An Answer to the SPIRO *versus* ANSA Dilemma in Cyclophosphazenes. Part VII*. Neither SPIRO nor ANSA: the BINOdicyclotriphosphazenes, $N_3P_3Cl_5$-[HN–$(CH_2)_n$–NH]$Cl_5P_3N_3$

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Abstract

Reactions of $N_3P_3Cl_6$ with cadaverine, H_2N–$(CH_2)_5$–NH_2, and higher cousins lead to unique final products in which two $N_3P_3Cl_5$ moieties are bridged through a [HN–$(CH_2)_n$–NH] entity in a two-ring assembly structure. This new type of configuration for the diamino-ligand, called BINO, is made conspicuous by concerted use of mass spectrometry and ^{31}P, ^{13}C and ^1H high resolution NMR.

Introduction

The so-called SPIRO [1] *vs.* ANSA [2] dilemma related to the molecular structure of products of reaction of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, with difunctional reagents is now well argumented and was recently clarified in our laboratory [3] thanks to X-ray crystallography.

Thus, conclusive evidence for a SPIRO structure were obtained in many cases: (i) upon reaction of $N_3P_3Cl_6$ with diamines [4–9], (ii), upon reaction of $N_3P_3Cl_6$ with spermidine and spermine [5, 6, 10], (iii), upon reaction of $N_3P_3Cl_6$ with diols [11, 12], (iv), upon reaction of $N_3P_3Cl_6$ with N-Methylethanolamine [13], (v), in the $N_3P_3Az_4$[HN–$(CH_2)_3$–NH] and $N_3P_3Az_4$[HN–$(CH_2)_4$–NH] derivatives [14, 15], and (vi), in several polyspirodicyclotriphosphazenes [16].

On the other hand, conclusive evidence for an ANSA structure was provided in two cases (i), upon reaction of $N_3P_3Cl_5(CH_3)$ with 3-amino-1-propanol [17, 18], and (ii), upon reaction of $N_3P_3Cl_6$ with 1,3-propylene glycol (as a side-product) in (1:2) stoichiometric conditions [12].

In other words, the linkage of a difunctional reagent to $N_3P_3Cl_6$ occurs very commonly in a SPIRO configuration and very rarely in an ANSA one.

Furthermore, a third configuration, coded as cross-linked or BINO [19], was made conspicuous in a side-product of the reaction of putrescine, H_2N–$(CH_2)_4$–NH_2, on $N_3P_3Cl_6$ in stoichiometric conditions [5]: indeed, this reaction leads to the SPIRO–$N_3P_3Cl_4$[HN–$(CH_2)_4$–NH] derivative as the very major final product and to the BINO–$N_3P_3Cl_5$-[HN–$(CH_2)_4$–NH]$Cl_5P_3N_3$ derivative in which two $N_3P_3Cl_5$ moieties are bridged through a HN–$(CH_2)_4$–NH entity in a two-ring assembly structure.

Owing to the fact that such a BINO derivative is never observed upon reaction of 1,3-diaminopropane, H_2N–$(CH_2)_3$–NH_2, with $N_3P_3Cl_6$ [4], we could expect that reactions of large diamines, *i.e.* H_2N–$(CH_2)_n$–NH_2 with $n \geqslant 5$, would lead preferentially to BINO derivatives *vs.* common SPIRO ones.

Actually, this is the case and this contribution reports on the synthesis and physico-chemical identity [20] of BINO–$N_3P_3Cl_5$[HN–$(CH_2)_n$–NH]Cl_5-P_3N_3 chemicals with $n \geqslant 5$, the case n = 4 being quoted as a reference.

Experimental

Synthesis

Reactions of diamines with $N_3P_3Cl_6$ in stoichiometric conditions were carried out in anhydrous ethyl ether as a solvent, in the presence of an amount of triethylamine just enough to pick up hydrogen chloride. Reactions were achieved after two days. The crude final products were submitted to SiO_2 column chromatography using CCl_4–CH_2Cl_2 (3:7) as eluent to remove traces of chlorhydrate and non-reactive $N_3P_3Cl_6$ starting material. The yield of such column chromatographies is good, *i.e.* about 85% (single flow): as an example, 8.2 g of crude final product for n = 10 leads to 2.1 g of $N_3P_3Cl_6$ and to 4.9 g of the expected BINO 10 chemical. However, 2 or 3 successive flows are needed for getting the final BINO derivatives in a very pure state. Thus, the real

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yield after such 2 or 3 chromatographies is poor, about 40% maximum.

It is noteworthy that the classical trick, commonly used in cyclophosphazene chemistry to remove non-reactive $N_3P_3Cl_6$, *i.e.* a washing of the crude final product with n-heptane, cannot be used here, BINO derivatives being as soluble as $N_3P_3Cl_6$ in hydrocarbons.

Elemental analysis data for the BINO derivatives purified in such a way are consistent with the expected BINO structure and not with its SPIRO cousin. As an example, data for BINO 6 are C% 9.88 ± 0.12, H% 2.00 ± 0.10, N% 15.08 ± 0.11 and Cl% 47.84 ± 0.19 when theoretical rates for a BINO and for a SPIRO structure are respectively: 9.76, 1.91, 15.17, 48.01 and 18.43, 3.61, 17.91 and 36.27.

Melting points of BINOs are gathered in Table I. Regular decreases are observed within both the sub-series where n is odd or even.

TABLE I. Melting Points of BINOs 4 to 10.

Compound	Melting Point (°C)
BINO 4	148
BINO 5	108
BINO 6	98
BINO 7	64
BINO 8	80
BINO 9	65
BINO 10	74

Mass Spectrometry

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

Mass spectra of BINO 4 and BINO 10 are presented as examples in Fig. 1. They are remarkably straightforward and every peak can be assigned in a very facile way.

In the high mass range, *i.e.* between m/z 500 and M^+ peaks, very few fragments (with very low intensity except in BINO 6) are observed which correspond to the successive loss of 1 to 5 Cl atoms from M^+. In every case, the M^+-1Cl peak is the highest within the series.

In the low mass range, *i.e.* between m/z 100 and m/z 350, 6 features are common to the whole

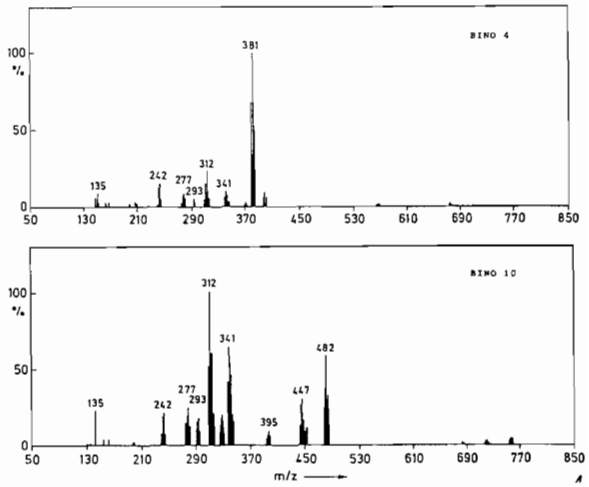


Fig. 1. 70 eV electron impact mass spectrum of BINO 4 and BINO 10.

spectra: m/z 135 (N_3P_3), m/z 242 ($N_3P_3Cl_3$), m/z 277 ($N_3P_3Cl_4$), m/z 293 ($N_3P_3Cl_4$–NH), m/z 312 ($N_3P_3Cl_5$) and m/z 341 ($N_3P_3Cl_5$–NH–CH_2).

It is noteworthy that the intensity of the m/z 312 peak grows up from BINO 4 (24%) to BINO 5 (56%) and to BINOs 6 to 10 so that this peak becomes the base peak (I = 100%).

Intensities of the m/z 341 peak within the series are: 10% for BINO 4, 53% for BINO 5, 24% for BINO 6, 41% for BINO 7, 60% for BINO 8, 21% for BINO 9 and 64% for BINO 10. Thus, the intensity of the m/z 341 peak increases with n within the odd sub-series and decreases within the even one.

The four other peaks are of minor importance and their intensities within the series fluctuate in a rather random manner. However, the m/z 135 signal, which characterizes the N_3P_3 cyclophosphazene ring itself, is ever observed as the outcome of the fragmentation: this observation, quite trivial in cyclophosphazenes, supports once more the non-aromatic Dewar islands electronic structure for phosphorus nitrogen rings [21].

In the medium mass range, *i.e.* between m/z 350 and m/z 500, 3 main peaks are observed:

1 The peak, coded as F1, corresponding to the $N_3P_3Cl_5$–NH–$(CH_2)_n$ fragment, which is the base peak (m/z 381 and m/z 395) for BINO 4 and BINO 5; its intensity decreases sharply from BINO 6 (m/z 409, 25%) to BINO 8 (m/z 437, 16%) and becomes rather negligible in BINO 9 (m/z 451, 3%) and BINO 10 (m/z 465, 5%);

2 The peak, coded as F2, corresponding to F1-1Cl, which appears only for BINOs 7 to 10 (m/z 405(8%), 419(30%), 433(18%) and 447(30%) respectively);

3 The peak, coded as F3, corresponding to F1 + 1NH, which also appears only for BINOs 7 to 10 (m/z 440(20%), 454(50%), 468(10%) and 482(59%) respectively).

Owing to the remarkable simplicity of their mass spectra and the trends, detailed above, about the magnitude of main peaks, some conclusions may be reasonably drawn about the relative fragility of chemical bonds in BINOs structures when the diamino bridge is lengthening.

(a) the rupture of the carbon–carbon bond in β position of NH groups occurs in the whole series (considering the m/z 341 fragment) with a propensity to increase with n in odd terms and to decrease with n in even terms;

(b) the likelihood of the rupture of the nitrogen–carbon bond in α position of NH groups is maximal for BINO 4 and BINO 5 (considering the F1 fragment) and drops down dramatically to BINO 10;

(c) the likelihood of the rupture of the exocyclic phosphorus–nitrogen bonds (considering the m/z 312 and the F3 fragments) increases with n prevailing definitely on any other bond breaking from BINO 7;

(d) phosphorus–chlorine bonds are intrinsically more stable than exocyclic phosphorus–nitrogen bonds upon electron impact, in contrast with what exists in SPIRO [4, 9] derivatives.

NMR Spectroscopy

^{31}P data

The ^{31}P NMR spectra of any BINO term, as recorded on a BRUCKER WH 90 instrument (36.43 MHz), is a complex multiplet *ca.* 20–21 ppm in CD_2Cl_2 with H_3PO_4 85% as a standard. Such multiplets give almost first-order A_2B spectra when recorded on a BRUCKER WH 250 instrument (101.27 MHz) and pure A_2B spectra from a BRUCKER WH 400 instrument (162.08 MHz).

Spectra for BINO 6 to 10 are gathered in Fig. 2 (101.27 MHz).

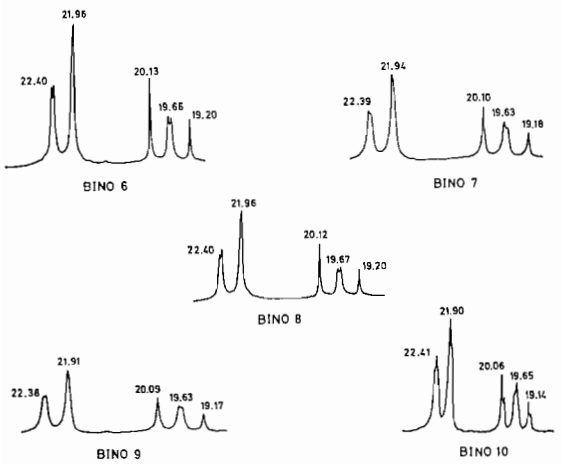


Fig. 2. ^{31}P NMR spectra of BINOs 6 to 10 (101.27 MHz).

Chemical shifts at 101.27 MHz (external standard) are higher by 1.36 ± 0.07 ppm than those recorded at 36. 43 MHz (internal standard). Table II shows real chemical shift values in internal standard conditions together with J(P–P) coupling constants. Spectra are nearly superimposable, J(P–P) being constant along the series, 47.27 ± 0.3 MHz.

TABLE II. ^{31}P Data for BINOs 6 to 10.

Compound	WH 90 δ(ppm)	WH 250 δ(ppm)	J(P–P)(Hz)
	22.27	22.40	
	21.71	21.96	
BINO 6	20.74	20.13	47.12
	19.69	19.66	
	18.80	19.20	
	22.34	22.39	
	21.85	21.94	
BINO 7	20.80	20.10	47.61
	19.75	19.63	
	18.85	19.18	
	22.46	22.40	
	21.57	21.96	
BINO 8	20.58	20.12	47.12
	19.52	19.67	
	18.62	19.20	
	22.25	22.38	
	21.77	21.91	
BINO 9	20.72	20.09	47.18
	19.75	19.63	
	18.86	19.17	
	22.34	22.41	
	21.77	21.90	
BINO 10	20.80	20.06	47.35
	19.75	19.65	
	18.78	19.14	

^{13}C data

^{13}C spectra from BRUCKER WH 250 instrument (62.90 MHz) for BINOs 6 to 10 are visualized in Fig. 3.

A step-by-step analysis of these spectra provides the assignment of Table III:

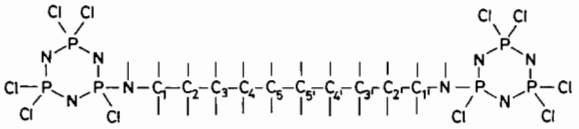
(i) for every carbon atom of the bridge, the corresponding chemical shift slightly increases with n: δ $C_{11'}$, as an example, varies from 41.28 ppm for BINO 6 to 41.43 ppm for BINO 10;

(ii) C_1 and $C_{1'}$ atoms, in α position of NH groups, are down-field shifted *vs.* other carbon atoms of the bridge;

(iii) δ $C_{nn'}$ steadily decreases from $C_{11'}$ to $C_{33'}$, increasing again from $C_{33'}$ to $C_{55'}$. This would suggest a lengthening of C_4–$C_{4'}$ (in BINO 8) and C_5–$C_{5'}$

TABLE III. ^{13}C Data for BINOs 6 to 10.

	$\delta C_{11'}$	$\delta C_{22'}$	$\delta C_{33'}$	$\delta C_{44'}$	$\delta C_{55'}$
BINO 6	41.28	30.71 30.61	26.20		
BINO 7	41.34	30.75 30.63	26.55	28.81	
BINO 8	41.34	30.79 30.64	26.55	29.14	
BINO 9	41.40	30.81 30.69	26.61	29.19	29.52
BINO 10	41.43	30.84 30.70	26.64	29.25	29.58



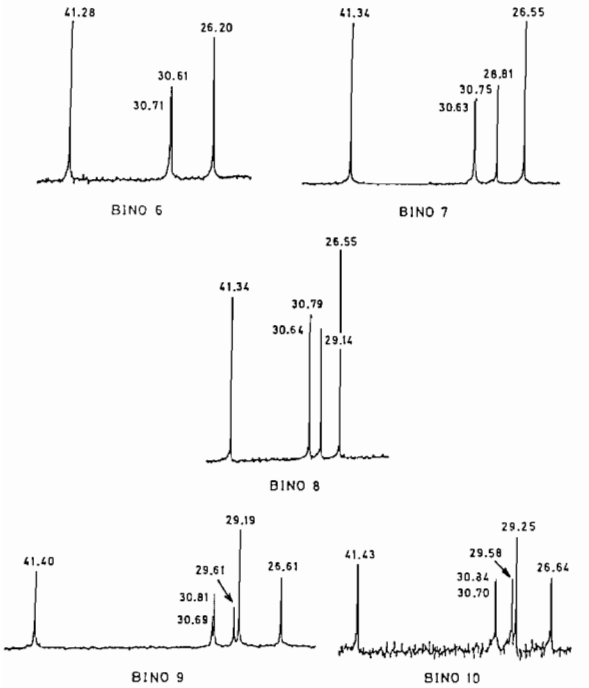


Fig. 3. ^{13}C spectra of BINOs 6 to 10 (62.90 MHz).

(in BINO 10) *vs.* other carbon–carbon bonds of the chain. This assumption will have to be supported by X-ray structures but it is still verified from X-ray structure of $N_3P_3Cl_4[HN-(CH_2)_3-N]-(CH_2)_4-[N-(CH_2)_3-NH]Cl_4P_3N_3$ where the central '$C_5-C_{5'}$-like' bond is noticeably longer (1.581 Å) than other C–C bonds in the $(CH_2)_4$ bridge (1.529 Å) [10].

^1H data

^1H data (250 MHz) are assembled in Fig. 4 and Table IV. $\delta H_{nn'}$ is quite constant for a given nn' couple and decreases gently when n varies from 1 to 3 to keep a constant value for n larger than 3. That means that the shortest C–H bonds in the bridge are linked to the most central carbon atoms (such as C_4 and $C_{4'}$ for BINO 8, C_5 and $C_{5'}$ for BINO 10) of the chain. This conclusion must still be confirmed by X-ray analyses now in progress.

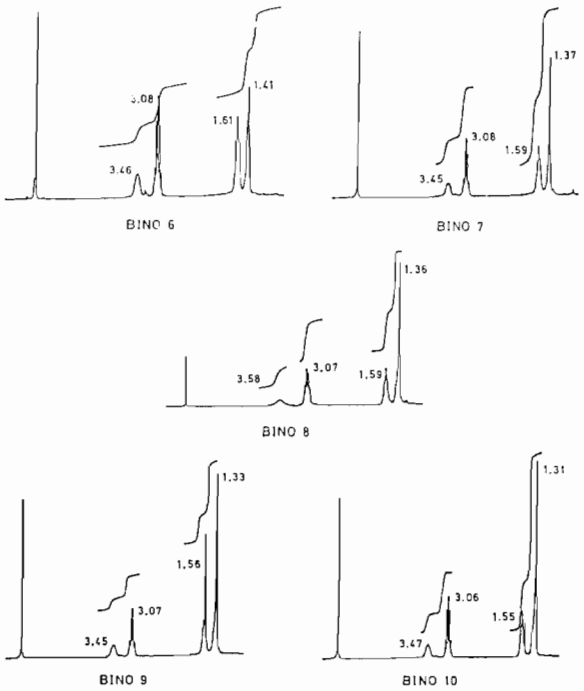


Fig. 4. ^1H data for BINOs 6 to 10 (250 MHz).

TABLE IV. ^1H data for BINOs 6 to 10.

	δ(N)H	$\delta H_{11'}$	$\delta H_{22'}$	$\delta H_{33'}$	$\delta H_{44'}$	$\delta H_{55'}$
BINO 6	3.46	3.08	1.61	1.41		
BINO 7	3.45	3.08	1.59	1.37	1.37	
BINO 8	3.58	3.07	1.59	1.36	1.36	
BINO 9	3.45	3.07	1.56	1.33	1.33	1.33
BINO 10	3.47	3.06	1.55	1.31	1.31	1.31

Conclusion

Reaction of cadaverine and higher cousins, *i.e.* $H_2N-(CH_2)_n-NH_2$ with $n \geqslant 5$, on hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, in stoichiometric conditions leads selectively to the BINO-$N_3P_3Cl_5$-$[HN-(CH_2)_n-NH]Cl_5P_3N_3$ final products in contrast with lower homologues, *i.e.* 1,3-diaminopropane (n = 3) and putrescine (n = 4), which lead to purely SPIRO–$N_3P_3Cl_4[HN-(CH_2)_3-NH]$ and a mixture (90:10) of SPIRO–$N_3P_3Cl_4[HN-(CH_2)_4-NH]$ and

of BINO–$N_3P_3Cl_5[HN-(CH_2)_4-NH]Cl_5P_3N_3$ moieties respectively. In other words, cadaverine, *i.e.* n = 5, constitutes the border between SPIRO and BINO areas for products of diamine reaction with $N_3P_3Cl_6$.

These BINO two-ring assembly structures may be considered as the first step to cyclophosphazenes polymerization according to Allcock [25]. Moreover, such BINO chemicals are chlorinated precursors of new vectorized antitumor agents in which the diamino bridge acts as a tumor finder [22] for delivering cyclophosphazenic active principles [3, 23] to neoplastic tissues more selectively [15, 24].

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