.0 22.4

TABLE IV

(N—H) stretching patterns for compounds **1**, **2**, **4**, **5** and **7** (concentration 10^{-4} to 10^{-3} mole/l in CCl_4)

Compound	ν(N—H) (cm^{-1}) A	B	C	
1	3430	3400	3375	
2	3437	3355	3250	
4	3440	3380	3223	
5	3415	3365	—	
7	3440	3365	—	

tion is supported by the fact that the ^{31}P NMR spectrum of compound **6**, i.e., $[N_3P_3(D4)_2]_2SPM$, in which such intramolecular interactions cannot occur, is definitely and A_2B-type one (Figure 3). Incidentally, the fact that the ABC/A′B′C′ splitting is larger for **2** than for **4** may be related to the larger shift (82 cm^{-1}) for **2**, when compared to the 60 cm^{-1} value for **4** (the larger the shift, the stronger are the intramolecular hydrogen bonds, and the larger is the ABC/A′B′C′ splitting).

Thus, all the NMR spectroscopic observations may be rationalized, except for the variable temperature NMR spectra of **2** and **4**, as mentioned above. However, the small temperature range which could be explored, as a result of the poor thermal stability of **2** and **4**, may reasonably be considered as too small for reaching the coalescence temperatures.

CONCLUSIONS

New derivatives of bis-(tetrachlorocyclotriphosphazenyl)-spermine are described by way of new illustrations of the B.A.S.I.C. system. ^{31}P NMR high-resolution spectroscopy reveals two conformers in compounds **2** and **4**, in contrast with unique conformations for compounds **1**, **5** and **6**. The existence of a side-conformation in **2** and **4** is due to intramolecular hydrogen bonding between NH groups of the SPIRO loop on one side and chlorine atom pairs on the other, such interactions vanishing when either the SPIRO loop is replaced by aziridinyl pairs or when Cl atoms are substituted by loops. X-ray structure determinations of **2** and **4** will be performed in order to check if this conformational equilibrium in solution remains in the solid state.

EXPERIMENTAL

Starting materials and methods.

The $N_3P_3Cl_4[HN—(CH_2)_n—NH]$ ($n = 2$ and 4) MONOSPIRO starting materials were prepared from $N_3P_3Cl_6$ (OTSUKA Chemical Co.) by previously reported procedures (see ref. 12 for $n = 2$ and ref. 5 for $n = 4$). The gem-$N_3P_3Az_2Cl_4$ starting material was prepared by reaction of aziridine with $N_3P_3Cl_6$ in a 2 : 1 molar ratio.

Spermine was obtained from Aldrich Corp. Diethyl ether and light petroleum (b.p. 35–55° C) were distilled over sodium. Triethylamine was distilled over sodium hydroxide and dichloromethane was distilled and kept over $MgSO_4$.

NMR spectra were recorded on a BRUKER WM 250 spectrometer operating at 62.9 MHz (^{13}C) and 101.2 MHz (^{31}P). For ^{31}P NMR, 85% H_3PO_4 was used as external reference and, for ^{13}C, $CDCl_3$ was used. ^{13}C and ^{31}P NMR chemical shifts were assigned under conditions of broad-band decoupling.

The course of the reactions was followed by ^{31}P NMR on a BRUKER AC 80 spectrometer.

Infrared spectra were obtained on KBr pellets and diluted solutions in CCl_4 on a FTIR BRUKER IFS 110 spectrometer.

DCI mass spectra were recorded on a R1010 RIBERMAG quadrupole mass spectrometer. The spectra were analyzed by means of a DEC PDP 8/M computer.

Elemental analyses were performed by the Microanalytical Service of CNRS, Vernaison, France.

All reactions were carried out under anhydrous conditions in three-necked round-bottomed flasks, fitted with pressure equalizing dropping funnels. The system was stirred magnetically and flushed with nitrogen.

Synthesis of $[N_3P_3Cl_2D4]_2SPM$, **4**.

A solution of spermine (2.42 g, 0.012 mol) and triethylamine (4.84 g, 0.048 mol) in 100 ml of a mixture of CH_2Cl_2 and CCl_4 (1/4) was added slowly (1 hour) to a cold stirred solution of $N_3P_3Cl_4D4$ (8.40 g, 0.023 mol) in 250 ml of a mixture of CH_2Cl_2 and CCl_4 (1/4). The reaction mixture was allowed to come to room temperature and stirred for two days until further changes of the ^{31}P NMR spectrum were no longer observed. The solid (triethylamine hydrochloride; 5 g (75%)) was removed by filtration and the solvents were removed under reduced pressure. The white crude powder left after removal of the solvents was washed three times with CCl_4, then with a mixture of CCl_4 and CH_2Cl_2, to yield 4.5 g of 4 (48% of theory). M.p. 230° C (dec).

Anal. calc. for $C_{18}H_{42}Cl_4N_{14}P_6$: C 27.62; H 5.37; P 23.78; mol. wt. 782. Found: C 26.63; H 5.38; P 23.36; mol. wt. 782 (mass spectrum 782 with ^{35}Cl). IR (in cm^{-1}): ν_{NH}: 3440(w), 3290(vs), δ_{NH}: 1750(s), ν_{CH_2}: asym. 2940(m), sym. 2880(m), δ_{CH_2}: asym. 1390–1420(m), sym. 1455(m), $\delta_{(CH_2)_n}$: 805(m) 840(m), ν_{NPN}: 1235(s), 1180(s), 1055(m), 960(m), ν_{PCl}: 550(s).

Synthesis of $[N_3P_3Cl_2D2]_2SPM$, **2**.

The procedure was identical to that described above, except that the solvents were 100 ml of diethylether and 100 ml of methylene chloride. The following quantities of reagents were employed: 3.35 g (0.01 mol) of $N_3P_3Cl_4D2$, 4.84 g (0.048 mol) of triethylamine and 1.80 g (0.009 mol) of spermine (in excess). The resulting solid (triethylamine hydrochloride: 4.20 g, (66%)) was removed by filtration. The solution was evaporated under reduced pressure and the resulting colourless oil was kept in hexane during 48 hours. The white crude powder formed was isolated to yield 3.70 g of **2** (51% of theory). M.p. 235° C.

Anal. calc. for $C_{14}H_{34}Cl_4N_{14}P_6$: C 23.14; H 4.68; P 25.61; mol. wt. 726. Found: C 22.09; H 4.67; P 24.99, mol. wt. 726 (mass spectrum). IR (in cm^{-1}) ν_{NH}: 3410(vs), ν_{CH_2}: asym. 2950(m), sym. 2870(m), $\delta_{(CH_2)_n}$: 835(m), ν_{NPN}: 1225(s), 1170(s), 1080(m), 920(m), ν_{P-Cl}: 540(s).

Synthesis of $[N_3P_3Cl_2Az_2]_2SPM$, **5**.

This preparation was allowed to proceed as above, except that the following quantities of reagents were used: $N_3P_3Cl_4Az_2$ 4 g (0.0108 mol), spermine 2.1 g (0.01 mol) (in excess for binding hydrogen chloride). After removal of a white solid (spermine hydrochloride, 2.40 g, yield 58%) and evaporation of solvents, a colourless oil was isolated. This oil was washed three times with carbon tetrachloride and was kept in heptane during 4 days. The white powder formed was isolated to yield a 40% of **5**. M.p. 200° C (dec.).

Anal. calc. for $N_{14}P_6Cl_4C_{18}H_{38}$: C 27.76; H 4.88; N 18.25; Cl 25.19; P 23.90; mol. wt. 778. Found: C 28.23; H 4.85; N 18.90; Cl 25.10; P 24.70; mol. wt. 778 (mass spectrum). IR (in cm^{-1}): ν_{NH} 3300–3400(vs), ν_{CH_2}: asym. 2940(s), sym. 2860(s), $\delta_{(CH_2)_n}$ 810(m), 865(m), ν_{CH_2}(Aziridine) 3080(w), 2990(w), ν_{NPN} 1170(s), 1220(s), 1080(s), 940(s), ν_{PCl} 535(s).

Synthesis of **7**.

Quantities of reagents: $N_3P_3Cl_4D4$ 2.15 g (0.006 mol), *N*-ethyl propylene diamine, 1.3 1.20 g (0.012 mol) (in excess to bind hydrogen chloride). **7** was formed in 60% yield. :

IR (in cm^{-1}): ν_{NH}: 3250(vs), ν_{CH_2}: asym. 2930(s), sym. 2870(s), δ_{CH_2}: 1390(w), 1440(w), $\delta_{(CH_2)_n}$: 800(s), 840(s), ν_{NPN}: 1240(s), 1170(s), 1050(s), 960(s), ν_{P-Cl}: 540(s).

REFERENCES

1. J-F. Labarre, *Top. Current Chem.*, **129**, 173 (1985) and references cited therein.
2. M. Willson, L. Lafaille, G. Commenges and J.-F. Labarre, *Phosphorus and Sulfur*, **25**, 273 (1985) and references cited therein.
3. G. Guerch, M. Graffeuil, J-F. Labarre, R. Enjalbert, R. Lahana and F. Sournies, *J. Mol. Struct.*, **95**, 237 (1982).
4. R. Enjalbert, G. Guerch, J-F. Labarre and J. Galy, *Z. Kristallogr. Mineral.*, **160**, 249 (1982).
5. G. Guerch, J-F. Labarre, R. Roques and J-F. Labarre, *J. Mol. Struct.*, **96**, 113 (1982).
6. N. El Murr, R. Lahana, J-F. Labarre and J-P. Declercq, *J. Mol. Struct.*, **117**, 73 (1984).
7. P. Castera, J-P. Faucher, G. Guerch, R. Lahana, A. Mahmoun, F. Sournies and J-F. Labarre, *Inorg. Chim. Acta*, **108**, 29 (1985).
8. J-F. Labarre, G. Guerch, F. Sournies, R. Lahana, R. Enjalbert and J. Galy, *J. Mol. Struct.*, **116**, 75 (1984).
9. P. J. Harris and K. B. Williams, *Inorg. Chem.*, **23**, 1495 (1984).
10. F. Sournies, J-F. Labarre, P. J. Harris and K. B. Williams, *Inorg. Chim. Acta*, **90**, L61 (1984).
11. F. Sournies, R. Lahana and J-F. Labarre, *Inorg. Chim. Acta*, **101**, 31 (1985).
12. Y. S. Babu, H. Manohar, K. Ramachandran and S. S. Krishnamurthy, *Z. Naturforsch.*, **33b**, 588 (1978).