Conclusive Statement of the So-called SPIRO *versus* ANSA Dilemma in Cyclophosphazenes for Polyamines as Polyfunctional Reagents

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Much interest has been generated in the past two decades on the so-called SPIRO [1] *versus* ANSA [2] dilemma related to the molecular structure of products obtained upon reaction of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, with difunctional reagents.

This contribution reviews the whole set of conclusive structural evidences we recently obtained, in favour of the SPIRO configuration when $N_3P_3Cl_6$ reacts with natural diamines (1,3-diaminopropane and putrescine) and other biogene relatives such as spermidine and spermine under stoichiometric conditions.

Reaction of $N_3P_3Cl_6$ with 1,3-diaminopropane leads quantitatively to the SPIRO $N_3P_3Cl_4$-[HN–$(CH_2)_3$–NH] moiety [3, 4] (Fig. 1); no ANSA form or DISPIRO side-products were observed in stoichiometric conditions.

In contrast, reaction of $N_3P_3Cl_6$ with 1,4-diaminobutane (putrescine) leads to two compounds: the major product, $N_3P_3Cl_4$[HN–$(CH_2)_4$–NH], has the expected SPIRO configuration [5] whereas the minor product displays the serendipitous two-ring bridged-assembly structure [6], coded as BINO structure, $N_3P_3Cl_5$[HN–$(CH_2)_4$–NH]$Cl_5P_3N_3$ (Fig. 2); no ANSA structure was ever observed here.

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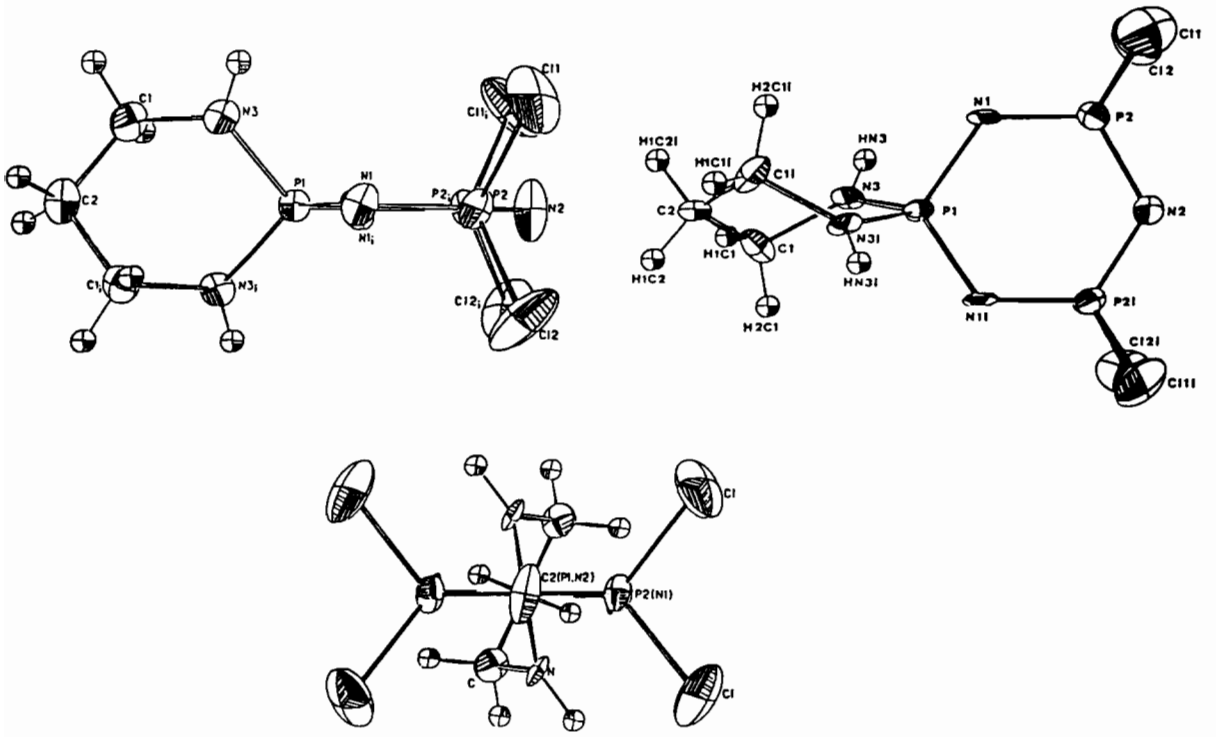

Fig. 1. Perspective views of the molecule showing (top left) the SPIRO structure, (top right) the puckering of the SPIRO loop and (bottom) the two-fold axis.

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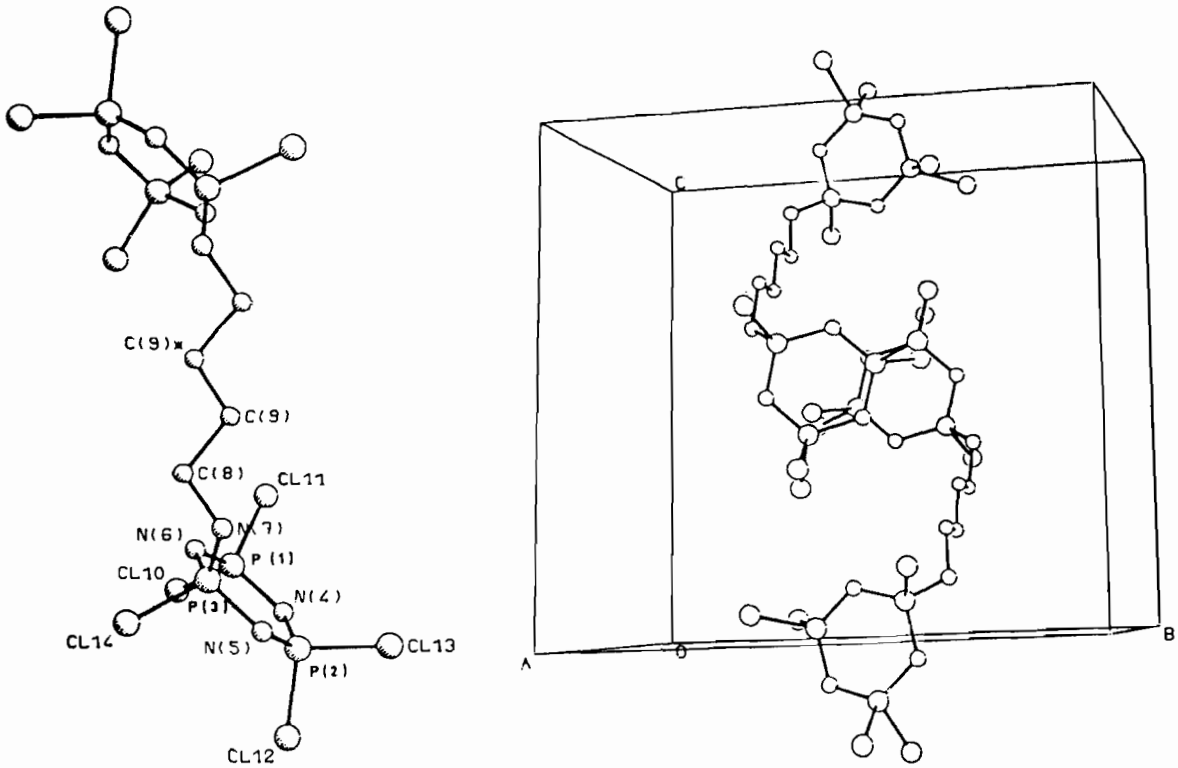

Fig. 2. Perspective views of the BINO 4 molecule and of its unit cell.

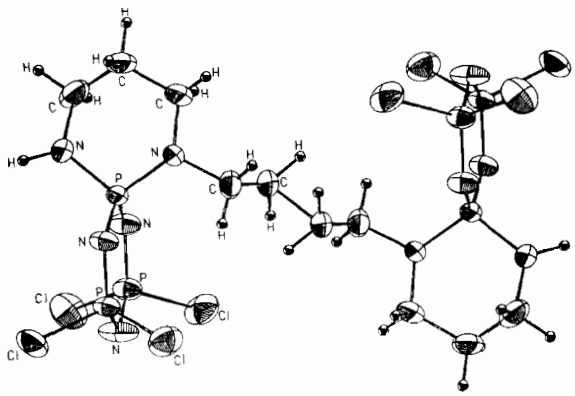

Fig. 3. Perspective view of the spermine derivative.

Incidentally, reaction of $N_3P_3Cl_6$ with higher homologs like 1,5-diaminopentane (cadaverin) leads quantitatively to the BINO $N_3P_3Cl_5$ [HN–$(CH_2)_n$–NH] $Cl_5P_3N_3$ ($n \geqslant 5$) [7].

Reaction of $N_3P_3Cl_6$ with spermine, H_2N–$(CH_2)_3$–NH–$(CH_2)_4$–NH–$(CH_2)_3$–NH_2, leads quantitatively to the DISPIRO3 BINO4 structure (Fig. 3) in which the two (NH_2, NH) couples of the spermine molecule are grafted in the SPIRO configuration on one $N_3P_3Cl_4$ entity each, the two $N_3P_3Cl_4$[HN–$(CH_2)_3$–N] moiety being bridged through the $(CH_2)_4$ methylenic chain [8].

Thus, it was deemed necessary to finally elucidate the nature of the product of the reaction of $N_3P_3Cl_6$ with spermidine, H_2N–$(CH_2)_3$–NH–$(CH_2)_4$–NH_2,

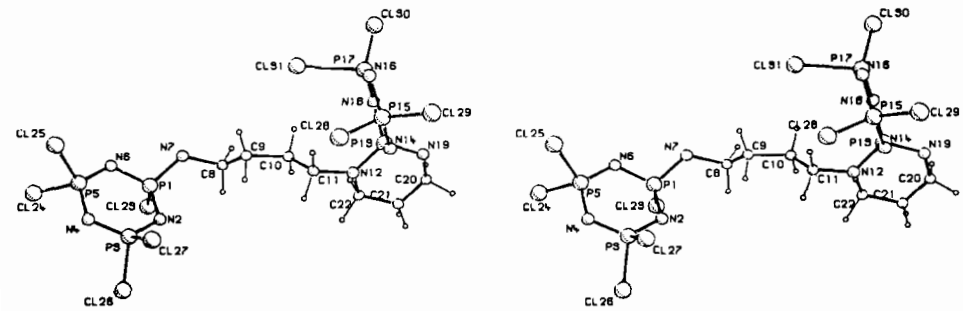

Fig. 4. Stereoscopic view of the spermidine derivative.

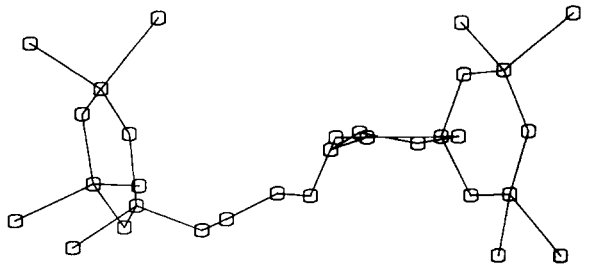

Fig. 5. Molecular pattern of the spermidine derivative with the best plane of the SPIRO loop perpendicular to the plane of the figure.

with the aim of achieving the structural investigation of chemicals obtained upon reaction of $N_3P_3Cl_6$ with natural, *i.e.*, biogene, polyamines, in stoichiometric conditions.

Reaction of spermidine on $N_3P_3Cl_6$ yields a unique product, MW = 731, which was identified by mass spectrometry and high-resolution NMR [8].

Single crystals were obtained through a slow evaporation of a solution of the final product in n-hexane (colourless cubic pieces with hexagonal cuts).

Preliminary investigations used the precession method and allowed the assignment of a monoclinic cell, actually $P2_1/n$. The crystal was transferred to a Syntex $P2_1$ computer-controlled diffractometer. 25 reflections were used in order to orient the crystal and to refine the cell dimensions. Cell parameters are a = 11.674(8), b = 27.833(12), c = 8.910(4) Å, β = 102.2(4)°, V = 2829(2) Å^3, Z = 4. The final R factor was 0.050.

A stereoscopic view of the molecule is shown in Fig. 4, in which the numbering of the atoms is indicated. This view emphasizes the SPIRO3 BINO4 structure which could be expected to exist on the basis of the 731 value for molecular weight as provided by mass spectrometry. The two six-membered phosphazene rings are not strictly planar and the two N_3P_3 planes within the molecule are not parallel, the angle between them being equal to 57.6(5)° (Fig. 5). A stereoscopic view of the four molecules in the unit cell is visualized in Fig. 6.

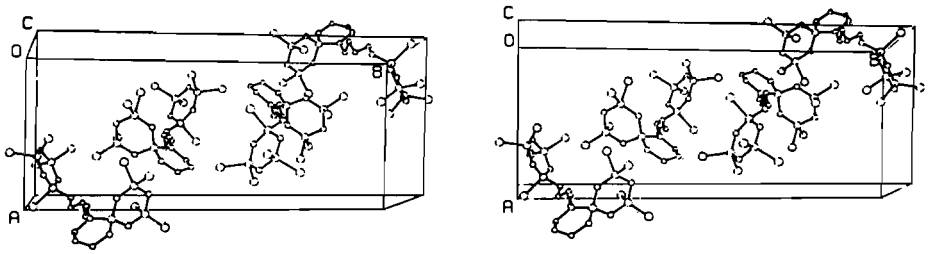

Fig. 6. Stereoscopic view of the unit cell for the spermidine derivative.

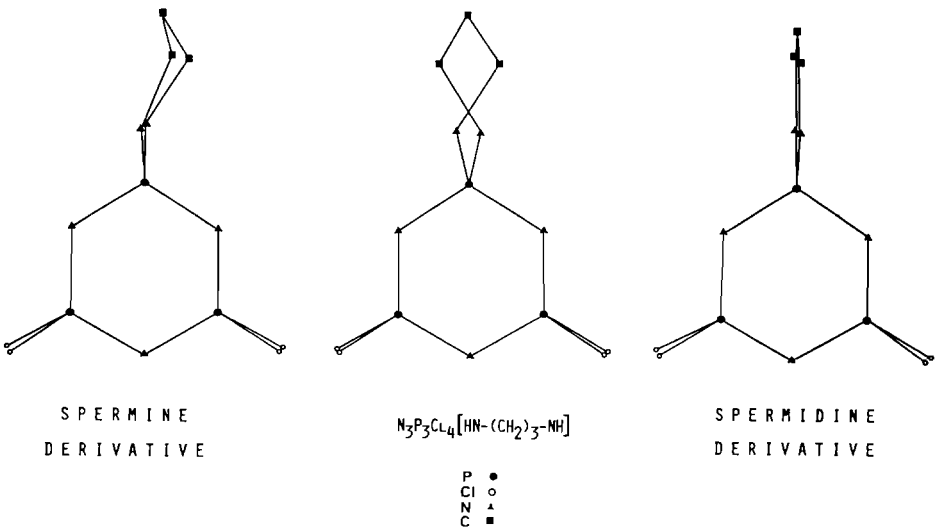

Fig. 7. Configuration of the loop in the SPIRO derivatives described here.

From Figs. 4 and 5, it appears that the SPIRO loop looks roughly planar, the distance from atoms of the loop to the best plane being lower than 0.14(3) Å. Such a quasi-planar configuration for the SPIRO loop has to be compared (Fig. 7) with the folding of the SPIRO loop in the $N_3P_3Cl_4$ [HN–$(CH_2)_3$–NH] molecule [4] (which can be described as an 'opened book' conformation), and with the slight 'chair' conformation of the two SPIRO rings present in the spermine derivative [8]. Quantum calculations are now in progress in order to approach the parameters the versatility of the SPIRO loop conformation depends on.

Thus, the SPIRO *versus* ANSA dilemma in cyclophosphazenes when polyamines are reacting with $N_3P_3Cl_6$ seems to be solved: SPIRO structures are made conspicuous, ANSA structures are never. In other words, polyamines display a manichean behaviour upon reaction of $N_3P_3Cl_6$, leading to very pure and well-defined chemicals. We have already made use of this remarkable selectivity for delivering some antitumor cyclophosphazenes more specifically to neoplastic tissues [9–11] thanks to the potentiality of putrescine as a tumor finder [12].

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