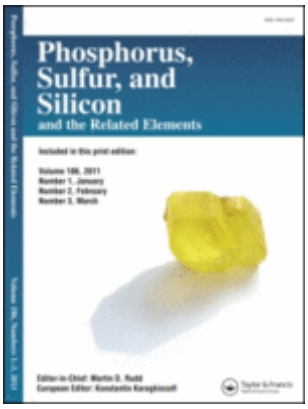

The Reactions of cyclotriphosphazene with 2-(2-hydroxyethylamino)ethanol. Spectroscopic studies of the derived products

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The Reactions of cyclotriphosphazene with 2-(2-hydroxyethylamino)ethanol. Spectroscopic studies of the derived products

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Abstract

The reactions of cyclotriphosphazene (**1**) with 2-(2-hydroxyethylamino)-ethanol (**2**) were investigated. 2-(2-hydroxyethylamino)-ethanol (**2**) is a tri-functional reagent consisting of both aliphatic hydroxyl and the secondary amino groups and its nucleophilic substitution reactions with cylotriphosphazene can lead to different product types; open chain, spiro, ansa, bridged and their mixtures. The reactions with one, two and three equimolar ratios of 2-(2-hydroxyethylamino)-ethanol, in the presence of NaH at 0-10^0 C and at room temperature gave the following cyclotriphosphazene derivatives: one mono-spiro, $N_3P_3Cl_4$[O-$(CH_2)_2$-NH-$(CH_2)_2$-O] (**3**, 1:1, r.t.); its isomer mono-ansa (**5**, 1:1, r.t.); one dispiro, $N_3P_3Cl_2$[O-$(CH_2)_2$-NH-$(CH_2)_2$-O]$_2$ (**4**, 1:1, r.t.); its isomer spiro-ansa (**6**, 1:2, r.t.); and one single-bridged compound with spiro substituted units, $N_3P_3Cl_3$[O-$(CH_2)_2$-NH-$(CH_2)_2$-O]$_3N_3P_3Cl_3$ (**7**, 1:3, at 0-10^0 C); as well as single-, $N_3P_3Cl_5$[O-$(CH_2)_2$-NH-$(CH_2)_2$-O]$N_3P_3Cl_5$ (**8**, 1:2, r.t.), double-, $N_3P_3Cl_4$[O-$(CH_2)_2$-NH-$(CH_2)_2$-O]$_2N_3P_3Cl_4$ (**9**, 1:2, r.t.), and tri-bridged, $N_3P_3Cl_3$[O-$(CH_2)_2$-NH-$(CH_2)_2$-O]$_3N_3P_3Cl_3$ (**10**, 1:3, at 0-10^0 C) derivatives. Triple-bridged derivative is the major product in this system. The structures of the novel-derived compounds were characterized by TLC-MS, FT-IR, elemental analysis, ^{1}H, and ^{31}P NMR spectral.

Key words: cylotriphosphazene, 2-(2-hydroxyethylamino)ethanol, spiro compounds, ansa compound, bridged derivatives

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1. Introduction

Due to having a variety of applications in science and technology, cylophosphazenes are an important class of inorganic cyclic systems [1, 2] and therefore, reactions of cyclotriphosphazene (**1**) with mono-, di- and polyfunctional nucleophilic reagents have been extensively studied by different research groups. The most important feature of the cyclophosphazene chemistry is that the halogen atoms attached to the phosphorus atoms in the cyclic system can be replaced by nucleophilic substitution reactions with various organic, inorganic or organometallic reagents and the compounds exhibit different physical, chemical and biological properties relative to the substituted ligands [1-47]. Cyclic phosphazenes-based derivatives have wide range of properties and applications such as electrical conductivity [24], liquid crystals [42, 45-48], chemosensors [28] and biologically active materials [14-20]. In recent years, many studies have been performed on cyclophosphazene derivatives to determine cytotoxic and antimicrobial activities and their interactions with DNA [20-23, 26, 27, 29-35].

The reactions of cyclotriphosphazene (**1**) with tri-functional nucleophilic reagents have been previously studied [49-53]. The reactions with spermidine (as a triamine) gave only one product, $N_3P_3Cl_4NH[(CH_2)_3NH(CH_2)_4NH]_2N_3P_3Cl_5$. This was confirmed by single crystal X-ray diffraction to have a 6-membered spiro ring, involving one N_3P_3 moiety and a bridge to a second such unit [49, 50].

On the other hand, from the reactions of cyclotriphosphazene with glycerol (as a triol) two isomeric products were reported to be in the form of an oil and a crystalline material [51-53]. While the oily fraction (as the major product) was assigned the 5-membered spiro structure, the crystalline one was identified as the 6-membered spiro structure, $N_3P_3Cl_4[O_3C_3H_6]$ [51-53].

We therefore wished to expand and clarify the reactivity and the substitution patterns of cyclotriphosphazene (**1**) with tri-functional nucleophilic reagents. And, in this study, hexachlorocyclotriphosphazatriene (**1**) was reacted with 2-(2-hydroxyethylamino)-ethanol (**2**, DEA) and the novel secondary amine containing spiro-, ansa- and bridged-cyclotriphosphazene derivatives (**3**-**10**, Figure 1) were synthesized. The structural characterization of the compounds was performed by using elemental analyses, MS, ^{1}H, ^{31}P-{^{1}H}, and ^{1}H{^{31}P} NMR spectral data.

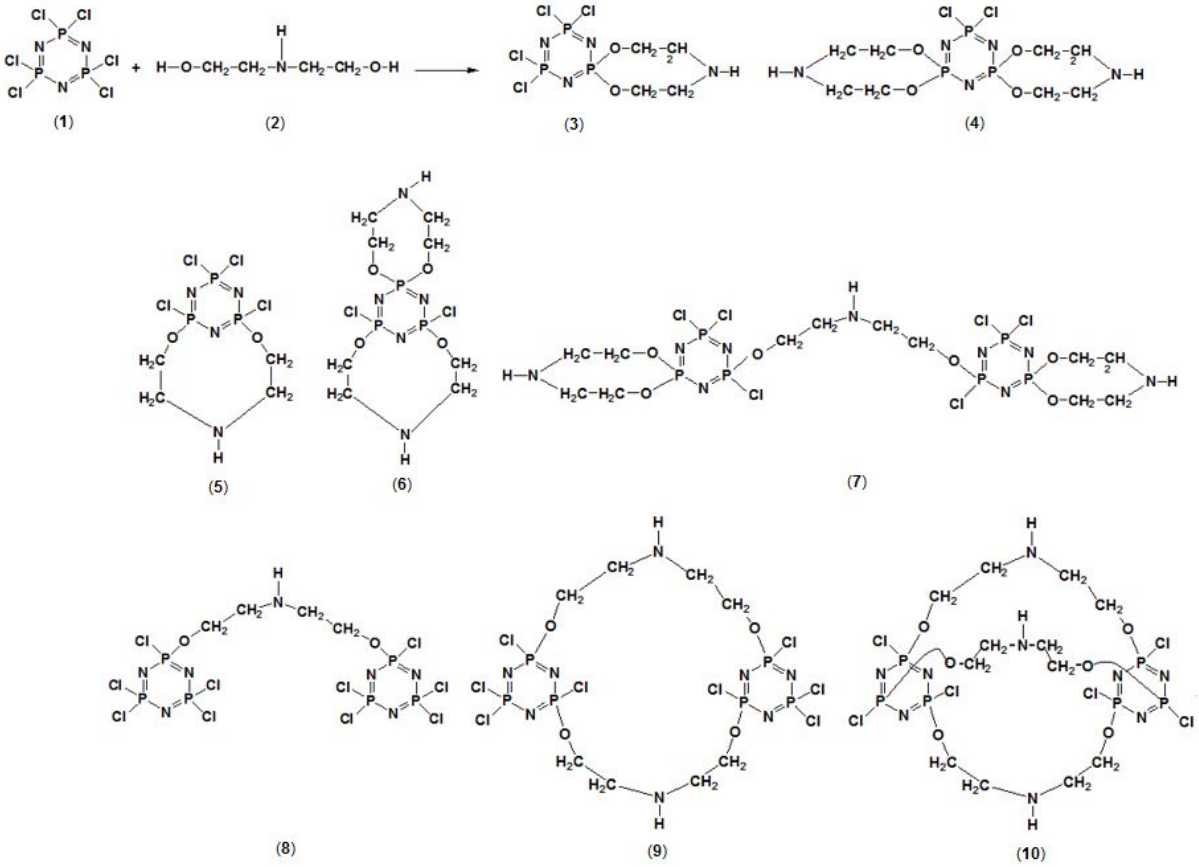

Figure 1. Structures of the synthesized cyclotriphosphazene derivatives (**3**-**10**).

2. Results and discussion

The reactions of cyclotriphosphazene, $N_3P_3Cl_6$ (**1**), with 2-(2-hydroxyethylamino)ethanol, HO-CH_2-CH_2-NH-CH_2-CH_2-OH (**2**), in excess of NaH, at 0-10^0 C and at room temperature, and in 1:1, 1:2 and 1:3 molar ratios gave the following novel *geminal*- and *non-gemial*-substituted cyclophosphazene derivatives: one mono *spiro*, $N_3P_3Cl_4$[O-$(CH_2)_2$-NH-$(CH_2)_2$O]

(**3**, 1:1, r.t. 27%); its ansa isomer (**5**, 1:1, r.t. 33%); one dispiro, $N_3P_3Cl_2[O\text{-}(CH_2)_2\text{-}NH\text{-}(CH_2)_2O]_2$ (**4**, 1:1, r.t. 19%); its spiro-ansa isomer (**6**, 1:2, r.t. 25%); and one single-bridged compound with spiro substituted units, $N_3P_3Cl_3[O\text{-}(CH_2)_2\text{-}NH\text{-}(CH_2)_2\text{-}O]_3N_3P_3Cl_3$ (**7**, 1:3, at 0-10^0 C, 14%); as well as single-, $N_3P_3Cl_5[O\text{-}(CH_2)_2\text{-}NH\text{-}(CH_2)_2O]N_3P_3Cl_5$ (**8**, 1:2, r.t. 23%); double-, $N_3P_3Cl_4[O\text{-}(CH_2)_2\text{-}NH\text{-}(CH_2)_2O]_2N_3P_3Cl_4$ (**9**, 1:2, r.t. 32%); and triple-bridged $N_3P_3Cl_3[O\text{-}(CH_2)_2\text{-}NH\text{-}(CH_2)_2O]_3N_3P_3Cl_3$ (**10**, 1:3, at 0-10^0 C, 45%) products. The structures of the compounds were verified by elemental analysis, TLC-MS, ^1H and ^{31}P NMR spectroscopy and the results are provided as part of the analytical data in the section on synthesis. The structures of the derived compounds (**3-10**) are exhibited in Figure 1.

^{31}P NMR spectra:

At first, the proton-decoupled ^{31}P NMR spectra of the reaction mixtures were measured to determine which product types were formed and their relative proportions. Then, proton-decoupled and proton-coupled ^{31}P NMR spectra were used to characterize the structures of the derived compounds. The new synthesized cyclophosphazene derivatives (**3-10**) contain $\equiv PCl_2$, $\equiv P(OR)_2$ and $\equiv P(OR)Cl$ groups and the ^{31}P NMR spectra are observed as A_2X (or A_2B) and AMX spin types [2a, 3, 11, 12, 56], which can be readily assigned by consideration of signal intensities, chemical shifts and coupling patterns. Selected ^{31}P NMR chemicals shifts and coupling constants of compounds (**3-10**) are summarized in Table 1. Within the A_2X (or AB_2) spin systems, the proton-coupled ^{31}P NMR spectra suggest that the A_2 parts of the spectra arise from $\equiv PCl_2$ (in compounds **3**, **8**); $\equiv P(OR)Cl$ (in compounds **5**, **6** and **9**) and $\equiv P(OR)OR$ (in compound **4**) groups, giving rise to doublet structures and the X parts of the spectra arise from $\equiv P(OR)_2$ (in compounds **3** and **6**), $\equiv PCl_2$ (in compounds **4, 5** and **9**) and the $\equiv P(OR)Cl$ (in compound **8**) groups, giving rise to triplet structures.

The proton-coupled ^{31}P NMR spectra allow identification of the lines due to the $\equiv P(OR)_2$ and $\equiv P(OR)Cl$ groups, where each group splits into further lines. Proton coupling experiments as

well as comparison with the earlier reported studies with difunctional and tri-functional reagents [5-7, 10, 49-53], allow unambiguous assignments of the structures. The proton-coupled and decoupled ^{31}P NMR spectra of compounds **3** and **4** are exhibited in Figure 2 and 3 respectively. In the triple-bridged cyclophosphazene derivative (**10**), the phosphorus atoms were substituted with P(OR)Cl groups and therefore, all the phosphorus atoms are chemically and magnetically in the same environment and the ≡P(OR)Cl groups are symmetrically located in the molecule. Therefore, the ^{31}P NMR spectrum gave rise to a single line (A_6 spin system), whereas all the other cyclophosphazene derivatives, as explained above, contain ≡PCl_2, ≡$P(OR)_2$ or ≡P(OR)Cl groups and the ^{31}P NMR spectra were observed as A_2X (or A_2B) spin types.

The ^{31}P NMR spectrum of the ansa compound (**5**) is of the A_2X, type with a doublet for the ≡P(OR)Cl and a triplet for the ≡PCl_2 groups at 16.80 and 25.80 ppm respectively. ^{31}PNMR proton coupling affects the A_2 (≡P(OR)Cl) part of the spectrum by showing further splitting on it. Cylophosphazene derivative **7** is a compound formed by interconnecting two mono-spiro structures with a single-bridged link and has an AMX spin system comprising both the spiro [≡$P(OR)_2$], the bridged [≡P(OR)Cl] and the ≡PCl_2 groups. Therefore, the phosphorus atoms situated in three different magnetic environments. Both phosphorus atoms within each group; the spiro [≡$P(OR)_2$, at 48 ppm] parts, the ≡PCl_2 parts (at 29.40 ppm) and the ≡P(OR)Cl moieties (at 1.60 ppm) are identical to each other and symmetrically located in the molecule. But those phosphorus atoms in three different groups are not in the same magnetic environment and therefore, it is of the AMX spin type. ^{31}P NMR proton-coupled spectrum gave rise to further splitting at 48.80 ppm and at 1.60 ppm for the spiro, ≡$P(OR)_2$ and the bridged, ≡P(OR)Cl moieties. Phosphorus proton decoupled and coupled NMR spectra of compound **7** are shown in Figures 4 and 5 respectively.

Table 1. Selected ^{31}P NMR parameters for compounds **3-10**[a]

Compound	δPCl_2[b]	$\delta P(OR)_2$[b]	$\delta P(OR)Cl$[b]	$^2JPCl_2$-$P(OR)_2$[c]	$^2JPCl_2$-P(OR)Cl[c]
(**3**)	22.40	14.60		68.70	
(**4**)	28.10		13.20		62.70
(**5**)	25.80		16.50		76.30
(**6**)		15.40	28.20		83.40[d]
(**7**)	29.40	48.80	1.60	[e]	[e]
(**8**) single-bridged	26.80		15.50		65.75
(**8**) double-bridged	27.50		20.30		64.30
(**10**) triple-bridged		8.62			

[a]In $CDCl_3$ (with respect to 85% phosphoric acid external reference) at 162 and 202.38 MHz.
[b]In ppm.
[c]In Hz.
$^2J P(OR)_2$-P(OR)Cl[d]
[e]Unresolved spectrum

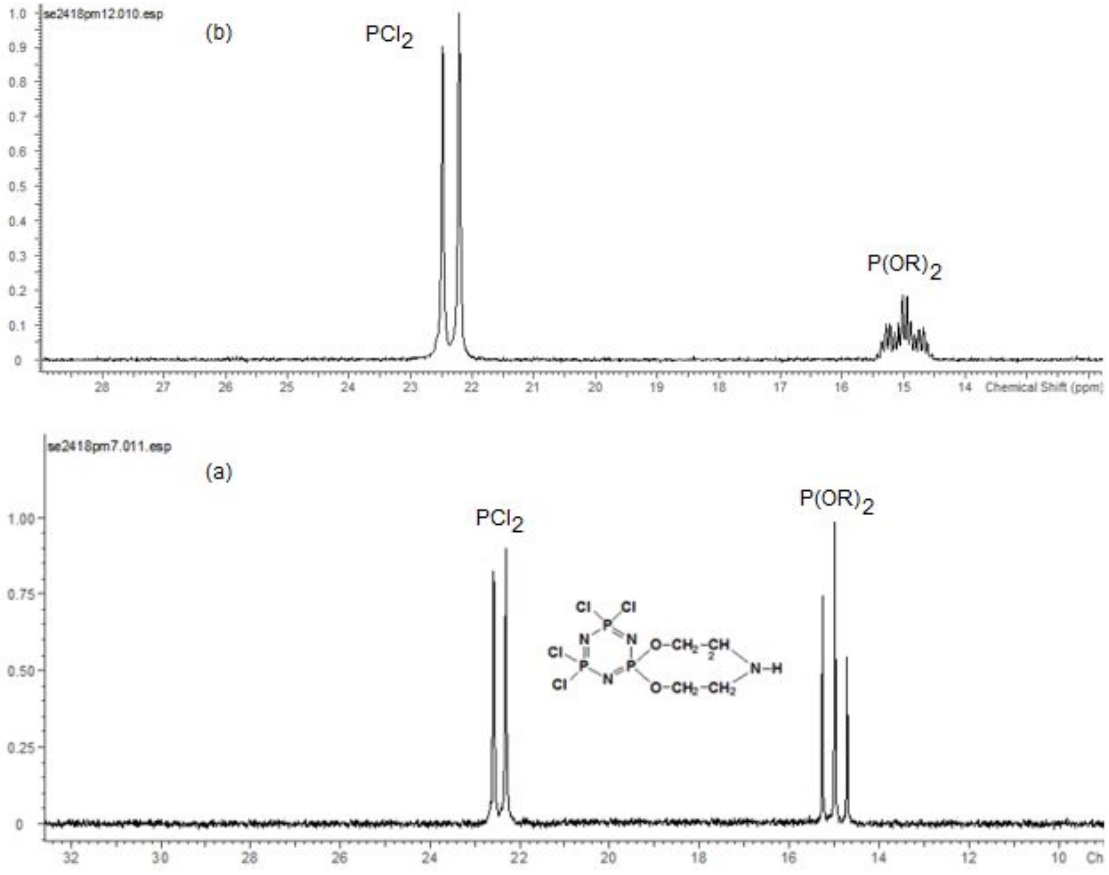

Figure 2. (a) ^{31}P-{^1H} and (b) ^{31}P{^1H} NMR spectrum of compound **3**, in $CDCl_3$ at 162.00 MHz, (room temperature), referenced to external 85% H_3PO_4.

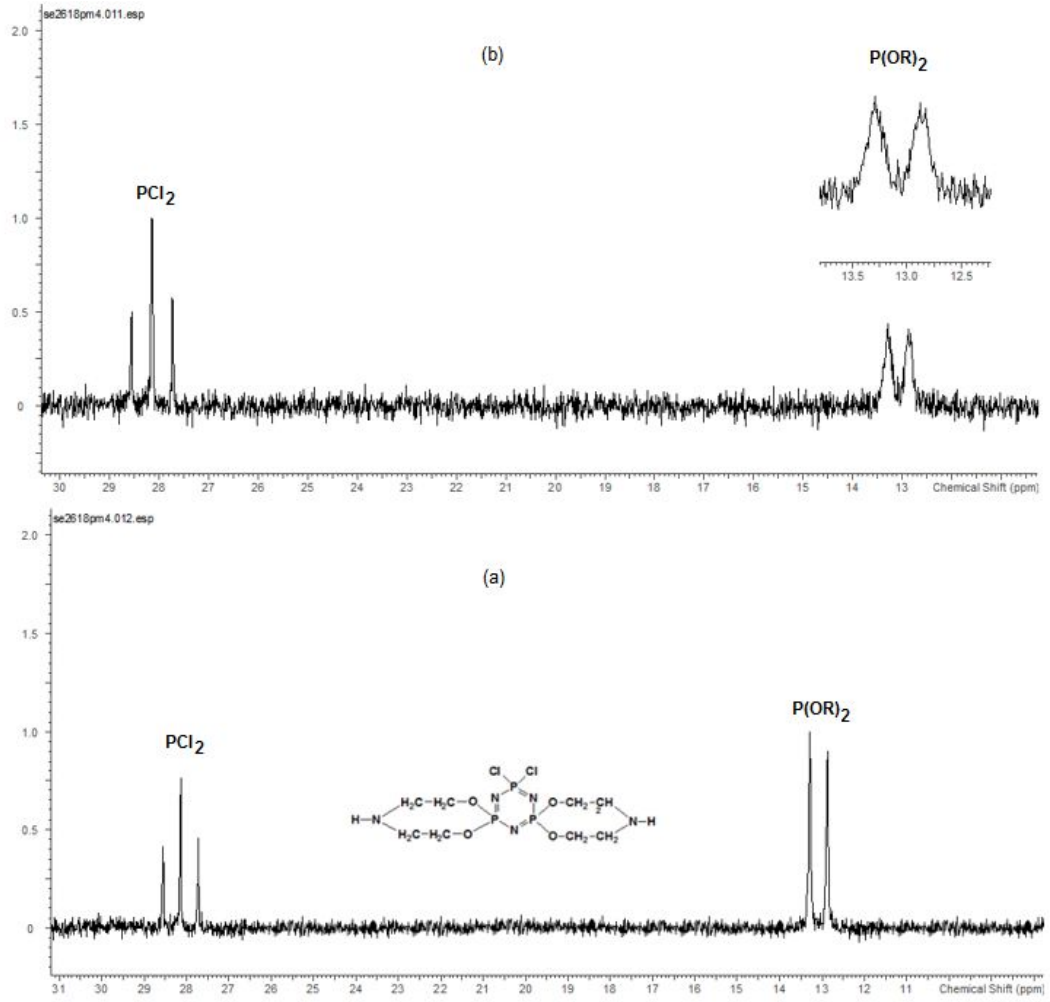

Figure 3. (a) ^{31}P-{^{1}H} and (b) ^{31}P{^{1}H} NMR spectra of compound **4**, in $CDCl_3$ at 162.00 MHz, (room temperature), referenced to external 85% H_3PO_4.

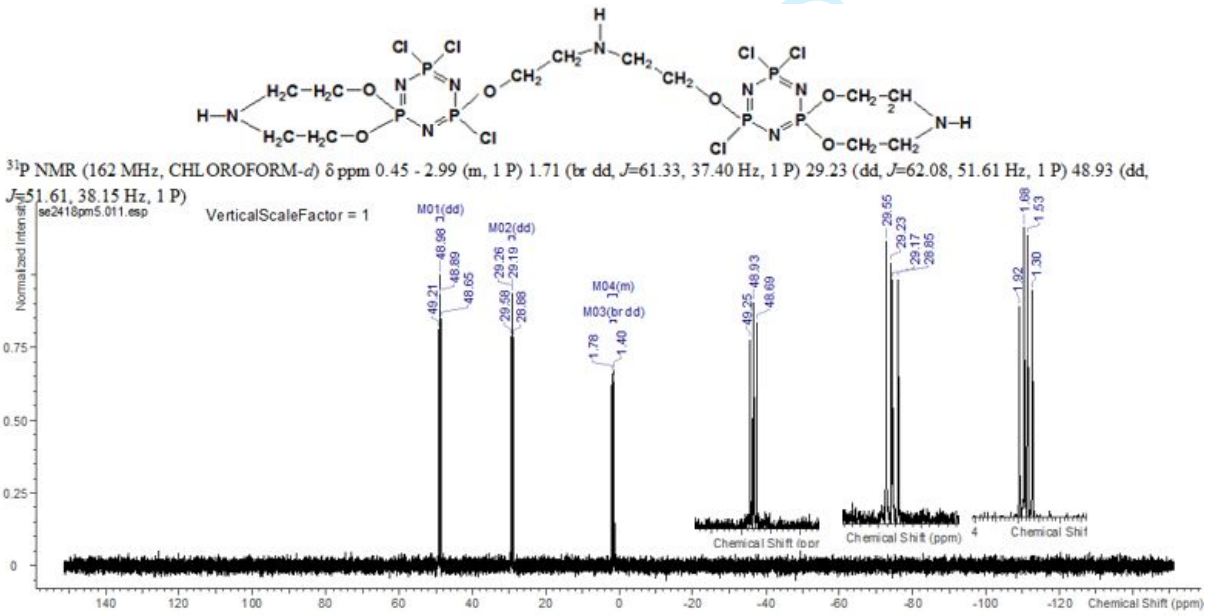

Figure 4. ^{31}P-{^{1}H} NMR spectrum of compound **7**, in $CDCl_3$ at 162.00 MHz, (room temperature), referenced to external 85% H_3PO_4.

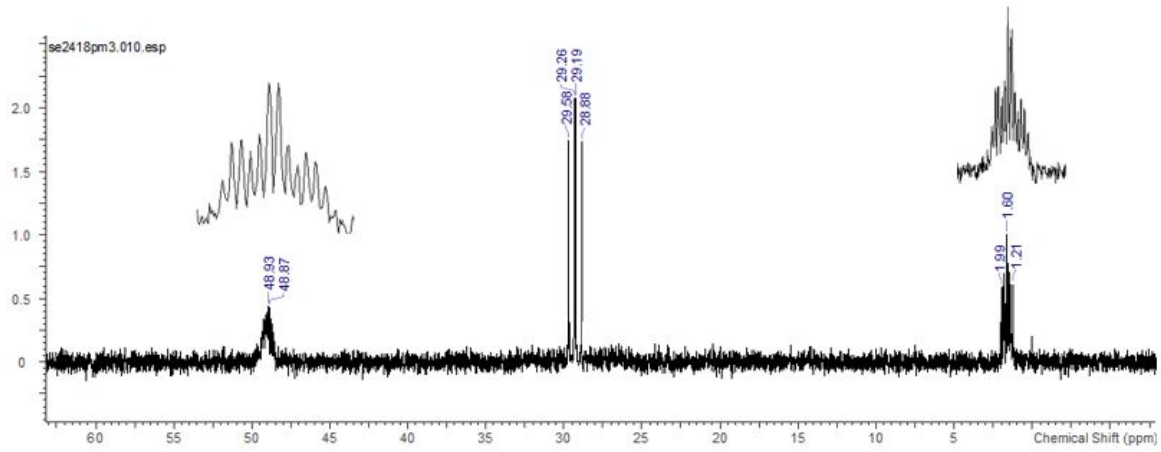

Figure 5. $^{31}P\{^{1}H\}$ coupled NMR spectrum of compound **7**, in $CDCl_3$ at 162.00 MHz, (room temperature), referenced to external 85% H_3PO_4.

^{1}H NMR data

In this system, the methylene and the amino-group protons occur in three different chemical environments depending on whether they are situated, *α*- and *β*- with respect to the oxygen atoms and *NH* protons. The ^{1}H NMR spectra of compounds (**4-7**) gave very complex multiplets with some overlapping signals and similar chemical shifts for the *POCH*$_2$ and the POCCH$_2$ protons. We observed much more complex splitting patterns for compounds (**6**) and (**7**) for the *POCH*$_2$ and *POCCH*$_2$ methylene protons, suggesting that the *α*- and *β*-methylene protons are not sufficiently resolved.

The α- and the β-methylene protons of the mono-spiro (**3**) compound within each methylene group are in the same magnetic environment and therefore, the mono-spiro derivative, has a relatively simple proton spectrum, giving a six line spectrum for the- methylene protons (*POCH*$_2$) at 4.46 ppm, from coupling with the neighboring β-methylene protons and the phosphorus nucleus. On the other hand the *β*-methylene protons (*POCH*$_2$-*CH*$_2$-*NH-)* give two quintets spectra at 1.62 ppm due to coupling with the two α-, N-H protons and with the phosphorus nucleus. The ^{1}H NMR spectra of compounds (**3**) and (**8**) are presented in Figures 6 and 7. The *α*- and the *β*-methylene protons are not chemically and magnetically equivalent in compounds **4** and **5**, in the ansa and in the spiro parts of compound **6**, and in the spiro and in the bridging units of compound **7**. For this reason, at 400 MHz, very complex and unresolved

spectra were observed for the α- and the β-methylene protons. Therefore, detailed consideration for the ^{1}H NMR spectra of the compounds (**4**-**7**) are not possible. However, we tried to simplify these spectra with comparing to our earlier reported studies based on difunctional and tri-functional reagents [3-7, 10, 49-53]. Selected ^{1}H NMR chemical shifts and coupling constants for the α- and the β-methylene protons are summarized in Table 2. In the *ansa* moiety (**5**) the two α- and the two β-methylene groups are equivalent, but the two methylene protons within each methylene group are non-equivalent as one faces towards, the other away from, the N_3P_3 ring and its spiro group. In the spiro part of the spiro-ansa compound (**6**) the α-methylene protons as well in the β-methylene protons are non-equivalent as the group above and below the phosphazene ring are in different chemical environment, those above the ring seeing the ansa group, those below the chlorine atoms. However, within each methylene group the two protons are equivalent. By contrast, in the ansa moiety the two α-methylene groups are equivalent. The same applies to the β-methylene groups, but all the methylene groups, α- and β-methylene protons have non-equivalent protons. The ^{1}H NMR spectrum of the bis-spiro derivative (**4**) is by far the most complex and also the most interesting, where two $POC\underline{H_2}$ and two $CC\underline{H_2}$ methylene groups are equivalent, but within each methylene group the two protons are non-equivalent due to their being part of a cyclic moiety and therefore the two protons of each methylene group see a different environment. In dispiro structures, the two spiro rings are equivalent as are the α- and the β-methylene groups above and below the rings. However, because each spiro group is flanked on one side by two chlorine atoms and on the other side by another spiro group, the two protons within each methylene group are non-equivalent. This non-equivalence was quite noticeable for the α-methylene protons and even more pronounced for the β-methylene protons. If such a non-equivalence is observed all the methylene groups could in principle give rise to AB quartets with further coupling to neighboring nuclei. Long-range virtual coupling with the two equivalent phosphorus nuclei will make a triplet of quartets for

the α-methylene protons and coupling with the β-methylene protons might, depending on Karplus relationship [54, 55], give rise to 36 or 48 lines.

Table 2. Selected ^{1}H NMR parameters for compounds **3**-**10**[a].

Compound	δPOCH_2[b]	δPCCH_2[b]	δNH[b]	^{3}J(PH)[c]
(**3**) mono-spiro	4.46	1.62	7.25	14.40
(**4**) bis-spiro	4.50/4.46	1.66	7.36	18.20
(**5**) mono-ansa	4.58/4.44	1.50	7.50	21.40
(**6**) spiro-ansa				
spiro part	4.49	1.66	7.26	[d]
ansa part	4.56/4.61	1.52	7.52	[d]
(**7**) spiro-bino	4.50/4.43		6.98/7.15/7.56	[d]
(**8**) single-bridged	4.32	1.45	7.56	12.60
(**9**) double-bridged	4.56	1.48	7.56	12.80
(**10**) triple-bridged	4.42	1.64	7.70	13.43

[a]In $CDCl_3$ (referenced to internal TMS internal) at 399.95 MHz. (room temperature).
[b]In ppm.
[c]Hz.
[d]Unresolved spectrum

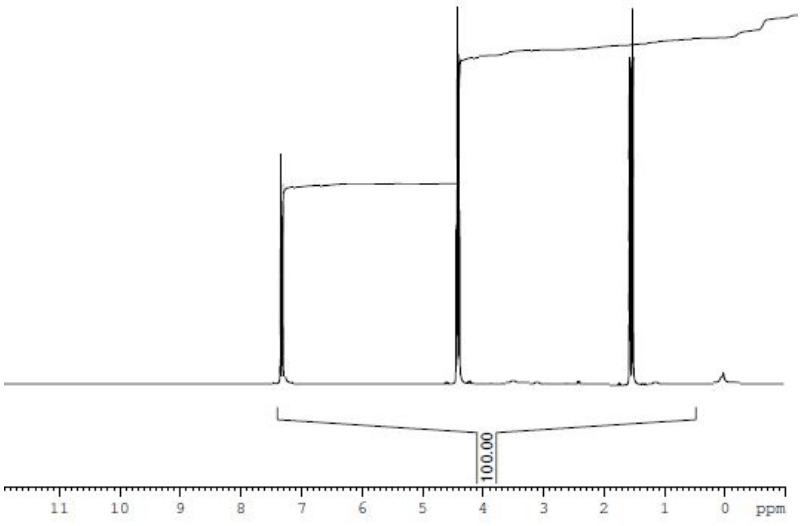

Figure 6. ^{1}H NMR spectrum of compound (**3**), at room temperature, in $CDCl_3$ (TMS as internal reference) and at 399.95 MHz.

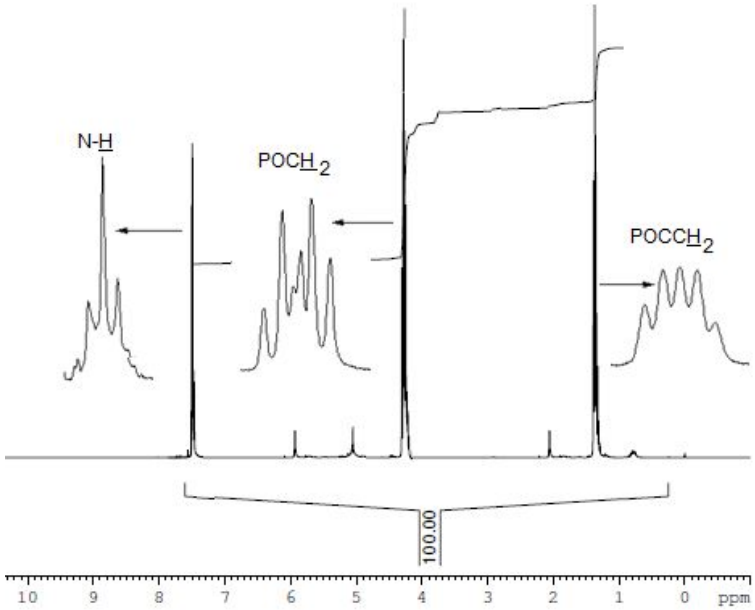

Figure 7. ^{1}H NMR spectrum of compound (**8**), at room temperature, in $CDCl_3$ (TMS as internal reference) and at 399.95 MHz.

3.3. Experimental

3.1. Materials

Reagent grade solvents were used throughout the work, benzene, light petroleum (b.p. 40–60◦C), petroleum ether, anhydrous diethyl ether, acetonitrile, butanol, n-hexane (>96%), dichloromethane (>99.0%), chloroform, acetone, THF, acetone (Sigma Aldrich). THF was distilled over a sodium-potassium alloy under an argon atmosphere. $CDCl_3$, deuteriated solvent for NMR spectroscopy (Sigma Aldrich), Silica gel (60, 0.063–0.200 mm Merck) was used for column chromatography, Kieselgel 60^0 254 (silica gel) precoated TLC plates (Merck). The following materials were also obtained from Sigma Aldrich Chemicals: Phosphonitrilic trimer (purified by fractional crystallization from hexane), (ninhydrine (0.5%w/v), 2-(2-hydroxyethylamino)ethanol (from Southampton University Laboratory), NaH (60% dispersion in mineral oil, which was removed by washing with dry n-heptane followed by decantation).

3.2. Methods

All reactions were monitored using Kieselgel 600 254 (silica gel) precoated TLC plates and sprayed with ninhydrine (0.5% w/v) in butanol solution, and developed at approximately

130 ^{0}C. UV for TLC measurements. Required separations of mixtures were carried out by crystallization techniques, TLC and by column chromatography using Kieselgel 60. (Merck 60, 0.063–0.200 mm; for 2 g crude mixture, 100 g silica gel was used in a column of 2.5 cm in diameter and 90 cm in length). Melting points were determined on a Hot Stage Microscopy and hot stage connected to a FP 800 central processor both fitted with a polarizing microscope at Southampton University. FT-IR spectra were recorded in Perkin Elmer BX II FT model spectrometer with a number of scans at 4 cm^{-1} resolution in the range 4000-350 cm^{-1}. Elemental analyses were obtained using a ThermoFinnigan Flash 1112 Instrument. ^{1}H NMR spectra were recorded using a Bruker AVIIIHD 400 MHz spectrometer (operating at 399.5 MHz, at Southampton University). Samples were dissolved in $CDCl_3$ and placed in 5 mm NMR tubes. Measurements were carried out using a $CDCl_3$ lock, TMS as internal reference, and sample concentrations of 15–20 $mgcm^3$. ^{13}C NMR spectra were recorded using a Bruker AVIIIHD 400 MHz spectrometer (operating at 100.63 MHz, at Southampton University), TMS was used as an internal reference. ^{31}P NMR spectra were recorded using a Bruker AVIIIHD 400 MHz spectrometer (operating at 161.97 MHz, at Southampton University); Measurements were carried out using a $CDCl_3$ lock and H_3PO_4 (85%) was used as an external reference. Mass spectra were recorded using a TLC/MS (obtained by a Bruker MicrOTOF LC/MS spectrometer using electro spray ionization (ESI) method). The NMR data may be found in Tables 2 and 3.

3.3. The reactions of hexachlorocyclotriphosphazatriene (1) with 2-(2-hydroxyethylamino)ethanol (2).

(**a**) One equivalent of compound **2**: Using an excess of NaH, in a mixture of THF/ethanol (3:1) at room temperature. Synthesis of 2,2-mono-spiro-2,2'-iminodiethoxy-4,4,6,6-tetrachloro-cyclotriphosphazatriene (**3**); 2,2,4,4-bis-spiro-2,2'-iminodiethoxy-6,6-dichloro-cyclotriphosphazatriene (**4**); and 2,4-ansa-2,2'-iminodiethoxy-2,4,6,6-tetrachloro-cyclotriphosphazatriene (**5**).

Cyclotriphosphazene (**1**, 2 g, 0.006 mol) and 2-(2-hydroxyethylamino)ethanol (**2**, 0.63 g, 0.006 mmol) were dissolved in dry THF (100 mL) in a 250 mL three-necked round-bottom flask. This mixture was stirred for 30 min at room temperature then two equivalents of NaH (0,29 g, 0.012 mol) in THF (30 mL) was added over a period of 30-40 min to this stirred solution under an argon atmosphere. The mixture was stirred (36 h) at room temperature until TLC indicated the completion of the reaction. The reaction mixture was filtered to remove sodium chloride and any other insoluble materials. Then the reaction mixture was followed on TLC silica gel plates using dichloromethane-hexane (3:1) as the eluent. The solvent was removed under reduced pressure and the resulting colorless solid was subjected to column chromatography using the mentioned solvent system as the mobile phase. Products were recrystallized from benzene : hexane (1:3) containing a few drops of light petroleum (b.p. 40-60^0 C). Three main fractions were synthesized as (**i**) the mono spiro derivative, $N_3P_3Cl_4[O\text{-}(CH_2)_2\text{-}NH\text{-}(CH_2)_2O]$ (**3**), recrystallized from dichloromethane-hexane (1:1.5) by adding a few drops of light petroleum (b.p. 40-60^0 C), yield 0.5 g, 27%, m.p. 128-129^0 C. Anal. Calc. for $N_4P_3Cl_4C_4H_9O_2$: C, 12.64; H, 2.38; N, 14.74, M, 379.94. Found: C, 12.63; H, 2.36; N, 14.52, M^+, 380.69. ^{1}H NMR ($CDCl_3$), δPOCH$_2$: 4.46, δPOCCH$_2$: 1.62, δPNH: 7.25, $^3J_{(PH)}$: 14.40 Hz. ^{31}P NMR ($CDCl_3$): δ: 22.40 (PCl_2), δ= 14.60 [$P(OR)_2$], $^2J_{(PP)}$: 68.70 Hz. (**ii**) The second product was identified as the dispiro derivative, $N_3P_3Cl_2[O\text{-}(CH_2)_2\text{-}NH\text{-}(CH_2)_2O]_2$ (**4**), 0.38 g, 19%, m.p. 174-176^0 C. Anal. Calc. for $N_5P_3Cl_2C_8H_{18}O_4$: C, 23.32; H, 4.40; N, 16.99, M, 412.17. Found: C, 22.99; H, 4.43; N, 16.95, M^+, 413.09. ^{1}H NMR ($CDCl_3$); δPOCH$_2$: 4.46/450, δPOCCH$_2$: 1.66, δPNH: 7.36, $^3J_{(PH)}$: 18.20. ^{31}P NMR ($CDCl_3$); δ: 28.10 (PCl_2), δ: 13.20 [$P(OR)_2$], $^2J_{(PP)}$: 62.70 Hz. (**iii**) The third product was identified as the mono-ansa derivative, $N_3P_3Cl_4[O\text{-}(CH_2)_2\text{-}NH\text{-}(CH_2)_2O]$ (**5**), 0.57 g, 33%, m.p., an oil. Anal. Calc. for $N_4P_3Cl_4C_4H_9O_2$: C, 12.64; H, 2.38; N, 14.74, M, 379.94. Found: C, 12.60; H, 2.40; N, 14.52, M^+, 380.69. ^{1}H NMR ($CDCl_3$), δPOCH$_2$: 4.44-

/4.58, δPOCCH$_2$: 1.50, δPNH: 7.50, ^{3}J$_{(PH)}$: 21.40 Hz. ^{31}P NMR (CDCl$_3$); δ: 25.80 (PCl$_2$), δ: 16.50 [P(OR)$_2$], ^{2}J$_{(PP)}$: 76.30 Hz.

(**b**) Synthesis of 2,4-ansa-6,6-spiro-2,2'-iminodiethoxy-2,4-dichloro-cyclotriphosphazatriene (**6**); 2,2,4,4,6,6-trispiro-2,2'-iminodiethoxy-cyclotriphosphazatriene (**7**); and 2,2,4,4-bino-2,2-iminodiethoxy-2,2',4,4',6,6,6',6'-octachloro-cyclotriphosphazatriene (**8**): Two equivalents of 2-(2-hydroxyethylamino) ethanol (**2**, 1.26 g, 0,012 mol) and cyclotriphosphazene (**1**, 2 g, 0.006 mol) were dissolved in a mixture of THF/ethanol (3:1, 120 mL) in a 250 mL three-necked round-bottomed flask under an argon atmosphere and the reaction mixture was cooled to 0^0 C in ice-bath. Then four equivalents of NaH (0.58 g, 0.024 mol) were dissolved in THF (15 mL) and added dropwise into the stirred solution under an argon atmosphere. The reaction mixture was then stirred at room temperature for about 48 h. The reaction was followed on TLC using dichloromethane-hexane (3:1) as the eluent for completion of the reaction. The reaction mixture was filtered to remove the NaCl salts and some other insoluble sticky materials. Together with the starting material (**1**), four spots were observed on TLC, using dichloromethane-hexane (2:1) as the mobile phase. The solvents were removed from the reaction mixture under reduced pressure and the resulting white-colored solids were subjected to column chromatography using the same solvent system as described above. Products were recrystallized from benzene:hexane (1:3) containing a few drops of light petroleum (b.p. 40-60^0 C). (**i**) The first product was identified as the single-bridged derivative, $N_3P_3Cl_5$[O-(CH$_2$)$_2$-NH-(CH$_2$)$_2$O]$N_3P_3Cl_5$ (**8**), yield 0.30 g, 23%, m.p. an oil. Anal. Calc. for $N_7P_6Cl_{10}C_4H_9O_2$: C, 6.60; H, 1.25; N, 13.47, M, 727.66. Found: C, 6.58; H, 1.29; N, 13.46, M$^+$, 728.59. ^{1}H NMR (CDCl$_3$); δPOCH$_2$: 4.32, δPOCCH$_2$: 1.45, δPH: 7.56, ^{3}J$_{(PH)}$: 12.60 Hz. ^{31}P NMR (CDCl$_3$); δ: 26.80 (PCl$_2$), δ: 15.50 [P(OR)Cl], ^{2}J$_{(PP)}$: 65.75 Hz. (**ii**) The second product was identified as the spiro-ansa derivative, $N_3P_3Cl_2$[O-(CH$_2$)$_2$-NH-(CH$_2$)$_2$O]$_2$ (**6**), yield 0.32 g, 25%, m.p. 162-164^0 C. Anal. Calc. for $N_5P_3Cl_2C_8H_{18}O_4$: C, 23.32; H, 4.40; N, 16.99, M, 412.17. Found: C, 23.21; H, 4.46; N, 16.94,

M^+, 413.17. ^1H NMR ($CDCl_3$); spiro part; δ$POCH_2$: 4.49, δ$POCCH_2$: 1.66, δPH: 7.26; ansa part; δ$POCH_2$: 4.56/4.61, δ$POCCH_2$: 1.52, δPH: 7.52, $^3J_{(PH)}$: unresolved spectrum. ^{31}P NMR ($CDCl_3$); δ: 15.40 [$P(OR)_2$], δ: 28.20 [P(OR)Cl], $^2J_{(PP)}$: 83.40 Hz.

(**iii**) The third product was identified as the double-bridged derivative, $N_3P_3Cl_4[O\text{-}(CH_2)_2\text{-}NH\text{-}(CH_2)_2O]_2N_3P_3Cl_4$ (**9**), yield 0.52 g, 32%, m.p. 242-244^0 C. Anal. Calc. for $N_8P_6Cl_8C_8H_{18}O_4$: C, 12.64; H, 2.39; N, 14.75; M, 759.89. Found: C, 12.63; H, 2.41; N, 14.73, M^+, 760.73. ^1H NMR ($CDCl_3$); δ$POCH_2$: 4.56, δ $POCCH_2$: 1.48, δPH: 7.56, $^3J_{(PH)}$: 12.80. ^{31}P NMR ($CDCl_3$); δ: 27.50 (PCl_2), δ: 20.30 [P(OR)Cl], $^2J_{(PP)}$: 64.30 Hz.

(**c**) Synthesis of 2,2,2',2'-spiro-2,2'-iminodiethoxy-4,4'-bino-2,2'-iminodiethoxy-4,4',6,6,6',6'-hexachloro-cylotriphosphazatriene: Three equivalents of compound **2**, reaction procedure as for (**b**), at 0-10 ^{0}C. (**i**) The first product was identified as the triple-bridged derivative, $N_3P_3Cl_3[O\text{-}(CH_2)_2\text{-}NH\text{-}(CH_2)_2O]_3N_3P_3Cl_3$ (**10**), 0.45 g, 30%, m.p. 260-263^0 C. Anal. Calc. for $N_9P_6Cl_6C_{12}H_{27}O_6$: C, 18.19; H, 3.43; N, 15.91; M, 792.1. Found: C, 18.17; H, 3.45; N, 15.89; M^+, 793.07. . ^1H NMR ($CDCl_3$), δ$POCH_2$: 4.42, δ$POCCH_2$: 1.64, δPH: 7.70, $^3J_{(PH)}$: 13.43. ^{31}P NMR ($CDCl_3$): δ = 8.62 [P(OR)Cl]. (**ii**) The second product was identified as the mono-spiro with a singly-bridged part, $N_3P_3Cl_3[O\text{-}(CH_2)_2\text{-}NH\text{-}(CH_2)_2O]_3N_3P_3Cl_3$ (**7**), 0.18 g, 14%, m.p. an oil. Anal. Calc. for $N_9P_6Cl_6C_{12}H_{27}O_6$: C, 18.19; H, 3.43; N, 15.91; M, 792.10. Found: C, 18.17; H, 3.47; N, 15.92, M^+, 793.07. ^1H NMR ($CDCl_3$); δ$POCH_2$: 4.43/4.50, δ$POCCH_2$: unresolved complex spectrum, δPNH: 6.98/7.15/7.56, $^3J_{(PH)}$: unresolved spectrum. ^{31}P NMR ($CDCl_3$); δ: 29.40 (PCl_2), δ: 1.60 [$P(OR)_2$], δ: 48.80 [P(OR)Cl], $^2J_{(PP)}$: unresolved.

Conclusion

In this study, spiro, ansa, bridged compounds as well as combination of these (**3**-**10**) were obtained by interacting hexachlorocyclotriphosphazatriene (**1**) with 2-(2-hydroxyethylamino)ethanol (**2**). The reactions of this tri-functional nucleophilic reagent (2) with compound **1** gave both the *geminal* and the *non-geminal* substitution patterns at the

PCl_2 moieties. The mono-spiro-bino substituted cyclophosphazene derivative (**7**) is the most interesting product for its regioselectivity and spectroscopic properties. The novel synthesized cyclotriphosphazene derivatives (**3-10**) were characterized by elemental analysis, TLC-MS, ^{1}H, and ^{31}P NMR spectral data.

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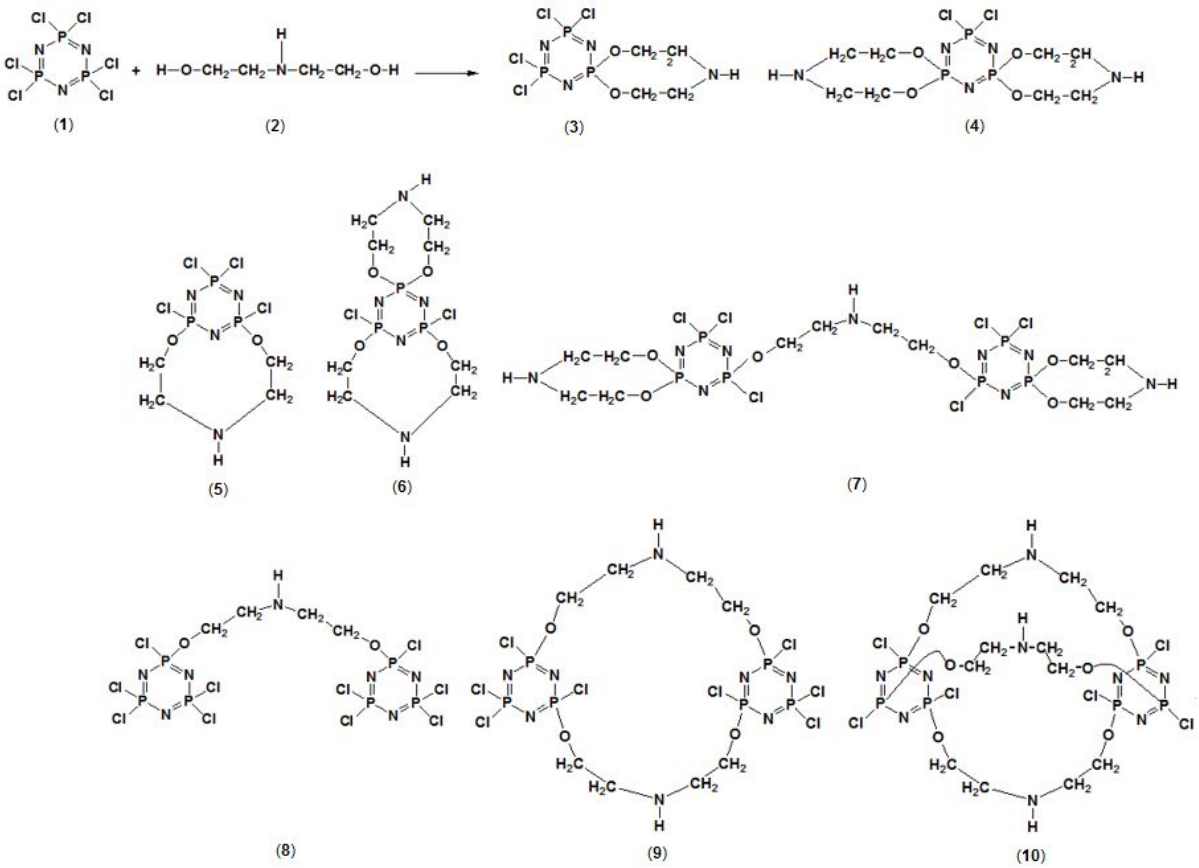

Figure 1. Structures of the synthesized cyclotriphosphazene derivatives (**3**-**10**).

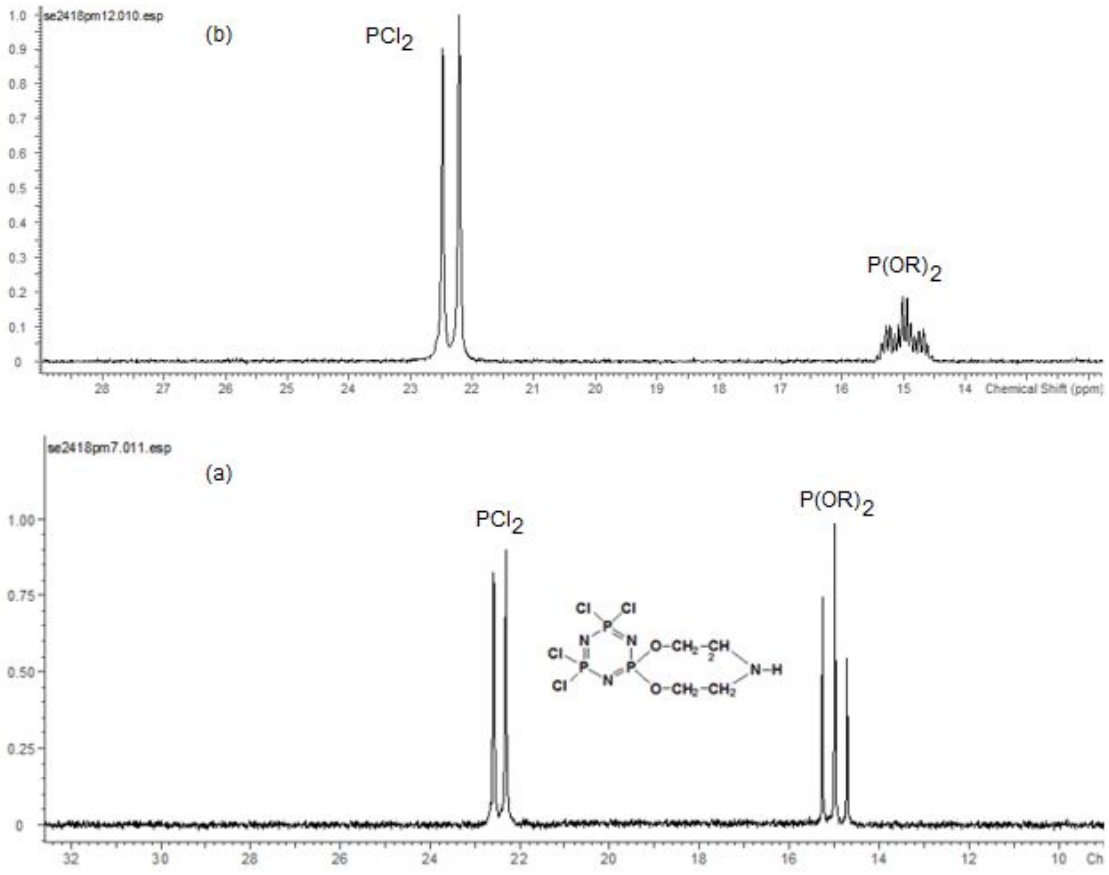

Figure 2. (a) ^{31}P-{^{1}H} and (b) ^{31}P{^{1}H} NMR spectrum of compound **3**, in $CDCl_3$ at 162.00 MHz, (room temperature), referenced to external 85% H_3PO_4.

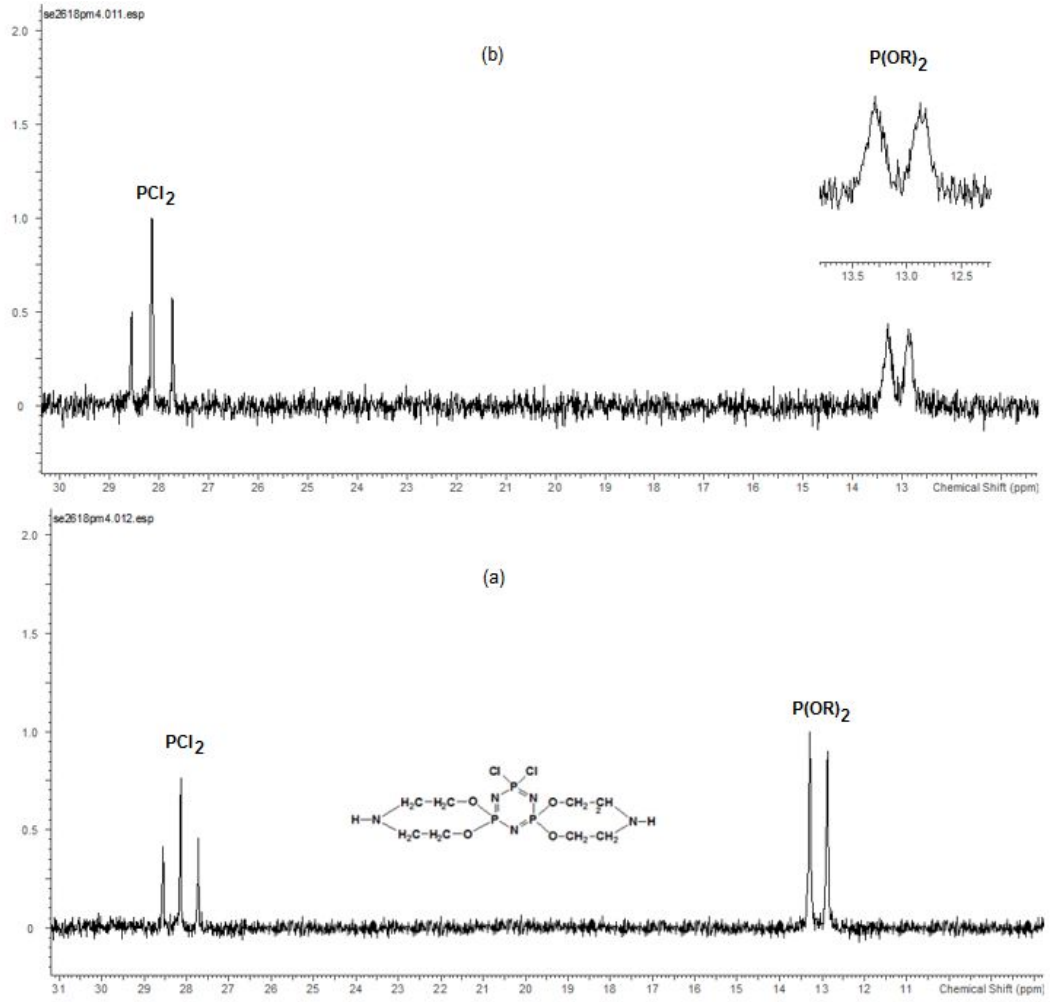

Figure 3. (a) ^{31}P-{^{1}H} and (b) ^{31}P{^{1}H} NMR spectra of compound **4**, in $CDCl_3$ at 162.00 MHz, (room temperature), referenced to external 85% H_3PO_4.

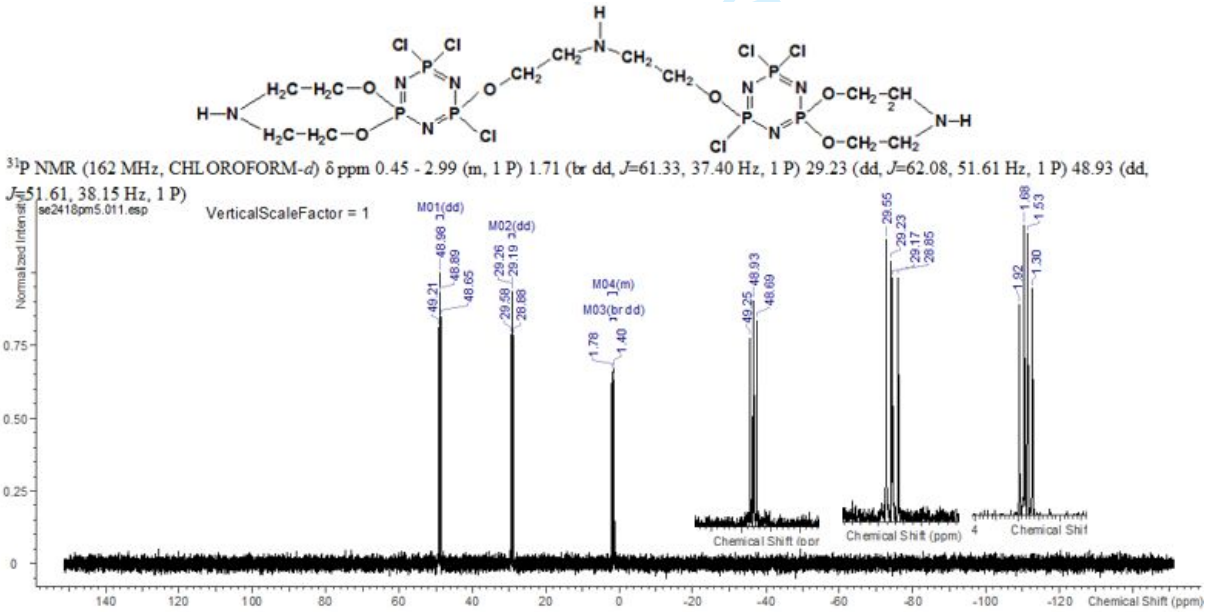

Figure 4. ^{31}P-{^{1}H} NMR spectrum of compound **7**, in $CDCl_3$ at 162.00 MHz, (room temperature), referenced to external 85% H_3PO_4.

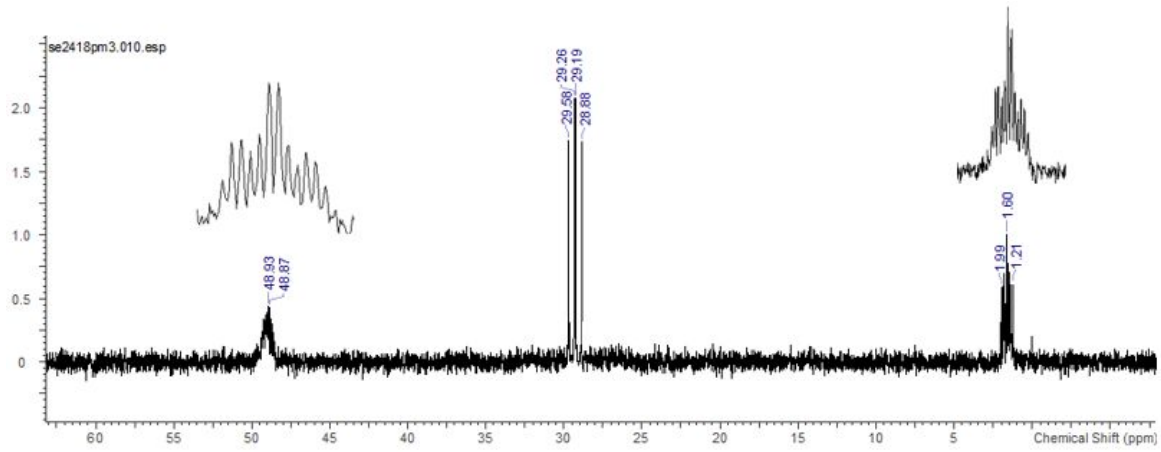

Figure 5. $^{31}P\{^{1}H\}$ coupled NMR spectrum of compound **7**, in $CDCl_3$ at 162.00 MHz, (room temperature), referenced to external 85% H_3PO_4.

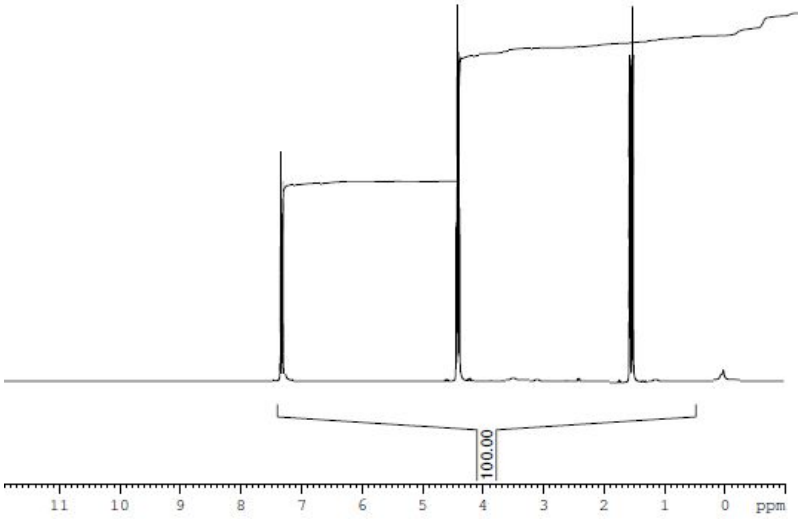

Figure 6. ^{1}H NMR spectrum of compound (**3**), at room temperature, in $CDCl_3$ (TMS as internal reference) and at 399.95 MHz.

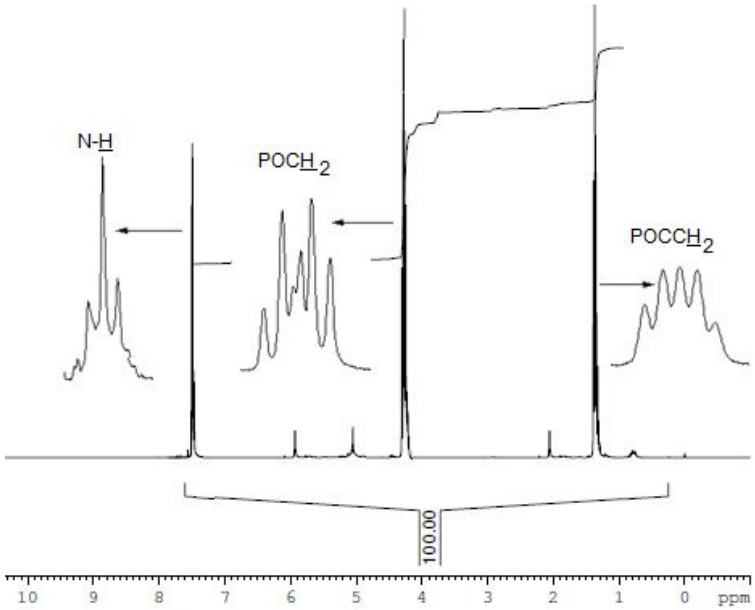

Figure 7. ^{1}H NMR spectrum of compound (**8**), at room temperature, in $CDCl_3$ (TMS as internal reference) and at 399.95 MHz.

Table 1. Selected ^{31}P NMR parameters for compounds **3-10**[a]

Compound	δPCl_2[b]	$\delta P(OR)_2$[b]	$\delta P(OR)Cl$[b]	$^2JPCl_2$-$P(OR)_2$[c]	$^2JPCl_2$-P(OR)Cl[c]
(**3**)	22.40	14.60		68.70	
(**4**)	28.10		13.20		62.70
(**5**)	25.80		16.50		76.30
(**6**)		15.40	28.20		83.40[d]
(**7**)	29.40	48.80	1.60	[e]	[e]
(**8**) single-bridged	26.80		15.50		65.75
(**8**) double-bridged	27.50		20.30		64.30
(**10**) triple-bridged		8.62			

[a]In $CDCl_3$ (with respect to 85% phosphoric acid external reference) at 162 and 202.38 MHz.
[b]In ppm.
[c]In Hz.
^2JP(OR)$_2$-P(OR)Cl[d]
[e]Unresolved spectrum

Table 2. Selected ^1H NMR parameters for compounds **3-10**[a].

Compound	δPOCH_2[b]	δPCCH_2[b]	δNH[b]	^{3}J(PH)[c]
(**3**) mono-spiro	4.46	1.62	7.25	14.40
(**4**) bis-spiro	4.50/4.46	1.66	7.36	18.20
(**5**) mono-ansa	4.58/4.44	1.50	7.50	21.40
(**6**) spiro-ansa				
spiro part	4.49	1.66	7.26	[d]
ansa part	4.56/4.61	1.52	7.52	[d]
(**7**) spiro-bino	4.50/4.43		6.98/7.15/7.56	[d]
(**8**) single-bridged	4.32	1.45	7.56	12.60
(**9**) double-bridged	4.56	1.48	7.56	12.80
(**10**) triple-bridged	4.42	1.64	7.70	13.43

[a]In $CDCl_3$ (referenced to internal TMS internal) at 399.95 MHz. (room temperature).
[b]In ppm.
[c]Hz.
[d]Unresolved spectrum