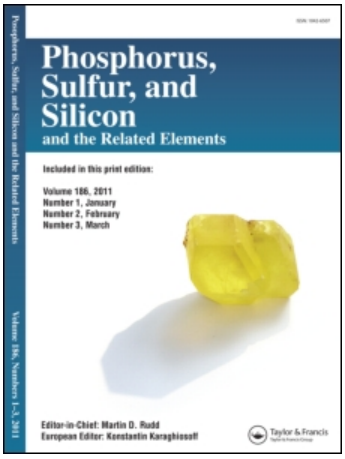


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

AN ANSWER TO THE SPIRO VS ANSA DILEMMA IN CYCLOPHOSPHAZENES. PART VIII. THE FIRST FUSED DISPIROCYCLOTRIPHOSPHAZENES, $N_3P_3CL_2[HN\text{-}(CH_2)_m\text{-}NH]$ $[HN\text{-}(CH_2)_N\text{-}NH](m \neq n = 2,3,4)$

Michèle Willson[a]; Louis Lafaille[a]; Gérard Commenges[b]; Jean-François Labarre[c]
[a] Laboratoire des Hétérocycles du Phosphore et de l'Azote, Université Paul Sabatier, Toulouse Cedex [b] Laboratoire de Chimie de Coordination du CNRS, Toulouse [c] Laboratoire Structure et Vie, Université Paul Sabatier, Toulouse Cedex

To cite this Article Willson, Michèle , Lafaille, Louis , Commenges, Gérard and Labarre, Jean-François(1985) 'AN ANSWER TO THE SPIRO VS ANSA DILEMMA IN CYCLOPHOSPHAZENES. PART VIII. THE FIRST FUSED DISPIROCYCLOTRIPHOSPHAZENES, $N_3P_3CL_2[HN\text{-}(CH_2)_m\text{-}NH]$ $[HN\text{-}(CH_2)_N\text{-}NH](m \neq n = 2,3,4)$', Phosphorus, Sulfur, and Silicon and the Related Elements, 25: 3, 273 — 287
To link to this Article: DOI: 10.1080/03086648508072743
URL: http://dx.doi.org/10.1080/03086648508072743

Phosphorus and Sulfur, 1985, Vol. 25, pp. 273–287
0308-664X/85/2503-0273/$20.00/0

AN ANSWER TO THE SPIRO VS ANSA DILEMMA IN CYCLOPHOSPHAZENES. PART VIII*. THE FIRST FUSED DISPIROCYCLOTRIPHOSPHAZENES, $N_3P_3Cl_2[HN—(CH_2)_m—NH][HN—(CH_2)_n—NH]$ ($m \neq n = 2,3,4$).

MICHÈLE WILLSON**, LOUIS LAFAILLE**, GÉRARD COMMENGES*** AND JEAN-FRANÇOIS LABARRE****(+).

** *Laboratoire des Hétérocycles du Phosphore et de l'Azote, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex.****Laboratoire de Chimie de Coordination du CNRS, 205 route de Narbonne, 31400 Toulouse.* ****Laboratoire Structure et Vie, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex.*

(*Received April 29, 1985; in final form June 28, 1985*)

The synthesis of the first fused DISPIROcyclotriphosphazenes was achieved upon reaction of a diamine $H_2N—(CH_2)m—NH_2$ (with m = 2,3,4) on the $N_3P_3Cl_4[HN—(CH_2)_n—NH_2]$ (with $n \neq m$) MONOSPIRO derivative in stoichiometric conditions. Molecular structures were ascribed by using both ^{31}P and ^1H high resolution NMR and electron-impact mass spectrometry.

The chemical shift of the phosphorus atoms bearing the loop varies linearly with the value of the corresponding NPN endocyclic angle. The synthesis of this fused derivatives occurs in quantitative yield. It leads the way for the covalent binding at demand on a cyclophosphazene antitumoral system of several natural polyamines as tumor finders in the SPIRO configuration.

INTRODUCTION

The so-called SPIRO[1] versus ANSA[2] controversy related to the molecular structure of the products of the reaction of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, with difunctional reagents has definitely been clarified recently.

Indeed, conclusive X-ray evidence for a SPIRO structure has been obtained in several cases (i) upon reaction of $N_3P_3Cl_6$ with 1,3-diaminopropane and 1,4-diaminobutane (putrescine) in various stoichiometric conditions[3–8], (ii) upon reaction of $N_3P_3Cl_6$ with spermidine and spermine[4,5,9], (iii) upon reaction of $N_3P_3Cl_6$ with diols,[10,11] (iv) upon reaction of $N_3P_3Cl_6$ with *N*-methylethanolamine[12], and (v) in the derivative $N_3P_3Az_4[HN—(CH_2)_3—NH]$.[13,14]

In contrast, no ANSA structure was ever observed with $N_3P_3Cl_6$ as the starting material.

However, such an ANSA structure is formed[15,16] when the monomethyl derivative of $N_3P_3Cl_6$, i.e. $N_3P_3Cl_5(CH_3)$, reacts with 3-amino-1-propanol.

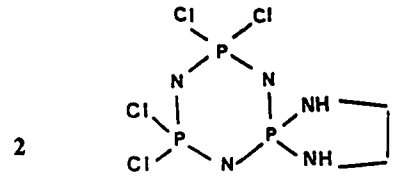
---

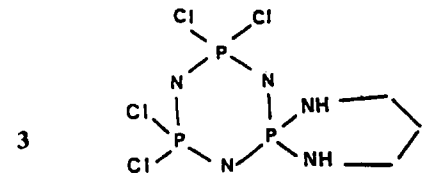
*Dedicated to the late Pr. F. MATHIS. For Part VII, see ref[18].

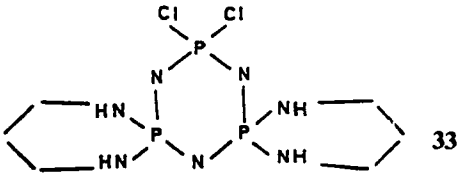
(+)Author to whom all correspondence should be addressed.

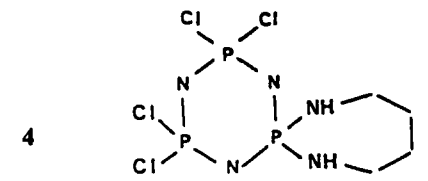
Incidentally, 1,5-diaminopentane (cadaverine) and higher analogs lead to two-ring assembly structures, coded as BINO structures,[17,18] in which two $N_3P_3Cl_5$ moieties are bridged through a diamino linkage.

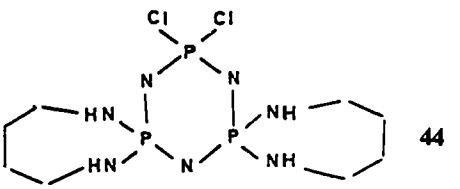
Furthermore, some combinations of SPIRO and/or ANSA and/or BINO configurations in the same molecule were recently made conspicuous in a few cases (i) upon reaction of $N_3P_3Cl_6$ with 1,3-propylene glycol (as a side-product) in (1 : 2) stoichiometric conditions[11] and (ii), in the DISPIRO-DIANSA-BINOdicyclo-

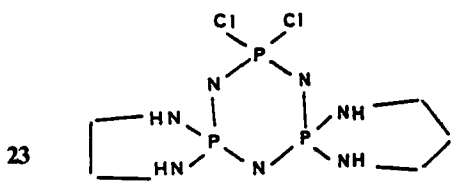


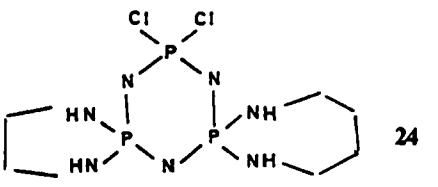












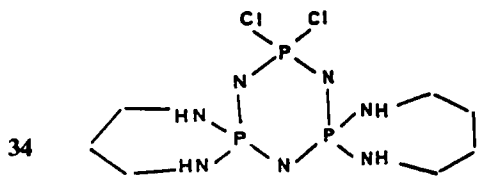


FIGURE 1 Nomenclature of SPIRO derivatives reported here.

triphosphazene obtained upon reaction of the ANSA compound described above with successively 1,3-diaminopropane and 1,6-diaminohexane[19].

In other words, any cyclophosphazene containing several SPIRO and/or ANSA and/or BINO moieties may be synthesized in a quantitative manner from now on. This new game for the chemist was recently labelled as "BASIC", i.e. **BINO-ANSA-SPIRO IN CYCLOPHOSPHAZENES**[19].

Actually, the POLYSPIROcyclotriphosphazenes which were described up-to-now were of a "symmetrical" type, i.e. they were produced upon reaction of the same difunctional reagent on $N_3P_3Cl_6$ in various stoichiometric conditions. In order to emphasize the regio-selective character of the BASIC game, it was of interest to attempt the preparation of "non-symmetrical" POLYSPIROcyclotriphosphazenes in which various difunctional reagents would be linked to the same N_3P_3 ring in SPIRO configurations. Such an attempt is in keeping with the general pattern of the covalent binding of antitumoral cyclophosphazenes to several natural polyamines as tumor finders with the aim of increasing drug selectively for malignant cells.[20]

The present contribution reports the synthesis and the physical identity (^{31}P and ^{1}H high-resolution NMR, mass spectrometry and IR spectroscopy) of new symmetrical and non-symmetrical DISPIROcyclotriphosphazenes (Fig. 1).

The nomenclature is the following: a MONOSPIRO derivative such as $N_3P_3Cl_4[HN—(CH_2)_n—NH]$ will be coded as *n* when a DISPIRO derivative such as $N_3P_3Cl_2[HN—(CH_2)_m—NH][HN—(CH_2)_n—NH]$ will be coded as *mn*.

EXPERIMENTAL

SYNTHESIS

The synthesis of every DISPIRO derivative was achieved upon reaction of the appropriate diamine, $H_2N—(CH_2)_n—NH_2$, on the $N_3P_3Cl_4$ [HN—$(CH_2)_m$—NH] MONOSPIRO compound in stoichiometric conditions.

Reactions were carried out from quantities about 20 mmoles of the MONOSPIRO starting materials in a mixture (50 : 50) of anhydrous ethyl ether and dichloromethane (as the solvent) at 0°C, in the presence of the amount of triethylamine or of diamine (used in excess) required for picking up hydrogen chloride. Triethylamine gives better yields than excess diamine with regard to crude final products but the complete elimination of $Et_3N \cdot HCl$ all along the purification of samples is much more tricky than in the case of diamine · HCl, owing to the relative solubility of both hydrochlorides in organic solvents: the former is indeed partially soluble in any solvent while the latter is rather less soluble.

Thus, compounds described here were prepared using an excess of the diamine reagent. The yield in crude final products was about 70–80%. Pure final products were obtained through several fractionated recrystallizations (yields within the 35–45% range). Chromatographic purifications are useless for this purpose owing to an irreversible binding of the products to the silica surface.

This synthetic process leads in a very facile way to any symmetrical or non-symmetrical DISPIRO or TRISPIRO derivative, except in the case of 1,2-diaminoethane where only the MONOSPIRO derivative can be prepared in a pure state. Indeed, reaction of this diamine both with $N_3P_3Cl_6$ in a 2 : 1 and 3 : 1 molar ratio and with the MONOSPIRO compound in 2 : 1 and 3 : 1 molar ratio never lead to the expected TRISPIRO **222** derivative, the formation of the DISPIRO system **22** being detected by ^{31}P NMR spectroscopy.

MASS SPECTROMETRY

Mass spectrometry was found on several occasions to be an adequate tool for monitoring the purity of cyclotriphosphazenes[21,22]. Thus, this technique was used once more to identify compounds and to control their purity.

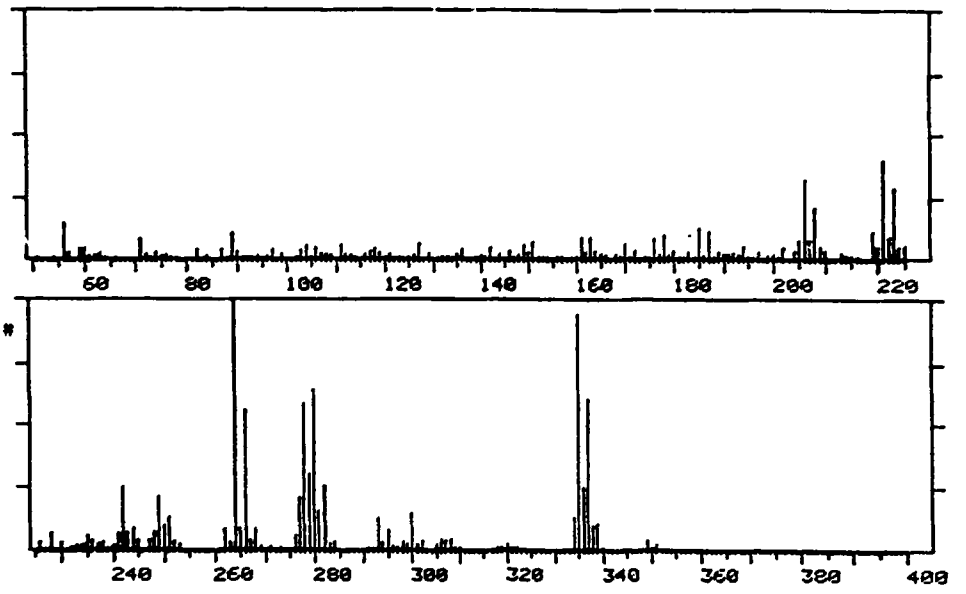


FIGURE 2 70 eV electron-impact mass spectrum of **23**.

The spectra were recorded on an R1010 Ribermag quadrupole mass spectrometer using a direct inlet system. The source temperature was 150°C, electron energy 70 eV. The spectra were analyzed by means of a DEC PDP 8/M computer and stored on disk. A small sample (about 1 μ g) was introduced into the probe, the temperature of which was then gradually increased from ambient temperature to 100°C, taking care that neither the electron multiplier nor the amplifier were in a satured condition at any time. The areas under the curves corresponding to the current carried by the various ions were calculated by computer.

The 70 eV electron-impact mass spectra of **3**, **4**, **33** and **44** were previously analyzed and published[3,7,8].

Mass spectra of **23**, **24** and **34** (coded hereinafter as $Cl_2D_2D_3$, $Cl_2D_2D_4$ and $Cl_2D_3D_4$) are visualized in Figs. 2 to 4.

First of all, a direct comparison of these three spectra shows that hydrogen transfers are much more frequent for **24** and **34** than for **23**, i.e. when a D_4 SPIRO loop does exist in the molecule.

Base peaks (I = 100%) for **23**, **24** and **34** correspond to the fragments $M^+ - D_3$ (*m/z* 264), $M^+ - D_4$ (*m/z* 264) and $M^+ - D_4$ (*m/z* 277) respectively. Then, D_4 is a more easily leaving loop than D_3, the D_2 loop being more stable than D_3 and D_4 in any case.

For every fragment containing two chlorine atoms, the loss of one Cl and of two Cl gives rise, systematically, to a weak F-1Cl peak and a large F-2Cl peak. Thus, the two Cl atoms of any F fragment depart simultaneously under fragmentation.

Considering the fragmentation of the Cl_2D_2 fragment (*m/z* 264, 100%) in **23** and **24**, the loss of 1 and 2Cl gives peaks at *m/z* 228 (6.9%) and 194(5.5%) for **23** and at *m/z* 228 (17.3%) and 194 (11.0%) for **24**. In contrast, the loss step by step (i.e. 1NH, 1NH + $1CH_2$, 1NH + $2CH_2$, 1NH + $2CH_2$ + 1NH) of the D_2 SPIRO loop gives peaks at *m/z* 249 (21.6%), 235 (6.0%), 221 (40.2%) and 206 (32.2%) for **23** and 249 (7.7%), 235 (9.1%), 221 (26.9%) and 206 (45.4%) for **24**. Thus, the Cl_2D_2 fragment looses its D_2 SPIRO loop as a whole preferentially to its pair of Cl atoms.

The foregoing observations can be summed up as follows: the electron impact fragmentation of a fused $Cl_2D_xD_y$ DISPIRO derivative goes through the loss first of a D_4 SPIRO loop, if any, then through the loss of the D_3 loop, if any, then through the loss of the D_2 loop, if any, and finally through the loss of the two chlorine atoms. In other words, the relative fragility of the various SPIRO loops and of the Cl_2 pair can be grouped as

$$D_4 > D_3 > D_2 > Cl_2.$$

Incidentally, according to this rule, the MONOSPIRO-$N_3P_3Cl_4$ [HN—$(CH_2)_2$—NH] derivative would have to be both chemically and physically extremely stable. This is actually the case, this compound may

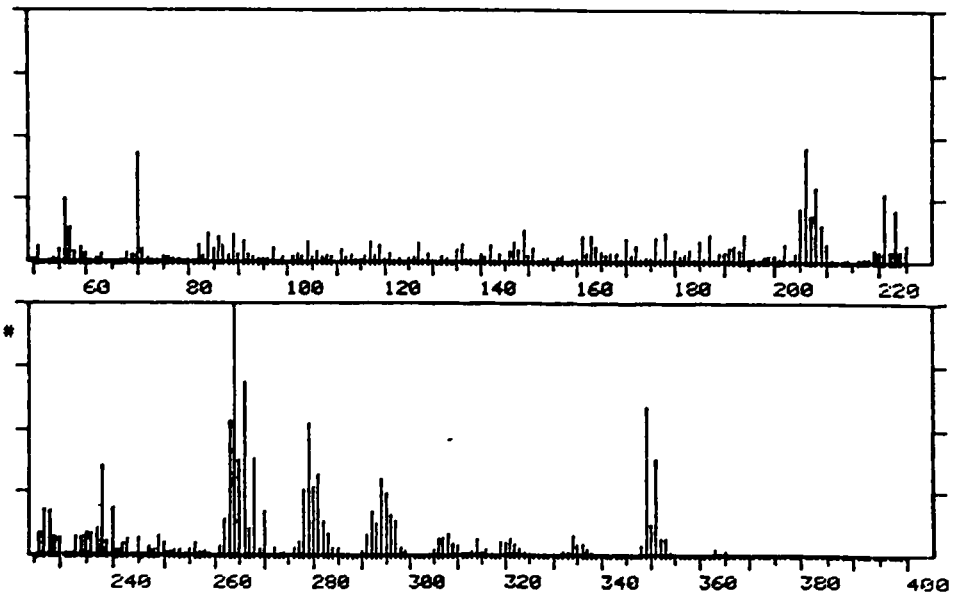


FIGURE 3 70 eV electron-impact mass spectrum of **24**.

be crystallized at the end of the synthetic process giving rise to huge (size about several mm^3) colourless cubic pieces with nice hexagonal cuts which remain unaltered in a moist atmosphere. The crystal structure of this chemical was determined in our laboratory[23], rendering reports about the hygroscopic behaviour of this chemical questionable[24].

The assignment of the spectra in Figs. 2 to 4 is straightforward. The intensity of non-identified peaks is less than 1%, proving the absence of any possible contaminant in the samples studied.

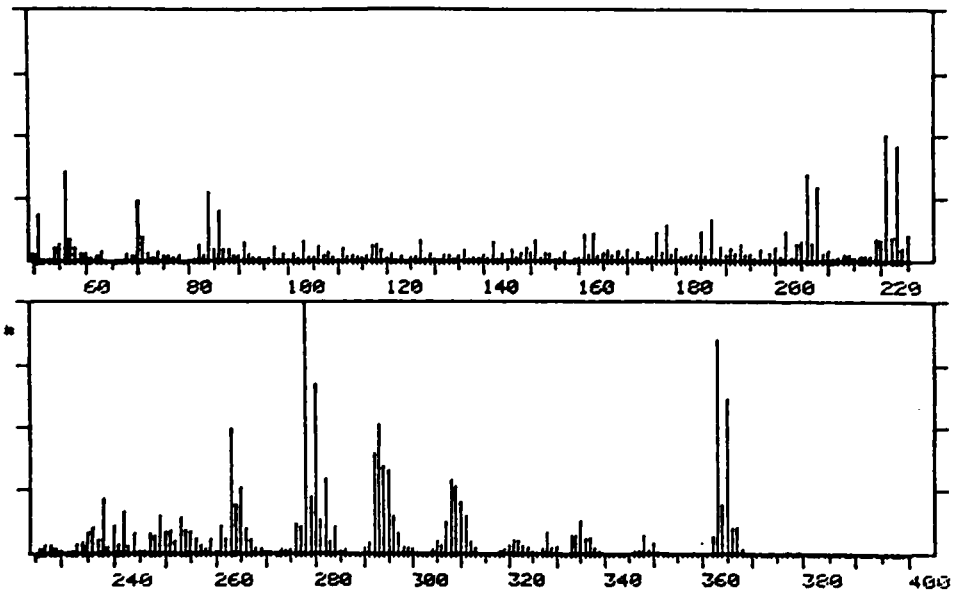


FIGURE 4 70 eV electro-impact mass spectrum of **34**.

NMR SPECTROSCOPY

^{31}P data. The ^{31}P NMR spectra, as recorded on a BRUKER WM 90 instrument (36.43 MHz), give almost first-order A_2B spectra for **3**, **4**, **22**, **33** and **44** and second-order unusuable spectra for **23**, **24** and **34**. NMR spectra of these three non-symmetrical DISPIRO derivatives, as recorded on a BRUKER WM 250 instrument (101.27 MHz), give rise to first-order ABC spectra which are shown in Fig. 5.

Incidentally, compound **2** gives a false singlet both at 36.43 and 101.27 MHz.

Chemical shifts δ and coupling constants J are listed in Table I.

Values of $\delta(PCl_2)$ are found within the range of 21–25 ppm. Thus, the chemical shift of the $P(Cl_2)$ atom is weakly affected by the nature of the SPIRO loop(s) grafted on the N_3P_3 ring.

In contrast, values of $\delta(P_{spiro})$ vary noticeably amongst the series, mainly for the D_3-bearing P atoms (coded hereinafter as PD_3): δ (PD_3) is indeed shifted to low field, from 8 ppm in **3** to about 13 ppm in **33**, **23** and **34**. The same feature is observed for $\delta(PD_2)$ and $\delta(PD_4)$ which vary from 22 ppm in **2** to 27–28 ppm in **22**, **23** and **24** and from 13 ppm in **4** to 16–17 ppm in **44**, **34** and **24**, respectively. It may be noted that this trend is going on, too when passing from the MONOSPIRO and DISPIRO derivatives studied here to the TRISPIRO compounds, **333** and **444**, described previously[7]: values of $\delta(PD_3)$ and $\delta(PD_4)$ are then equal to 18 and 21 ppm, respectively.

Fig. 6 shows the variations of $\delta(PD_x)$ as a function of x and of the number of SPIRO loops grafted on the N_3P_3 ring.

In 1966, LETCHER and VAN WAZER[25] suggested several factors the chemical shift of a phosphorus atom would depend on, i.e. the electronegativity χ_x of its ligands, the π electron n_π content of the bonds around it and mainly its hybridization character θ. They proposed the well-known formula

$$\Delta\delta = -a\Delta\chi_x + b\Delta n_\pi + c\Delta\theta.$$

Actually, the first and the second term of this equation cannot account for the very significant variations of $\delta(PD_x)$: the replacement of a pair of Cl atoms by the two NH groups of the SPIRO loop indeed corresponds to a very low contribution $\Delta\chi_x$ ($\chi_{Cl} = 2.97$, $\chi_{NH} = 3.41$)[26] when the π content of the bonds around this (PD_x) atom, i.e. mainly the π content of the phosphorus-nitrogen endocyclic bonds in the N_3P_3 ring, remains very similar whatever x, on the basis of DEWAR's island model[27–30].

Thus, variations of $\delta(PD_x)$ within the series studied here must depend, essentially, on the variation, $\Delta\theta$, of the angles around the corresponding phosphorus atom and, presumably, on the variation of the endocyclic NPN angle. This assumption was previously put forward for explaining the variation of $\delta(PD_x)$ when passing from compound **3**[3] to compound **4**[8]: X-ray crystallography has proved, indeed, that the D_3 loop stretches the N_3P_3 ring along the two-fold axis[31] much more than the D_4 loop does[5,8], the (PD_3) atom of **3** appears to be in a pseudo-tetrahedral situation, the four associated phosphorus-nitrogen bonds being practically equal and the endocyclic NPN angle being drastically decreased, that is much smaller than in any other trimeric cyclophosphazene. In other words, such a T_d-like environment for a phosphorus atom belonging to a trimeric ring looked unique for cyclotriphosphazenes and explained why the chemical shift of (PD_3) is at such high field. In compound **4**, the D_4 loop induces the same distortion into the N_3P_3 ring, however to a smaller extent: the corresponding $\delta(PD_4)$ is then low field shifted, relative to $\delta(PD_3)$ in **3**. At last, the observed value for $\delta(PD_2)$ in **2** appears to be the "normal" one, that is the one corresponding to a non-distorted N_3P_3 ring. We may note that this approach to the rationalization of the variations of $\delta(PD_x)$ is supported by the fact that conclusive evidences from X-ray crystallography about the non-distortion of the N_3P_3 ring under the grafting of ethanolamino D_2 loops was recently provided in the literature[12].

Several relationships between $\delta^{31}P$ and bond angles at P atoms have been established during the last decades on various types of phosphorus compounds: such attempts were proposed, e.g. for phosphonates, phosphinates, phosphines and phosphites[32–36] and, more recently, for some thio-oxo-phosphonates[37], thio-oxo-dithiaphosphonates[38] and fluorotetrazaphosphoranes[39].

In our case, Fig. 7 shows that there exists quite a linear relationship between $\delta(PD_x)$ and the NPN endocyclic angle, as shown by X-ray crystallography for **3**[31], **4**[5,8], **333**[7], **2**[23] and for the SPIRO-$N_3P_3Az_4$[HN—$(CH_2)_3$—NH] derivative, coded as Az_4D_3[14]. The R factor is equal to 0.992. Incidentally, the graft of three D_3 loops on the N_3P_3 ring (compound **333**) re-equilibrates the ternary symmetry of it *vs* the very stretched situation which exists in MONOSPIRO **3**: NPN endocyclic angles are indeed 111.5° in **3** vs 114.5° in **333** (usual value in trimeric cyclophosphazenes ca. 119°).

Concerning the values of the coupling constants in table I, there is more uncertainty. Several attempts at correlating $^2J_{PP}$ in cyclotriphosphazenes with the electronegativity of the ligands were previously unsuccessful[40–43]. Thus, we shall just make some remarks about the variation of $^2J_{PP}$ observed in our series:

(i) the smallest values for $^2J_{PP}$ (around 41–44 Hz) are observed for the coupling between (PCl_2) and (PD_3) entities;

(ii) in the middle δ range, $^2J_{PP}$ is about 46–47 Hz for couplings between (PD_2) and (PD_3), (PD_2) and (PD_4) together with (PD_3) and (PD_4) moieties;

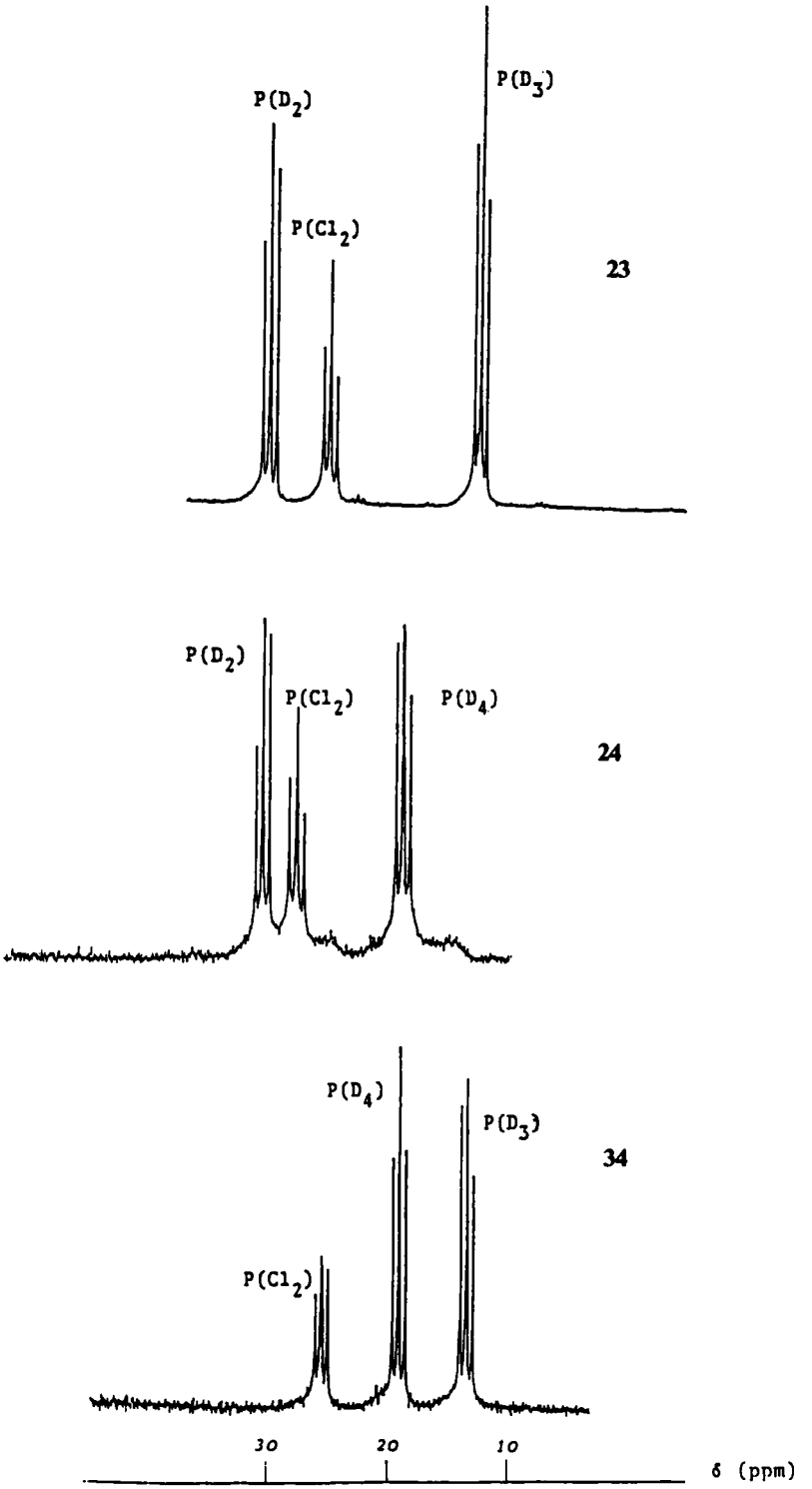
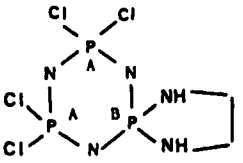
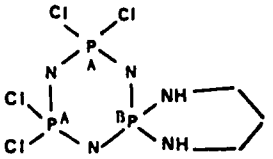
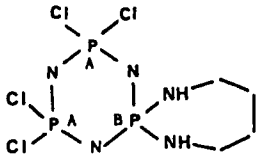
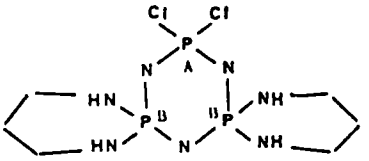
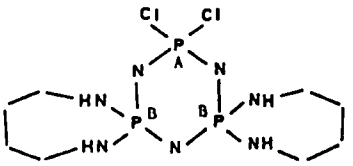
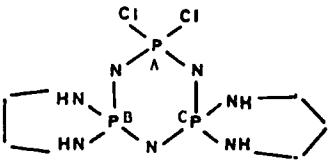
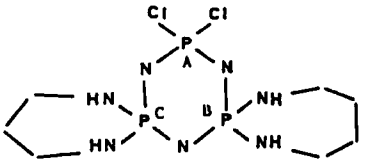
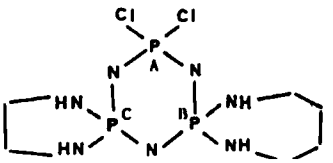


FIGURE 5 ^{31}P NMR spectra (101.27 MHz) of compounds **23**, **24** and **34** (in CD_2Cl_2).

TABLE I

^{31}P = chemical shifts δ(ppm) and coupling constants J_{PP} (Hz) of SPIRO derivatives (101.27 MHz)

		δ(ppm) 31p	Spin System	J(Hz) J(pp)
2		*A* 22 *B* 22	A_2B	—
3		*A* 21 *B* 8	A_2B	*AB* 44.0
4		*A* 21 *B* 13	A_2B	*AB* 47.0
33		*A* 21 *B* 13	AB_2	*AB* 41.7
44		*A* 24 *B* 16	AB_2	*AB* 47.0
23		*A* 22 *B* 27 *C* 13	*ABC*	*AB* 50.1 *AC* 46.4 *BC* 46.4
34		*A* 23 *B* 17 *C* 13	*ABC*	*AB* 50.2 *AC* 41.5 *BC*47.6
24		*A* 25 *B* 17 *C* 28	*ABC*	*AB* 56.1 *AC* 50.2 *BC* 46.4

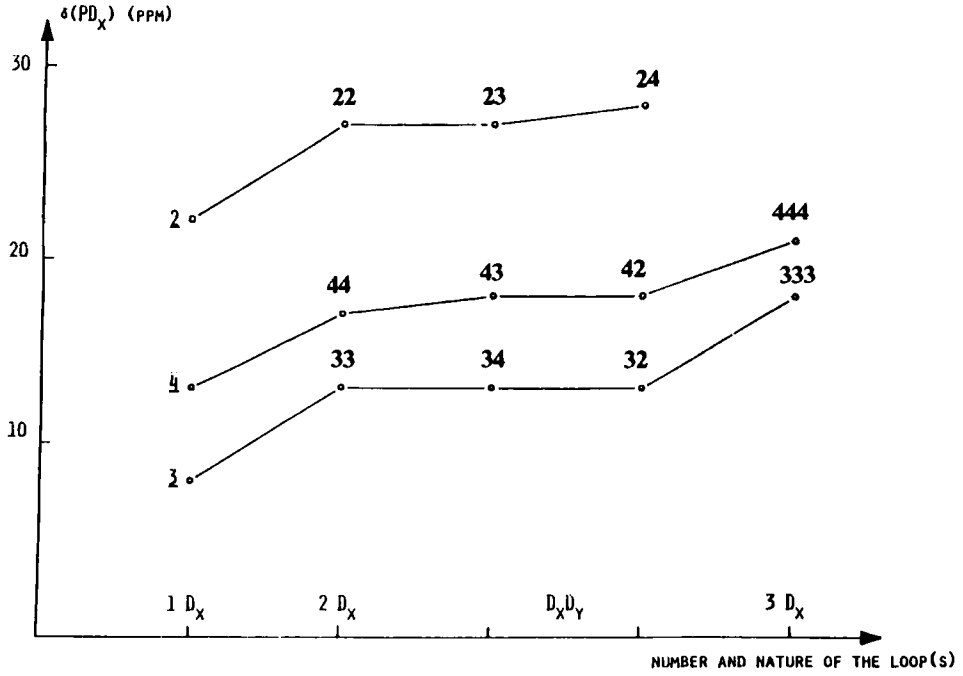


FIGURE 6 Evolution of the chemical shift for loop-bearing P atoms as a function of the number of loops and of the nature of the loop.

(iii) the largest values for $^2J_{PP}$ (between 50 and 56 Hz) correspond to couplings between (PCl_2) and (PD_2), together with couplings between (PCl_2) and (PD_4).

It is noteworthy that the largest $^2J_{PP}$ values are observed for couples of P atoms whose neighbourhood is the closest to the normal situation in cyclotriphosphazene (see above).

^1H NMR Data. ^{1}H NMR spectra were recorded at 298K on a BRUKER WM 250 instrument (250 MHz). Chemical shifts, δ, and coupling constants, J, are reported in Table II.

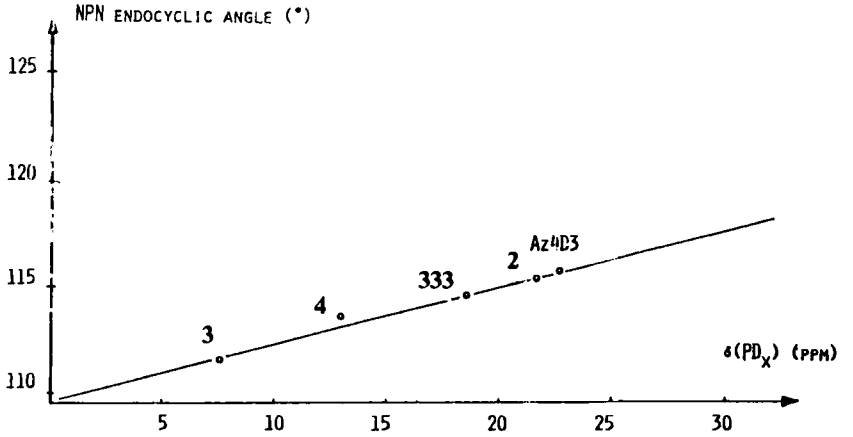
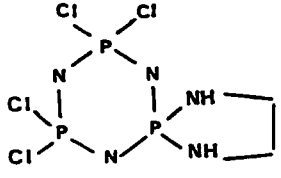
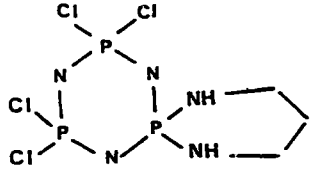
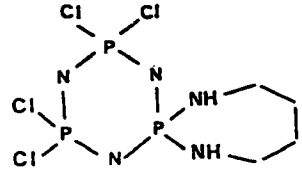
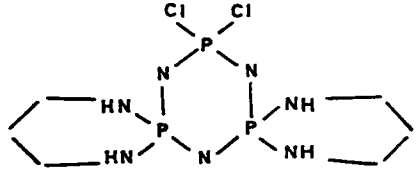
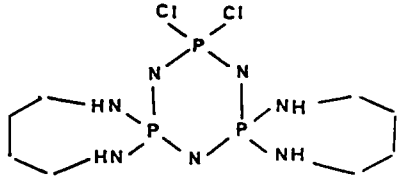
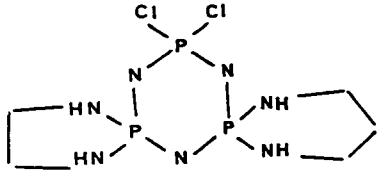
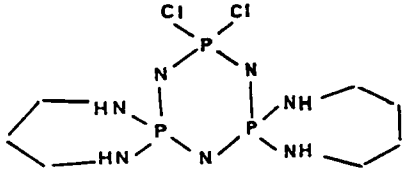
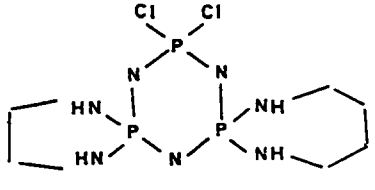


FIGURE 7 Linear relationship between the chemical shift of the loop-bearing P atom(s) and the value of the endocyclic NPN angle.

TABLE II

^{1}H-NMR Spectra Chemical Shifts δ(ppm) and Coupling Constants J(Hz) of SPIRO derivatives (101.27 MHz)

		δ_{NH}	δ_{NCH_2}	δ_{CCH_2}	$^2J_{PNH}$	$^3J_{PNCH}$	$^4J_{PNCCH}$	$^3J_{HNCH}$	$^3J_{HCCH}$
2		2.10	3.40	—	6.50	12.45	—	1.70	equivalents
3		2.81 and 1.60	3.30	1.78	—	15.77	1.37	4.80	5.83
4		3.10	3.15 and 3.06	1.64	13.37	20.92	—	7.20	< 2
33		2.49 and 1.52	3.30	1.69	—	—	—	≃ 5	≃ 5.5

44		3.10	3.00	1.60	13.37	20.92	—	7.20	< 2
23		271 2.68 and 1.68	3.34 3.28	— 1.67	— —	12.62 —	— —	≅ 2 ≅ 5	equivalents —
34		2.59 and 1.60 3.18	3.27 3.02 and 2.98	1.64 1.60	— —	— —	— —	— —	— —
24		2.50 2.87	3.31 3.03	— 1.60	7.8 9.5	11.9 20	— —	1.70 7.10	— —

Experimental values of $^3J_{H...H}$ and $^3J_{P...H}$ coupling constants follow the KARPLUS relationship,

$$J(\theta) = A\cos^2\theta + B\cos\theta + C$$

where θ is the dihedral angle and A, B and C are constants for a particular molecular framework.

For $^3J_{HNCH}$ these constants are $A = 8.5$ Hz (from 0 to 90°) or 9.5 Hz (from 90 to 180°), $B = 0$ Hz and $C = -0.3$ Hz.

For compound **2**, the 1.7 Hz value is in agreement with a HNCH dihedral angle close to 60° which is consistent with the quasi-planar character of the D_2 SPIRO five-membered loop in it. For compound **3** containing a six-membered loop, the theoretical mean value (5 Hz), calculated taking into account the rapid inversion of the HNCH dihedral angle which varies from 0° (8 Hz) to 120° (2 Hz) fits the experimental value (4.8 Hz) well. For compound **4**, containing a seven-membered loop, the HNCH dihedral angle varies from 150° (7 Hz) to about 30° (6 Hz) and the experimental value (7.2 Hz) is close to the 6–7 Hz range.

Incidentally, the calculated values (using the KARPLUS relationship with $A = 8.5$ or 9.5 Hz, $B = 0$ Hz and $C = -0.3$ Hz) of $^3J_{HCCH}$ for twisted and chair conformations of the six-membered loop of compound **3** are 4.75 Hz and 2.5 Hz respectively. The experimental value, i.e. 5.83 Hz, is close to the former, in agreement with X-ray crystal data.

For $^3J_{PNCH}$, KARPLUS constants are $A = 25.4$ Hz, $B = -8.4$ Hz and $C = 1.9$ Hz, respectively.

In the case of the derivatives containing at least one D_3 loop, i.e. **3**, **33**, **23**, **34**, an interesting feature is noted: both their proton NMR and IR spectra (**44** see below) reveal two types of N<u>H</u> protons. As an example, the NMR spectrum of **3** in CD_2Cl_2 gives two N<u>H</u> signals at 1.60 and 2.81 ppm, respectively.

A critical survey of the whole set of X-ray crystal structures[3,5,7,8,31] for SPIRO derivatives show that SPIRO loops display essentially two types of conformation, hereinafter coded as **twisted** and **chair**, the chair conformation being the most common. However, the twisted conformation occurs in compound **3** owing to the presence of two intermolecular hydrogen bonds per molecule (2.08Å) in the unit cell which stabilize the twisted conformation. A quantum mechanical study of the twisted *vs* chair flip-flop shows

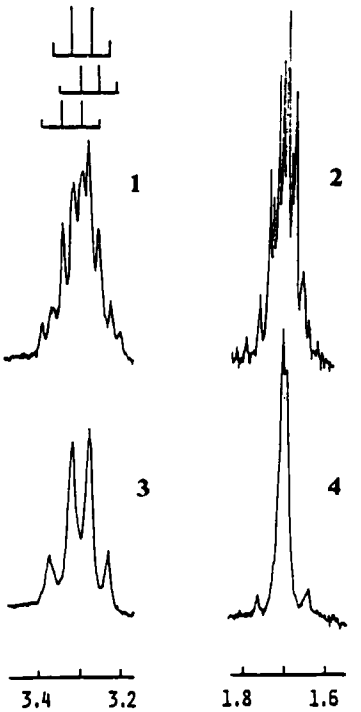


FIGURE 8 AB spectra for C<u>H</u>$_2$ protons in α and β positions in the six-membered loops of compound **33** (^{31}P decoupled, in CD_2Cl_2). 1 and 2: methylenic protons patterns without homonuclear decoupling, 3: C<u>H</u>$_2$ protons in α position under homonuclear decoupling of the C<u>H</u>$_2$ protons in β position; 4: C<u>H</u>$_2$ protons in β position under homonuclear decoupling of C<u>H</u>$_2$ protons in α position.

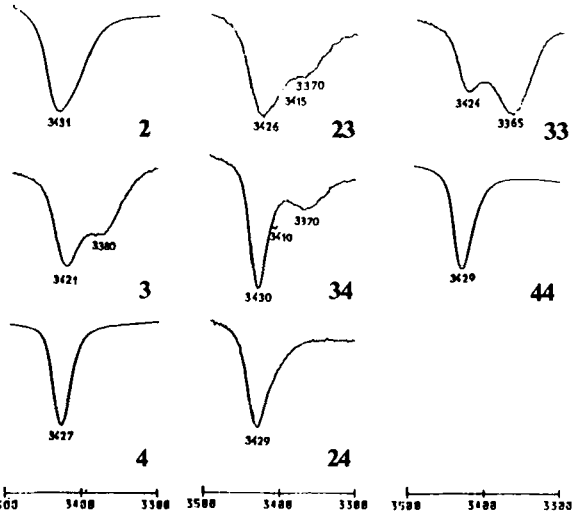


FIGURE 9 IR spectra of SPIRO derivatives reported here in the 3300–3500 cm^{-1} range on diluted solutions in CH_2Cl_2 (FTIR Bruker IFS 110 instrument).

that the energy gap between these two patterns is low[45] per se and becomes negligible in the absence of the strong hydrogen bonds mentioned above. Thus, NMR and IR spectra being recorded in solution, we may predict that some amount of the chair conformation will appear in such conditions because of a decrease of intermolecular hydrogen bonding.

Then, the presence in the NMR and IR spectra of **3** of two types of N<u>H</u> signals is due to a conformational equilibrium between the twisted and chair forms which exist in solution (the two NH protons, $N\underline{H}_1$ and $N\underline{H}_2$, of each form being, of course, intrinsically equivalent).

The fact that the two $N\underline{H}_1$ and $N\underline{H}_2$ signals are observed simultaneously in the ^1H NMR spectrum of **3** is actually due to the fact that the inversion rates t_1 and t_2 of the equilibrium

$$N\underline{H}_1(\delta_1) \underset{t_2}{\overset{t_1}{\rightleftharpoons}} N\underline{H}_2(\delta_2)$$

are smaller than the N<u>H</u> proper relaxation time T_2 (notice the very broad character of the two N<u>H</u> bands). This explanation is supported by the fact that the two N<u>H</u> signals disappear upon double irradiation of each of them, i.e. either at 1.60 or at 2.81 Hz.

The same peculiar feature is observed in any other compound containing at least one D_3 loop (**33**, **23** and **34**): two N<u>H</u> signals are indeed systematically observed at 298K in their spectra. Moreover, the graft of a second SPIRO loop induces an additional lack of symmetry with respect to the structure of compound **3** itself which makes protons of methylenic groups within the loops no more equivalent, despite of rapid inversion of these loops. Successive decouplings reveal a significant non-equivalence of the C<u>H</u>$_2$ protons in α position to the N<u>H</u> groups and a much less pronounced no-equivalence of C<u>H</u>$_2$ protons in the β position, if any. Fig. 8 shows the AB spectra obtained under suitable decoupling for C<u>H</u>$_2$ protons in α and β positions, respectively, for compound **33**.

D_3 loop-containing chemicals display the same peculiar behaviour in their IR spectra. Spectra were recorded on an FTIR BRUKER IFS 110 instrument on diluted solutions in CH_2Cl_2. Two NH bands are systematically observed for **3**, **33**, **23** and **34**, while one unique NH band appears for **2**, **4**, **44** and **24** (Fig. 9)[44,46].

CONCLUSION

The synthesis of the first fused DISPIROcyclotriphosphazenes was achieved upon reaction of a diamine, $H_2N-(CH_2)_m-NH_2$ (with $m = 2, 3, 4$) on the $N_3P_3Cl_4[HN-(CH_2)_n-NH]$ ($n \neq m$) MONOSPIRO derivative using a 1 : 1 stoichiometric ratio. Molecular structures were assigned, using both ^{31}P and ^1H high resolution NMR and electron-impact mass spectrometry. D_3 loop-bearing MONOSPIRO and DISPIRO "fused or not" cyclotriphosphazenes display a peculiar feature both in NMR and IR

spectroscopy, based on a conformational equilibrium between the twisted and the chair forms of D_3 loops which can be detected via NH resonances.

The synthesis of these fused DISPIROcyclotriphosphazene is quantitative and stereospecific. It constitutes, then, a new example of the BASIC molecular game and leads the way for the covalent binding at demand of several natural polyamines as tumor finders in the SPIRO configuration on a cyclophosphazenic system.

REFERENCES

1. S. S. Krishnamurthy, K. Ramachandran, A. R. Vasudeva Murthy, R. A. Shaw and M. Woods, *Inorg. Nucl. Chem. Lett.*, **13** 407 (1977).
2. M. Becke-Goehring and B. Boppel, *Z. Anorg. Allg. Chem.*, **322** 239 (1963).
3. G. Guerch, M. Graffeuil, J-F. Labarre, R. Enjalbert, R. Lahana and F. Sournies, *J. Mol. Struct.*, **95** 237 (1982).
4. G. Guerch, Ph.D. Thesis n° 1118, Paul Sabatier University, Toulouse, France, December 2, 1983.
5. G. Guerch, J-F. Labarre, R. Lahana, F. Sournies, R. Enjalbert, J. Galy and J-P. Declercq, *Inorg. Chim. Acta*, **83** L33 (1984).
6. N. El Murr, Ph.D. Thesis n° 2991, Paul Sabatier University, Toulouse, France, June 7, 1984.
7. N. El Murr, R. Lahana, J-F. Labarre and J-P. Declercq, *J. Mol. Struct.*, **117** 73 (1984).
8. G. Guerch, J-F. Labarre, R. Roques and F. Sournies, *J. Mol. Struct.*, **96** 113 (1982).
9. J-F. Labarre, G. Guerch, F. Sournies, R. Lahana, R. Enjalbert and J. Galy, *J. Mol. Struct.*, **116** 75 (1984).
10. S. R. Contractor, M. B. Hursthouse, L. S. Shaw, R. A. Shaw and H. Yilmaz, International Conference on Phosphorus Chemistry, Nice, France, September, 1983, Abstract n° 174.
11. S. R. Contractor, M. B. Hursthouse, H. G. Parkes, L. S. Shaw, R. A. Shaw and H. Yilmaz, *Chem. Comm.*, **1984**, 675.
12. V. Chandrasekhar, S. S. Krishnamurthy, H. Manohar, A. R. Vasudeva Murthy, R. A. Shaw and M. Woods, *J. Chem. Soc.*, **1984**, 621.
13. G. Guerch, J-F. Labarre, G. Levy and F. Sournies, ANVAR-CNRS French Patent n° 82-19768, November 25, 1982 (world extension: October 25, 1983).
14. J-F. Labarre, G. Guerch, F. Sournies, F. Spreafico and S. Filippeschi, *J. Mol. Struct.*, **117** 59 (1984).
15. P. J. Harris and K. B. Williams, *Inorg. Chem.*, **23** 1495 (1984).
16. R. Enjalbert, J. Galy, P. J. Harris, K. B. Williams, R. Lahana and J-F. Labarre, *J. Am. Chem. Soc.*, 1985 in press.
17. G. Guerch, J-F. Labarre, R. Lahana, R. Roques and F. Sournies, *J. Mol. Struct.*, **99** 275 (1983).
18. P. Castera, J-P. Faucher, G. Guerch, R. Lahana, A. Mahmoun, F. Sournies and J-F. Labarre, *J. Mol. Struct.*, **108** 29 (1985).
19. F. Sournies, J-F. Labarre, P. J. Harris and K. B. Williams, *Inorg. Chim. Acta*, **90** L61 (1984).
20. J-L. Sassus, M. Graffeuil, P. Castera and J-F. Labarre, *J. Mol. Struct.*, **108** 23 (1985).
21. B. Monsarrat, J. C. Promé, J-F. Labarre, F. Sournies and J. C. Van de Grampel, *Biomed. Mass Spectrom.*, **7** 405 (1980).
22. F. Sournies, R. Lahana and J-F. Labarre, *Inorg. Chim. Acta*, **101** 31 (1985) and references herein.
23. M. Willson, R. Lahana and J. Jaud, to be published.
24. Y. S. Babu, H. Manohar, K. Ramachandran and S. S. Krishnamurthy, *Z. Naturforsch.*, **33b** 588 (1978).
25. J. H. Letcher and J. R. Van Wazer, *J. Chem. Phys.*, **44** 815 (1966).
26. cf. for example: F. Gallais, D. Voigt and J-F. Labarre, *J. Chim. Phys. Fr.*, **62**, 761 (1965) and references herein.
27. M. J. S. Dewar, E. A. C. Lucken and M. A. Whitehead, *J. Chem. Soc.*, **1960**, 2423.
28. J-P. Faucher, Ph.D. Thesis n° 690, Paul Sabatier University, Toulouse, France, December 11, 1975.
29. J-P. Faucher, J-F. Labarre and R. A. Shaw, *Z. Naturforsch*, **31b**, 677 (1976).
30. J-F. Labarre, *Structure and Bonding*, **35** 1 (1978) and references herein.
31. R. Enjalbert, G. Guerch, J-F. Labarre and J. Galy, *Z. Krist.*, **160** 249 (1982).
32. E. D. Dennis, Ph.D. Thesis, Harvard University, Cambridge, Massachusetts, 1968.
33. D. W. Allen and J. C. Tebby, *J. Chem. Soc.*, **B** 1970, 1527.
34. G. M. Blackburn, J. S. Cohen and I. Weathrall, *Tetrachedron*, **27** (1971) 2903.
35. L. D. Quin and J. J. Breen, *Org. Magn. Reson.*, **5** 17 (1973).
36. J. G. Verkade, *Bioinorg. Chem.*, **3** 165 (1974).
37. J-P. Dutasta, J-B. Robert and L. Wiesenfeld, (1981) in "Phosphorus Chemistry" (L. D. Quin and J. G. Verkade, eds.), pp. 581–584, *Amer. Chem. Soc. Symp. Ser.*, N° 171, Washington, D.C., USA.

38. J. Martin and J-B. Robert, *Org. Magn. Reson.*, **15** 87 (1981).
39. J. E. Richman and R. B. Flay, *J. Am. Chem. Soc.*, **103** 1291, 5265 (1981).
40. F. Heatley and S. M. Todd, *J. Chem. Soc.*, **A** 1966, 1152.
41. E. G. Finer, *J. Mol. Spectr.*, **23** 104 (1967).
42. H. R. Allcock, "Phosphorus-Nitrogen Compounds", Academic Press, New York, 1972.
43. K. Schumann and A. Schmidpeter, *Phosphorus*, **3**, 51 (1973).
44. R. Mathis, M. Willson, F. Mathis, J-F. Labarre, G. Guerch, R. Lahana, A. Mahmoun and F. Sournies, *Spectrochim. Acta*, **41A** 573 (1985).
45. R. Lahana, F. Crasnier and J-F. Labarre, *Inorg. Chim. Acta*, **90** L65 (1984).
46. R. Mathis, T. Bouissou, M. Willson, L. Lafaille and J-L. Labarre, to be published.