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ORIGINAL ARTICLES

Synthesis and structural characterization of geminal and non-geminal 1,1,3,3-tetramethylguanidine substituted derivatives of cyclotriphosphazene: Thermal and spectroscopic investigations of the products

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ABSTRACT
The reactions of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$ (**1**) with 1,1,3,3-tetramethyl-guanidine (**2**) in (1:1:2, 1:2:4 and 1:3:6) stoichiometries in THF and dichloromethane solutions under reflux yield a total of **4** novel products: three non-geminal derivatives, $N_3P_3Cl_4[NCN_2(CH_3)_4]_2$ (**3**), $N_3P_3Cl_3[NCN_2(CH_3)_4]_3$ (**4**) and $N_3P_3Cl_2[NCN_2(CH_3)_4]_4$ (**5**); and one hexa-substituted product, $N_3P_3[NCN_2(CH_3)_4]_6$ (**6**). The structures of **3**-**6** have been determined mainly by elemental analysis, MS, ^{31}P and ^{1}H NMR spectral data. Furthermore, thermal characteristics of the synthesized compounds **4** and **6** were evaluated using Differential Scanning Calorimetric (DSC) measurements. NMR spectroscopic data, product types and relative yields are compared with those of the previously investigated derivatives of $N_3P_3Cl_6$ (**1**) with mono and difunctional reagents.

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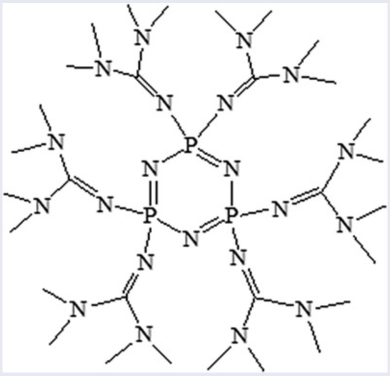
Phosphazene; tetramethylguanidine; geminal product; nongeminal product; Differential Scanning Calorimetry

GRAPHICAL ABSTRACT



Introduction

The reactions of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$ (**1**) with difunctional reagents usually occur in pair wise substitution and can lead to spirocyclic, ansacyclic or intermolecular condensation products.[1–23] Reactions with monofunctional reagents in general give rise to open-chain geminal and non-geminal products.[23–31] Amine-based nucleophilic substitution reactions are the most studied ones in the cyclophosphazene chemistry.[1,8,9,21] These reactions usually proceed through both S_N1 and S_N2 mechanisms and form the aminophosphazene derivatives. Many secondary amines such as dimethylamine, diethylamine, pyrolidine, piperidine and primary amines such as methylamine give rise to non-geminal derivatives; ammonia and *t*-butylamine give geminal products. It has also been observed that ethylamine, isopropylamine, benzylamine and *N*-methylaniline give both geminal and non-geminal products.[30] In those of the reactions, in which steric hindrance increases, geminal substitution increases as well. Proton abstraction/chloride elimination mechanism has been proposed in the literature to explain that *t*-butylamine, which is bulky and has strong electron donatin properties, provides geminal products.[30,31] In addition to the steric hindrance, it is found that (haloethyl)amines due to electronic influence also give geminal isomers.[32]

The present work reports the substitution reactions of $N_3P_3Cl_6$ (1) with 1,1,3,3-tetrametyl-guanidine, which give geminal and non-geminal substituted derivatives or mixture of both (**3**-**6**). Cyclotriphosphazenes have a wide range of properties and applications such as anti-cancer reagents,[33–35] tumor growth inhibitors,[36,37] antimicrobial

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/gpss.

reagents[38] and biomedical activities.[39–41] We therefore decided to study the reactions of hexachlorocyclotriphosphazene with 1,1,3,3-tetrametylguanidine and we would like to examine the biological activities of the derived products (**3**-**6**) in our future studies.

Results and discussion

The electron donating ability, the steric properties of the nucleophile and the solvent used determine the substitution patterns of cyclotriphosphazenes. If the electron donating ability of the nucleophile in the first substitution is high, this causes an increase in electron density at the phosphorus atom, resulting in a partial negative charge at the phosphorus atom, and making it difficult for the second substitution at the same phosphorus atom (≡P(R)Cl).

The reactions of $N_3P_3Cl_6$ (**1**) with 1,1,3,3-tetramethylguanidine in 1:1:2, 1:2:4 and 1:3:6 stoichiometries gave the following isolated and characterized derivatives: one *cis* non-geminal product, $N_3P_3Cl_4[NCN_2(CH_3)_4]_2$ (**3**, 1.2 g, 38%); one tris-nongeminal product, $N_3P_3Cl_3[NCN_2(CH_3)_4]_3$ (**4,** 1.6 g, 48%,); one tetrakis non-geminal product, $N_3P_3Cl_2[NCN_2(CH_3)_4]_4$ (**5,** 0.93 g 34%) and one hexa-substituted product, $N_3P_3[NCN_2(CH_3)_4]_6$ (**6,** 1.63 g, 49%). The hexa-substituded derivative **6** is isolated in larger amount than the other products (structures of the compounds are shown in Scheme 1). The synthesized compounds (**3**-**6**) were characterized by elemental analysis, MS, ^1H and ^{31}P NMR spectroscopy and the related results are provided in Tables 1 and 3.

^{31}P and ^1H NMR data

The spectra can be understood by comparison to those of the derivatives with long and short chain difunctional reagents.[2,16–20,22] The ^1H NMR spectra of non-geminal (**3** and **4**), geminal (**6**) and the mixture of the germinal/nongeminal (**5**) products show great similarity in the -C$\underline{H}_3$ chemical shifts. The -NCH_3 protons are about 0.4 ppm more shielded than those of the corresponding *N,N* dimethylpropane-diamine derivatives. The expected small shielding on moving from di- and tri-substituted non-geminal products to hexa-substituted derivative **6** is observed for the -C$\underline{H}_3$ protons as well.

Compounds **4** and **6**, whose NMR spectra and mass spectrometry results indicat these to be non-geminal $N_3P_3Cl_3[NCN_2(CH_3)_4]_3$ and hexa-substituted $N_3P_3[NCN_2(CH_3)_4]_6$ (germinal/non-geminal) products. According to our previous experience as well as based on comparison with the diol derivatives,[2,15,22] these compounds could have in principal a uniform ^{31}P NMR spectrum (A_3 type spin system). At low or medium field strengths, they give rise to an A_3 spin system, single line, due to the chemically and magnetically equivalent phosphorus nuclei.

The ^{31}P NMR spectra of both compounds show conclusively that they possess non-geminal substitution pattern. It is also known that there is a competitive formation of *cis* and *trans* derivatives in the nucleophilic substitution. In this system, we found that nitrogen-bonding of $-N=CN_2(CH_3)_4$ reagent to the ≡PNCl group gives *cis*-products. In the case of the *trans* isomers the spectrum would be of AB_2 type.

Proton decoupled ^{31}P NMR spectra of the reaction mixtures (1:1:2 and 1:3:6) are presented in Figures 1 and 2, respectively.

The ^{31}P NMR spectra of compounds $N_3P_3Cl_4[NCN_2(CH_3)_4]_2$ (**3**) and $N_3P_3Cl_2[NCN_2(CH_3)_4]_4$ (**5**) exhibit A_2B and A_2X type spectra, respectively. Proton coupling effects the A_2 parts of the former and the A_2 and X parts of the later (≡P(NR)$_2$ and ≡P(NR)Cl, where each group splits into further lines). As mentioned above, two structures are possible here depending on whether the $-N=CN_2(CH_3)_4$ groups have a *cis* or a *trans* orientation. In the case of *cis* and *trans* mixtures, two sets of lines would be observed in the ≡P(NR)Cl region. Proton coupling experiments as well as comparison with the reported former diamine and diol derivatives,[2,15–22] allow unambiguous assignment of the structures.

The ^{31}P NMR spectra of compounds **3**-**6** are shown in Figures 3–6, respectively. Selected ^{31}P NMR chemical shifts and $2J_{PP}$ values of the compounds are summarized in Table 1.

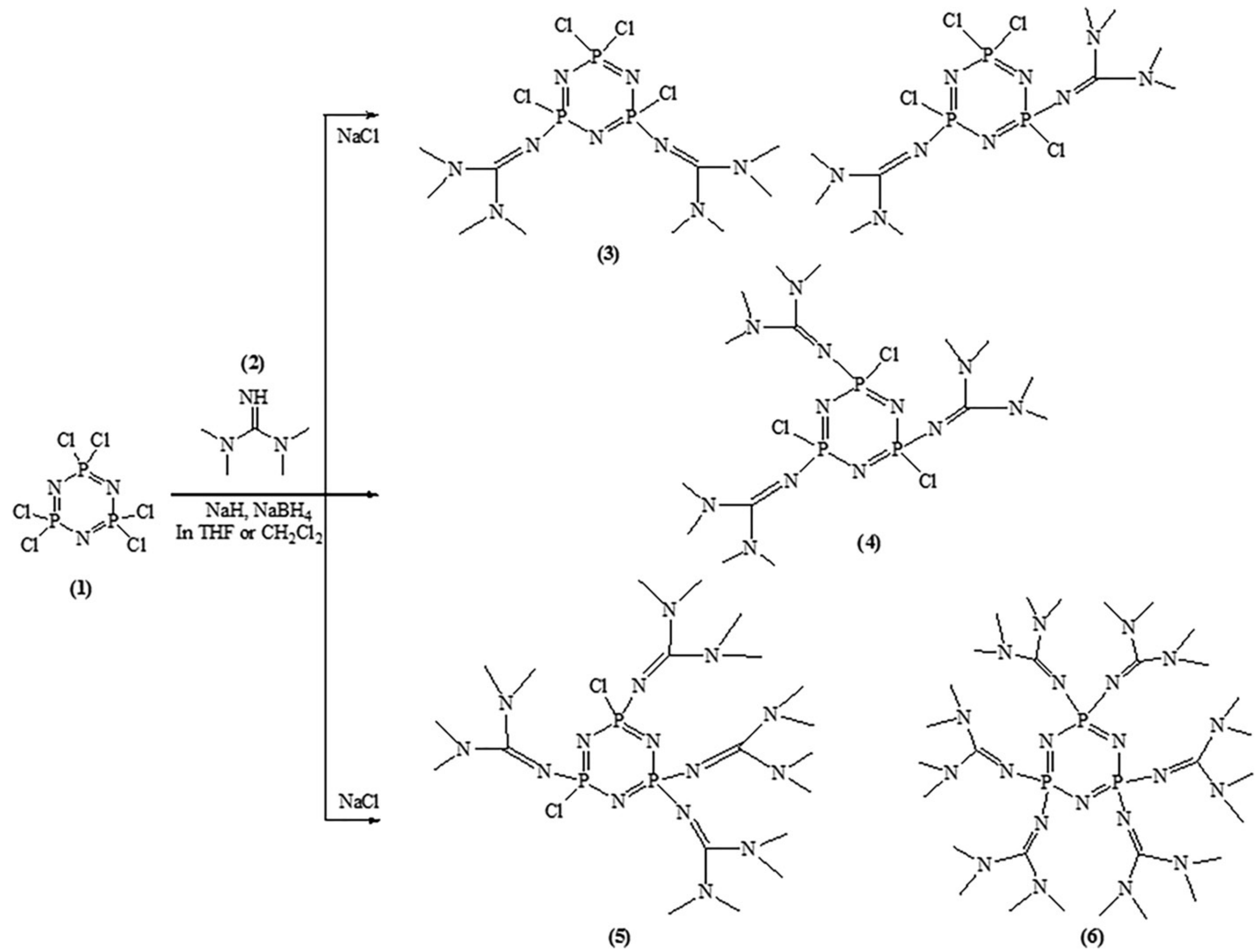
Thermal analysis

In this study, the melting behavior of 1,1,3,3-tetramethylguanidine derivatives **4** and **6** was investigated. The positions and enthalpies of the thermal peaks were determined and assigned in Table 2 and the thermograms for both derivatives are shown in Figure 7. Two sharp and almost linear endothermic peaks were found for both compounds (**4** and **6**). The endothermic peaks located respectively at 144 °C (ΔH° 15) and 147 °C (ΔH° 17) for compounds 4 and 6, were assigned for pre-transition events. However, endothermic peaks were located at 157 °C (ΔH° 69) and 155 °C (ΔH° 41) for compounds **4** and **6**, respectively. The latest ones were encountered as peaks of main phase transition temperature (Tm) associated with main melting processes. The endothermic and sharp melting peaks located at higher temperature indicate good crystal state of both derivatives.[42–47] No exothermic event was monitored for both derivatives.

Experimental

Materials

Reagent grade solvents were used throughout the work, benzene, light petroleum (b.p. 40–60 °C), anhydrous diethyl ether, dichloromethane, chloroform and THF (May and Baker Ltd., London), deuterated solvents for NMR spectroscopy, 1,1,3,3-tetramethylguanidine (Aldrich Chem. Co. Ltd.), $NaBH_4$ and NaH (Aldrich Chem. Co. Ltd), hexachlorocyclotriphosphazene (Shin Nisso Kako Co. Ltd., Tokyo, Japan). Solvents were dried by conventional methods. Hexachlorocyclotriphosphazene was purified by fractional crystallization from hexane. Dichloromethane and THF were distilled over sodium–potassium alloy under an atmosphere of dry argon. TLC/silica gel (Merck 60, 0.063–0.200 mm) was used for column chromatography.



Scheme 1. Cyclotriphosphazene derivatives with 1,1,3,3-tetramethylguanidine.

Table 1. Selected $^{31}P\{^1H\}$ and ^1H NMR parameters for compounds **3-6**[a].

		^{31}P chemical shift				
Compound	δPCl_2[b]	$\delta P(NR)Cl$[b]	$\delta P(NR)_2$[b]	$2J[P(NR)Cl\text{-}PCl_2]$[c]	$2J[P(NR)_2\text{-}PCl_2]$[c]	^1H chemical shift -NCH_3
$N_3P_3Cl_6$ (**1**)	19.9					
3	23.6	17.2		47.3		1.06
4		23.5				1.07
5		25.3	20.5		45.9	1.10
6			17.41			1.30

[a] In $CDCl_3$ (with respect to 85% phosphoric acid external reference) at 202.38 MHz.
[b] In ppm.
[c] In Hz.

Methods

All reactions were monitored using Kieselgel 60° 254 (silica gel) precoated TLC plates and sprayed with ninhydridine (0,5% w/v) in butanol solution, and developed at approximately 130 °C. Separations of products were carried out 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 with a Hot Stage Microscopy at Southampton University and hot stage connected to a FP 800 central processor both fitted with a polarizing microscope. Elemental analyses were obtained using a Thermo Finnigan Flash 1112 Instrument. ^1H NMR spectra were recorded using a Varian INOVA 500 MHz spectrometer and (operating at 499 MHz), and a Bruker DRX 500 MHz spectrometer. 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 mg/cm^3. ^{31}P NMR spectra were recorded using a Varian INOVA 500 MHz spectrometer (operating at 202 MHz) in $CDCl_3$ and 85% H_3PO_4 was used as external reference. Mass spectra were recorded using a Bruker MicrOTOF LC/MS spectrometer using electro spray ionization (ESI) method. Microanalyses were carried out at the University of Bilecik micro analytical service. All experiments and analyses of the obtained thermograms

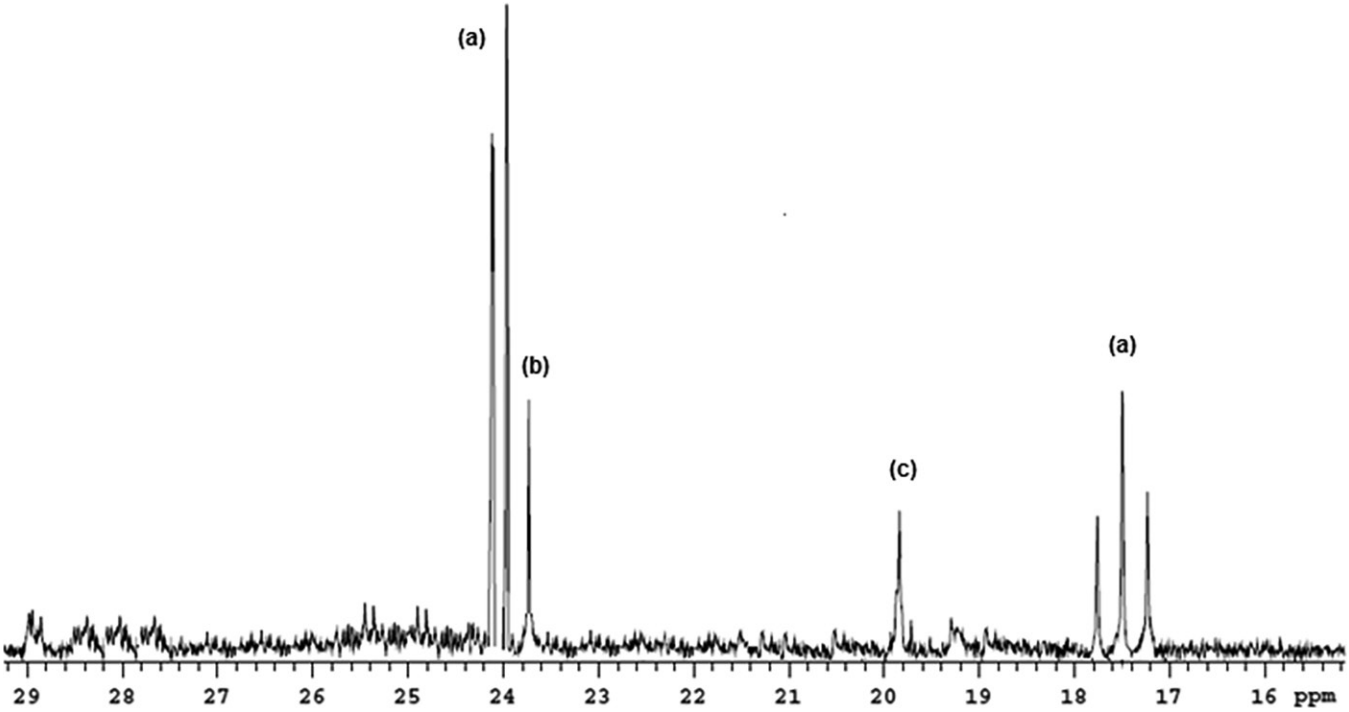


Figure 1. Proton decoupled ^{31}P NMR spectrum of the reaction mixture (1:1:2): (a) compound **3**, (b) compound **4**, (c) trimer (**1**), in $CDCl_3$ at 202.38 MHz, room temperature, referenced to external 85% H_3PO_4.

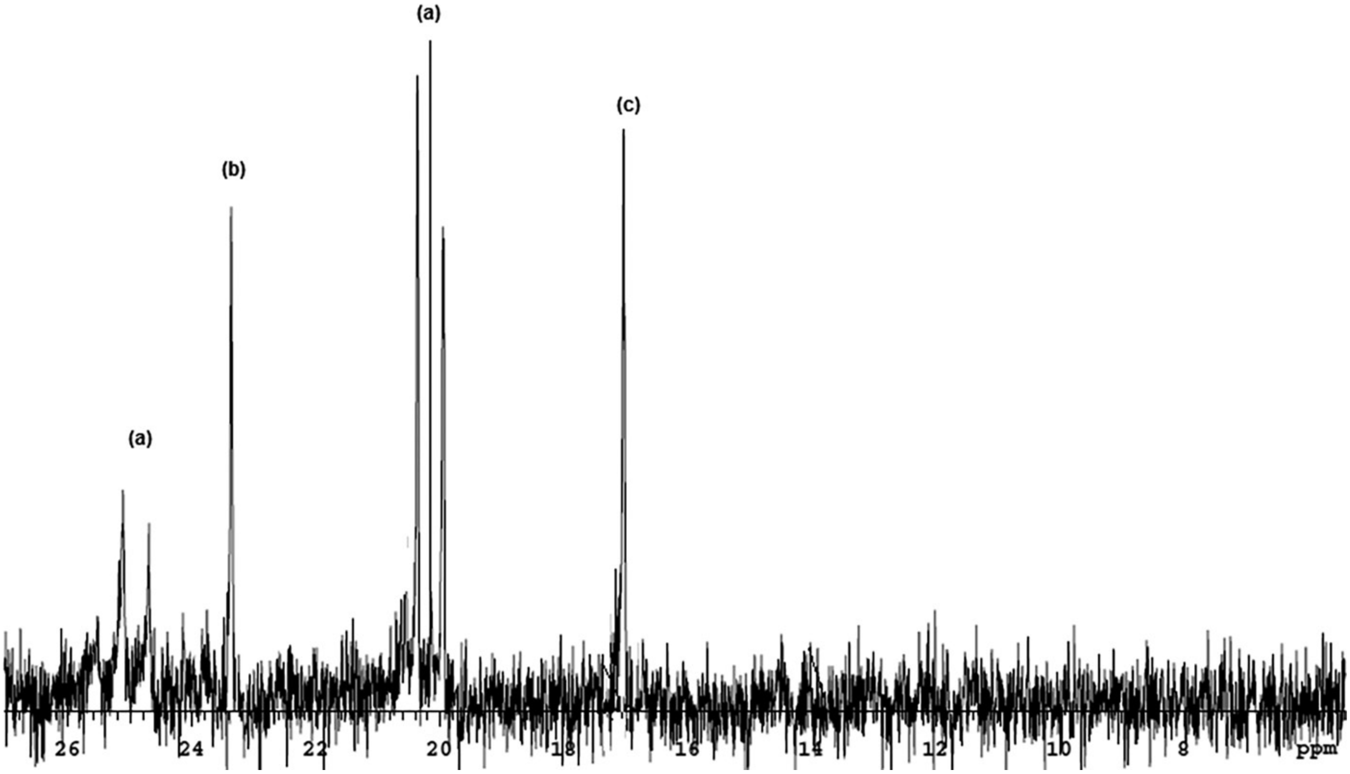


Figure 2. Proton decoupled ^{31}P NMR spectrum of the reaction mixture (1:3:6): (a) compound **5**, (b) compound **4**, (c) compound **6**, in $CDCl_3$ at 202.38 MHz, room temperature, referenced to external 85% H_3PO_4.

were performed using DSC Q2000instrument (*TA Instruments,* US) and thermal analysis software (*Universal Analysis 2000, TA Instruments,* US), respectively.[48] Elemental analyses of the reported products are found in Table 3 and the NMR data are compiled in Table 1.

Reactions of hexachlorocyclotriphosphazene (1) with 1,1,3,3 tetramethylguanidine (2)

Reactions were carried out with one, two and three equivalents of 1,1,3,3-tetramethyl-guanidine, under reflux, in excess of NaH, in THF or dichloromethane solutions.

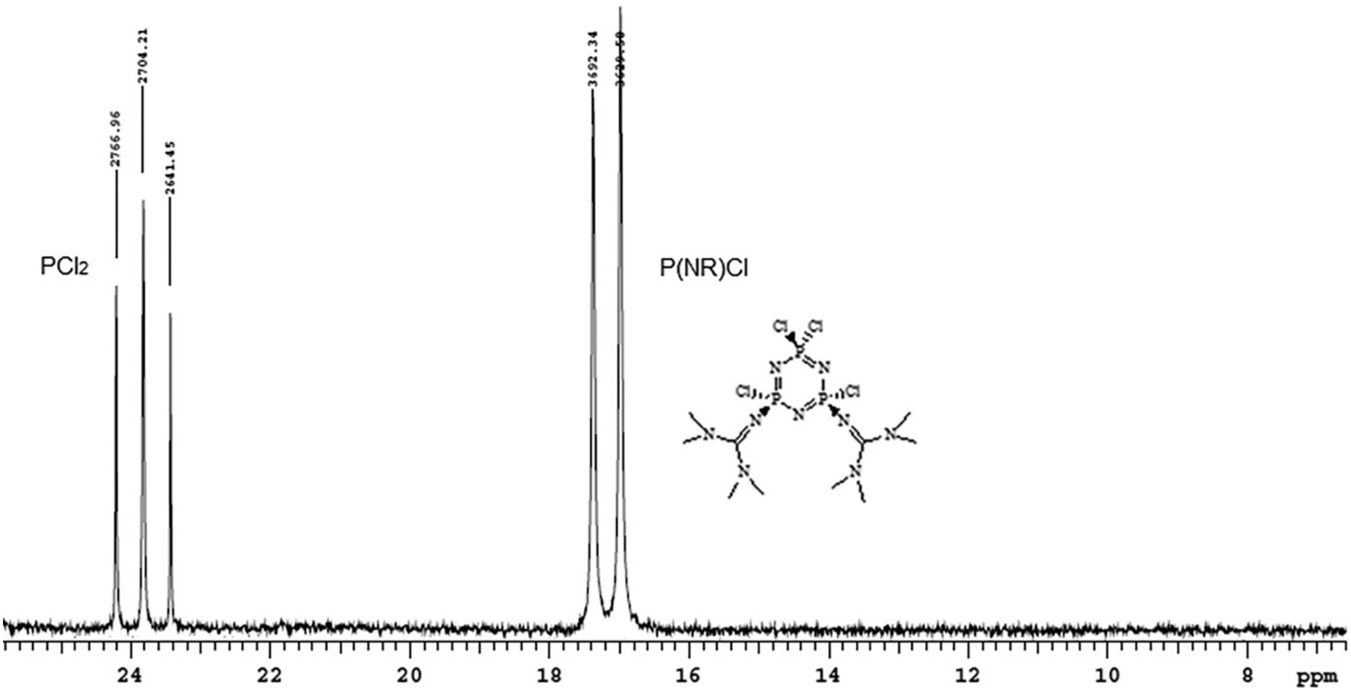


Figure 3. Proton decoupled ^{31}P NMR spectrum of compound **3**: in $CDCl_3$ at 202.38 MHz, room temperature, referenced to external 85% H_3PO_4.

One equivalent of compound 2

Hexachlorocyclotriphosphazatriene (**1**; 4.00 g, 11.59 mmol) was dissolved in 120 mL of dry THF and placed in a 250 mL three-necked round-bottomed flask. This mixture was stirred for 15 minutes at room temperature and two equivalents of NaH (0.56 g 23.19 mmol) in THF (20 mL) was added quickly to this solution and left stirring for approximately 30 min. To this solution, one equivalent of 1,1,3,3-tetramethylguanidine (**2**; 1.33 g, 11.59 mmol) in THF (15 mL) was added dropwise with stirring. Then the reaction mixture was boiled under reflux approximately 26 h and TLC using benzene-diethyl ether (2:1) revealed essentially the formation of two major and one minor products. The reaction mixture was filtered to remove the sodium chloride formed and the other insoluble materials. The solvent was removed at reduced pressure and the resulting brownish colored oil was subjected to column chromatography using benzene–diethyl ether (4:1) as the eluent.

i. The first product was isolated as disubstituted *cis* non-geminal derivative, $N_3P_3Cl_4[NCN_2(CH_3)_4]_2$ (**3**), an oil, yield (1.2 g, 38%). Found: C, 23.92; H, 4.84; N, 25.10%; M^+ 503; $C_{10}H_{24}N_9P_3Cl_4$ requires: C, 23.86; H, 4.77; N, 25.05%; M, 503.
ii. The second product was identified as tri-substituted non-geminal derivative $N_3P_3Cl_3[NCN_2(CH_3)_4]_3$ (**4**), m.p. 157-158 °C, yield (1.6 g, 48%,). Found: C, 31.00; H, 6.27; N, 28.86%; M^+ 582; $C_{15}H_{36}N_{12}P_3Cl_3$ requires: C, 30.93; H, 6.18; N, 28.86%; M, 582.

Two equivalents of compound 2

Reaction procedure as for one equivalent of 1,1,3,3-tetramethylguanidine (**2**). In dichloromethane, in excess of NaH, stirring time was approximately 32 h. Three main fractions were obtained: (**i**) The first phosphazene derivative was identified as *cis* non-geminal derivative **3**: yield 0.65 g (35%). (**ii**) The second phosphazene derivative was identified as tri-substituted non-geminal derivative **4**: yield 0.38 g (21%). (**iii**) Third compound was identified as the tetra-substituted non-geminal derivative **5**: yield 0.26 g (16%).

Three equivalents of compound 2

Hexachlorocyclotriphosphazene, (**1**; 4.00 g, 11.59 mmol) was dissolved in THF (120 mL) and placed in a 250 mL three-necked round-bottomed flask. To this solution 6 equivalents of NaH (1.67 g, 69.56 mmol) in THF (25 mL) was added quickly. 1,1,3,3-Tetramethylguanidine (**2**; 4.00 g, 34.78 mmol) in THF (15 mL) was then added to this mixture while stirring at room temperature (1 h). Then the reaction mixture was boiled under reflux for further 42 h and the the course of the reaction was followed on TLC silica gel plates using benzene/diethyl ether (5:2). After cooling the reaction mixture to room temperature, the sodium hydrochloride and the other insoluble materials were filtered off and the filtrate was concentrated (15 mL). TLC revealed the formation of two major and one minor product. Separation of these compounds was achieved by using column chromatography (120 g, silica gel and a solvent system of benzene:dichloromethane (3:1) as the eluent. (**i**) The first cyclophosphazene derivative was identified as the tri-substituted non-geminal derivative **4**, yield (0.35 g, 16%), recrystallized from light petroleum (b.p. 40–60 °C) containing a few drops of benzene. (**ii**) The second compound was isolated as the hexa-substituted derivative, $N_3P_3[NCN_2(CH_3)_4]_6$ (**6**), recrystallized from light petroleum (b.p. 40-60 °C) containing a few drops of benzene, m.p., 154–155 °C, yield (1.63 g, 49%). Found: C, 43.98; H, 8.84; N, 35.89%; M^+, 819. $C_{30}H_{72}N_{21}P_3$ requires: C, 43.96: H, 8.79; N, 35.90%; M, 819. (**iii**) The third

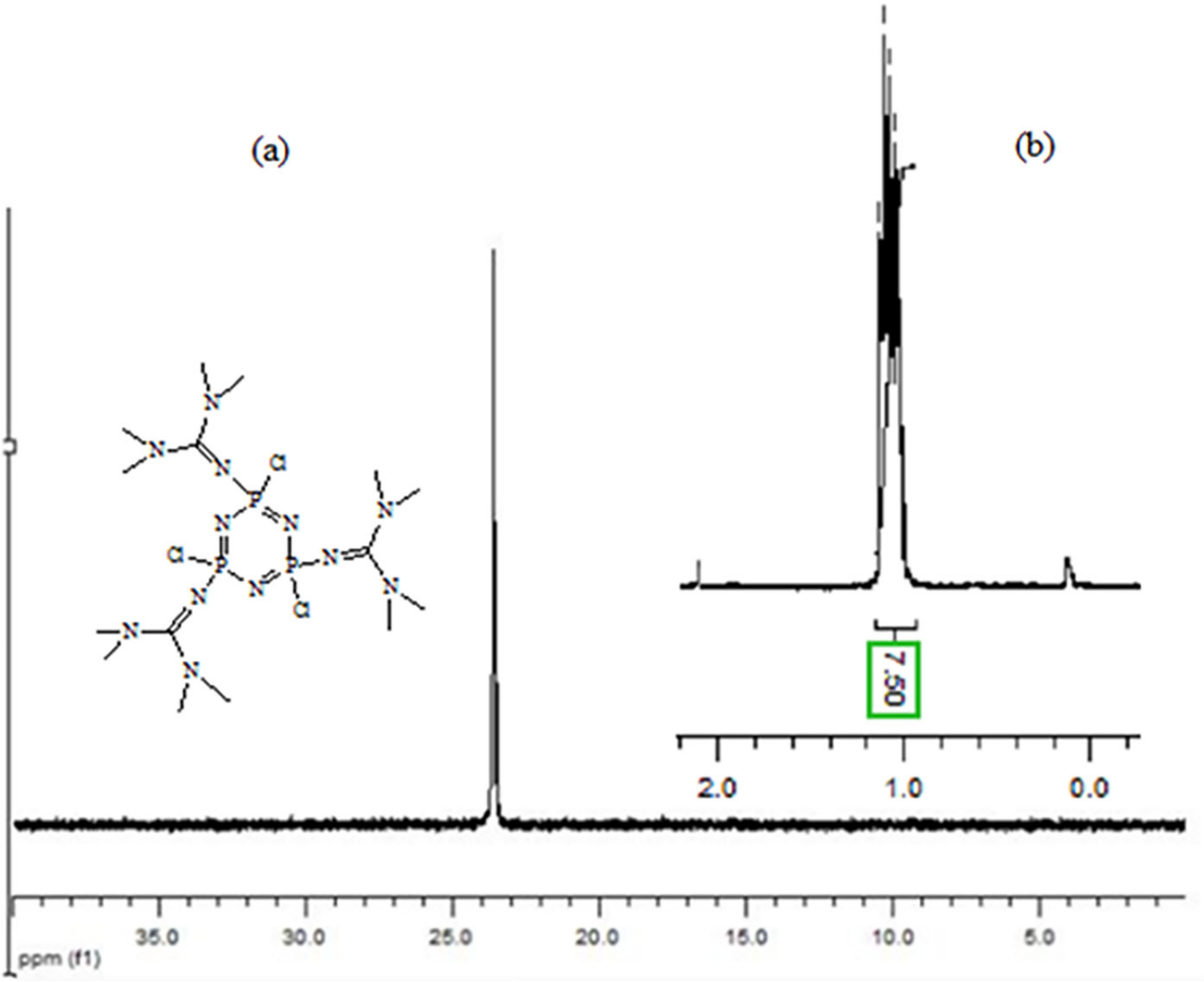


Figure 4. (a) Proton decoupled ^{31}P NMR spectrum of compound **4**: in $CDCl_3$ at 202.38 MHz, room temperature, referenced to external 85% H_3PO_4. (b) ^1H NMR spectrum of compound **6**: in $CDCl_3$, at 499 MHz, room temperature with respect to internal TMS.

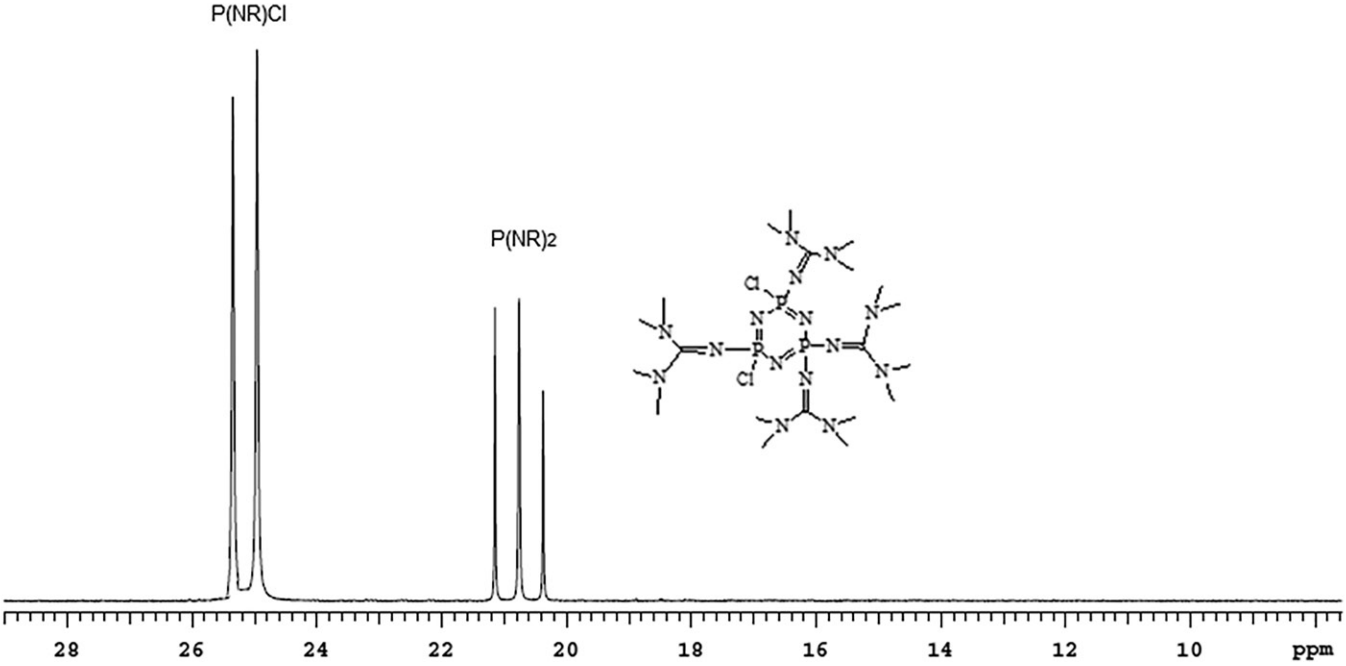


Figure 5. Proton decoupled ^{31}P NMR spectrum of compound **5**: in $CDCl_3$ at 202.38 MHz, room temperature, referenced to external 85% H_3PO_4.

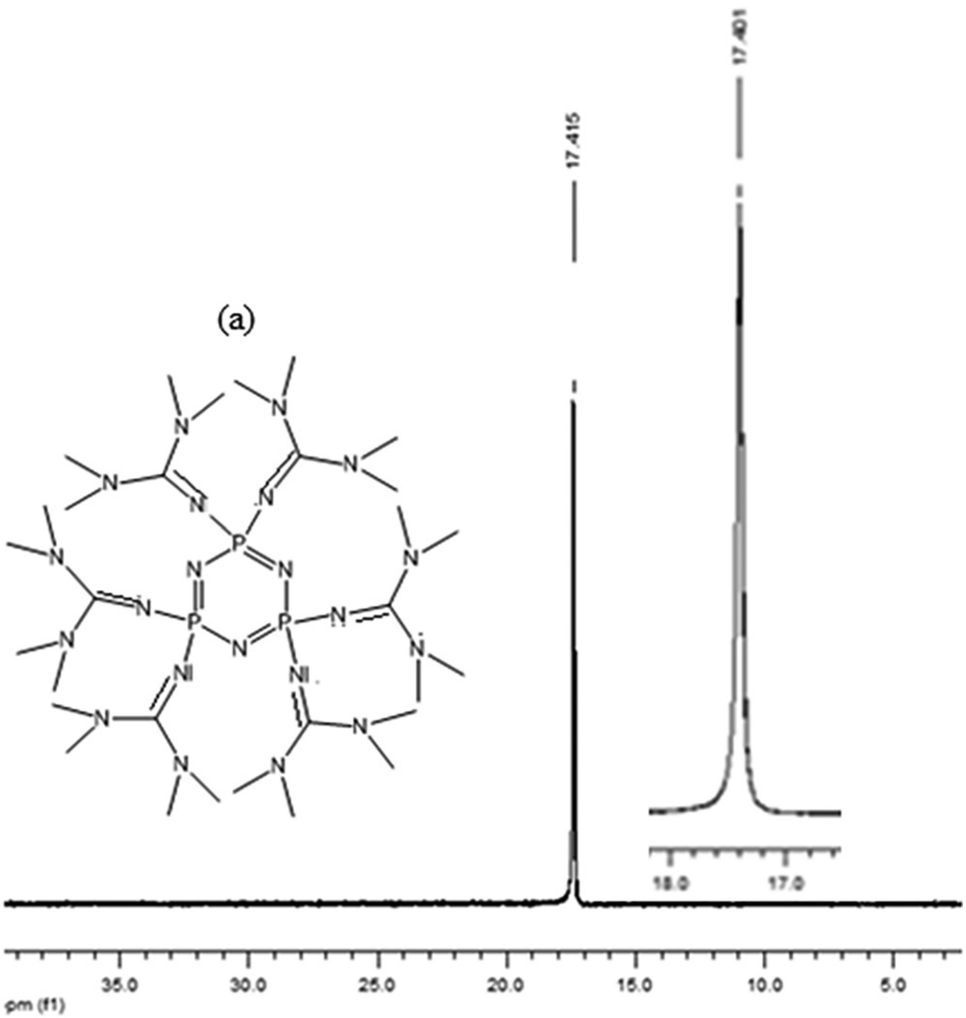


Figure 6. Proton decoupled ^{31}P NMR spectrum of compound **6**: in $CDCl_3$ at 202.38 MHz, room temperature, referenced to external 85% H_3PO_4.

Table 2. Thermal behavior of cyclophosphazene derivatives **4** and **6** with 1,1,3,3-tetramethylguanidine substituents.

Compound	Peak character	Peak position (°C)	Enthalpy-ΔH°(J/g)	Phase transitions
$N_3P_3Cl_3[NCN_2(CH_3)_4]_3$ (**4**)	Endothermic	144	15	Pre-transition
	Endothermic	157	69	Main melting p.
$N_3P_3[NCN_2(CH_3)_4]_6$ (**6**)	Endothermic	147	17	Pre-transition
	Endothermic	155	41	Main melting p.

compound was identified as the tetra-substituted non-geminal derivative, $N_3P_3Cl_2[NCN_2(CH_3)_4]_4$ (**5**), m.p. 181-185 °C, yield (0.93 g, 34%). Found: C, 36.35.58; H, 7.31; N, 31.77%; M^+ 662.1; $C_{20}H_{48}N_{15}P_3Cl_2$ requires: C, 36.31; H, 7.26; N, 31.77%; M, 661.

DSC experiments

Compounds **4** and **6** were prepared in the aluminum hermetic DSC sample pans and the pans were sealed for the experiment. To avoid the calorimetric pan effect the empty and sealed pan was used as a reference. DSC thermograms were obtained in a thermal region from 20 °C to 220 °C at a scanning rate (ramp) of 5 °C/min. This scanning rate was used to obtain thermal event temperatures in between the real thermodynamic value. The peak position temperature was used to define the melting temperature for accurate analysis. Enthalpies (ΔH° J/g) were calculated by linearly dividing the integrating peak area to the sample weight. The system was purged with nitrogen (N_2) gas at a constant rate of 50 mL/min throughout of the experiment. The number of cycles was 1. All the experiments and analyses of the obtained thermograms were performed using DSC Q2000instrument (*TA Instruments*, US) and thermal analysis software (*Universal Analysis 2000, TA Instruments*, US), respectively.[48]

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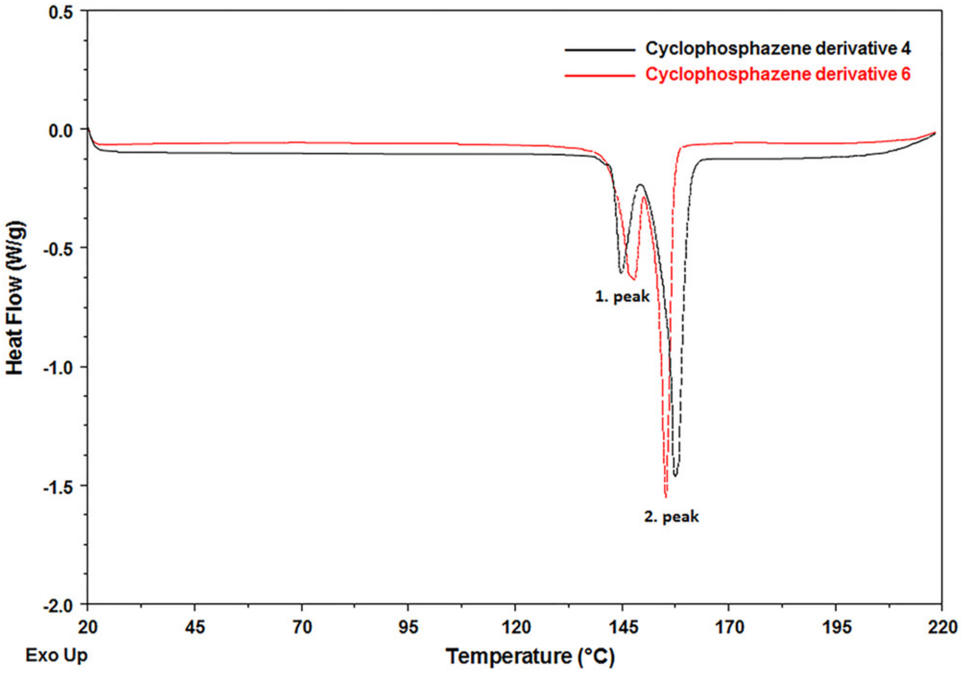

Figure 7. DSC thermograms of cyclophosphazene derivatives **4** and **6**.

Table 3. Analytical data and the percentage yields of cyclophosphazene derivatives **3-6**.

Analytical data (%)		Calculated			Found				Mass
Comp	Formula	C	H	N	C	H	N	$[M+H]^+$	M
3	$C_{10}H_{24}N_9P_3Cl_4$	23.86	4.77	25.05	23.92	4.84	25.10	504	503
4	$C_{15}H_{36}N_{12}P_3Cl_3$	30.93	6.18	28.86	31.0	6.27	28.86	583.1	582
5	$C_{20}H_{48}N_{15}P_3Cl_2$	36.35	7.31	31.77	36.31	7.26	31.77	662.1	661
6	$C_{30}H_{72}N_{21}P_3$	43.96	8.79	35.90	43.98	8.84	35.89	820.4	819
The percentage yields (in 1:1 and 1:3 mole ratios)									
Compound (%)				1:1		1:2		1:3	
3	$N_3P_3Cl_2[NCN_2(CH_3)_4]_2$			38		35			
4	$N_3P_3Cl_3[NCN_2(CH_3)_4]_3$			48		21		16	
5	$N_3P_3Cl_2[NCN_2(CH_3)_4]_4$					16		34	
6	$N_3P_3[NCN_2(CH_3)_4]_6$							49	

Disclosure statement

No potential conflict of interest was reported by the authors.

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