	SAKARYA UNIVERSITY JOURNAL OF SCIENCE	
	e-ISSN: 2147-835X http://www.saujs.sakarya.edu.tr	
	Received 26.01.2018 Accepted 10.05.2018	Doi 10.16984/saufenbilder.384736

Reactions of cyclochlorotriphosphazatriene with 1-amino-2-propanol. Calorimetric and spectroscopic investigations of the derived products.

Sedat TÜRE1[1]*, Rafig GURBANOV[2], Murat TUNA[3]

Abstract

Reactions of hexachlorocyclotriphosphazatriene, $N_3P_3Cl_6$ (**1**) with 1-amino-2-propanol (**2**), in (1:1, 1:2 and 1:3) mole ratios, in excess of NaH, in THF and acetonitril solutions yield a total of **6** novel products: one mono-open chain, $N_3P_3Cl_5$[HN-CH_2-CH(CH_3)-OH] (**3**); one monospiro, $N_3P_3Cl_4$[O-CH(CH_3)-CH_2-NH] (**4**); one *trans* bis-open chain, $N_3P_3Cl_4$[HN-CH_2CH(CH_3)-OH]$_2$ (**5**); one dispiro, $N_3P_3Cl_2$[O-HC(CH_3)-CH_2-NH]$_2$ (**7**); one tri-open chain, $N_3P_3Cl_3$[HN-CH_2CH(CH_3)-OH]$_3$ (**6**); and one tri-spiro, N_3P_3[O-HC(CH_3)-CH_2-NH]$_3$(**8**) derivatives. These compounds have interesting structural aspects as well as physical properties. Their structures were established by elemental analysis, TL-MS, ^{31}P and ^{1}H NMR spectral data. Stability constants were determined using a simple potentiometric titration. For evaluation of melting behavior and purity of derivatives (**7**) and (**8**), thermal transition peaks and their corresponding enthalpies were determined via DSC technique. Spectroscopic data, product types and relative yields are compared with those of the previously investigated derivatives of $N_3P_3Cl_6$ (**1**) with aliphatic difunctional reagents.

Key words: Hexachlorocyclotriphosphazene, 1-amino-2-propanol, spiro compounds, open chain compounds, DSC analysis

1. INTRODUCTION

Due to their substitution patterns, phosphazenes potentially have more variations than carbon analogs such as benzene that are limited because these allow only one substitution in a particular location in the ring. In the past, phosphazenes have been studied for their properties both as linear polymers [1-5], and cyclic structures [6-29, 30]. Their general electronic structure has also been studied [11], focusing on the interactions between the nitrogen and phosphorus atoms linear or cyclic geometries. Intramolecular reactions of short chain difunctional nucleophiles,

*Corresponding Author
[1] Bilecik Şeyh Edebali University, Art and Science Faculty, Departmant of Chemistry, sedat.ture@bilecik.edu.tr
[2] Bilecik Şeyh Edebali University, Art and Science Faculty, Departmant of Molecular Biology and Genetic, ratig.gurbanov@bilecik.edu.tr
[3] Sakarya University, Art and Science Faculty, Departmant of Chemistry, tuna@sakarya.edu.tr

such as amino-alcohols and mercapto-alcohols with trimer $(NPCl_2)_3$ (**1**), can yield geminal/non-geminal open-chain or spirocyclic products [12-15]. First, dinucleophil may replace only one chlorine atom to produce open chain structure. Second, the dinucleophile may replace two chlorine atoms at the same phosphorus atom to form geminal open chain or spirocyclic structures [16-19]. Third, chlorine units on adjacent phosphorus atoms may be replaced to produce non-geminal open chain products 18-19, 35]. General replacement patterns of 1-amino-2-propanol formations are shown in Figure 1.

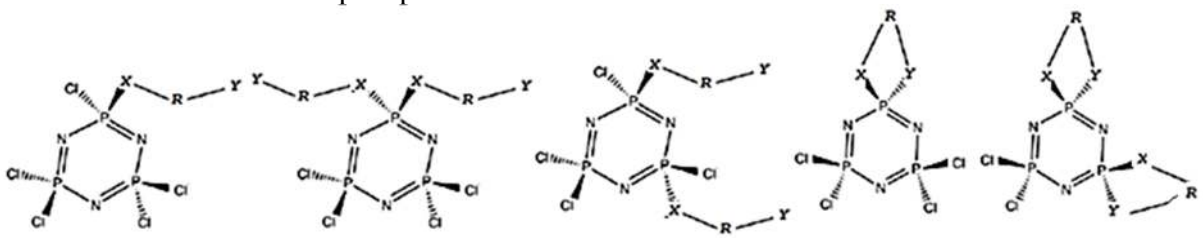


Figure 1. Substitution patterns of cyclotriphosphazene (**1**) withshorter chain dinucleophiles.X and Y are heteroatoms (i.e., O or N).

Amino alcohols contain both an amine and an alcohol group. Amino alcohol derivatives have been used as coupling partners in addition to catalysts in the synthesis of many compounds. Enantiomerically pure beta-amino alcohols play an increasingly important role in pharmaceutical therapeutics and as chiral auxiliaries in organic synthesis. Amino alcohol derivatives are currently being studied for modulating antimicrobial and antifungal activities and the physiochemical properties of drug molecules. The amino alcohol group is found in many antibiotics, such as ethambutol, which is used in the treatment of tuberculosis. The additions of 1,2-carbonyl compounds, ring closure reactions, conjugate additions and α-functionalization are carried out efficiently with β-amino alcohols as catalysts. The availability of β-amino alcohols from a chiral pool (eg, L-amino acids) makes them an attractive class of versatile promoters for use in modern organic synthesis.

In this paper we strive to understand heteroatom chain length, nucleophilic tendency to donate electrons or react at the electron-poor sites on the phosphorus atoms, and the likelihood substitution patterns of compound formation. In addition, melting and crystallization behavior of compounds **6** and **7** were characterized.

The reactions of cyclophosphazene (**1**) with the 1-amino-2-propanol (**2**) in excess of NaH (Figure **2**) gave predominately spiro derivatives (**4**, **7**, **8**) as well as giving mono- (**3**), bis- (**5**) and tris- (**6**) open chain products. Similar findings were reported with shorter chain lenght of difunctional reagents e.g.1,2-ethane-diamine and amino-alcohols [32]. With longer chain lengths of the spacer $(CH_2)_n$ group in difunctional reagents, bridged compounds predominated to intramolecular formations [30-35]. These results are in contrast to the reactions of shorter chain diamines, where are for thermodynnamic reasons generally spirocyclic products were synthesised [33].

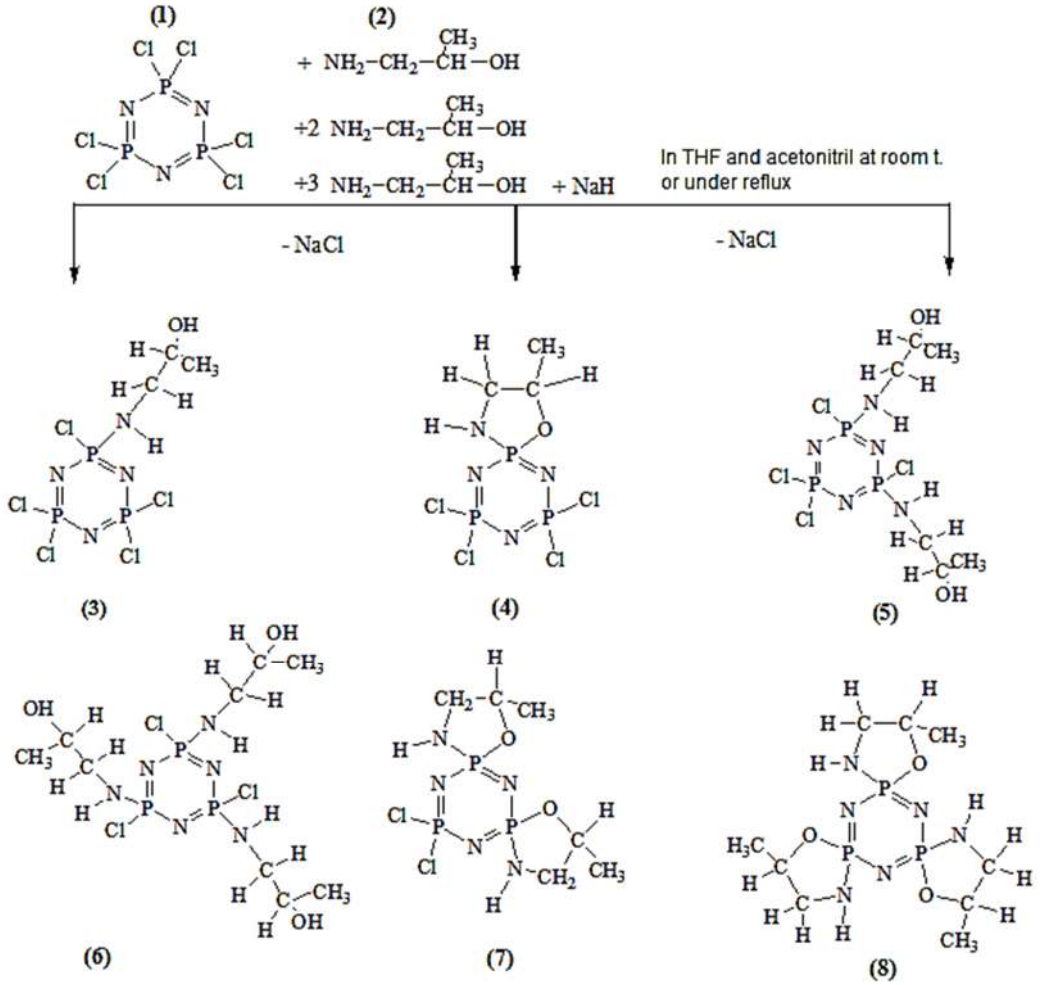


Figure 2. Structures of cyclophosphazene derivatives with 1- amino-2-propanol.

2. RESULTS AND DISCUSSION

The reactions of $N_3P_3Cl_6$ (**1**) with 1-amino-2-propanol in 1:1:2, 1:2:4 and 1:3:6 stoichiometries gave the following isolated and characterized derivatives: one mono-open chain compound, $N_3P_3Cl_5$[NH-CH_2-$CH(CH_3)$-OH] (**3**, 19%); one *trans* bis-open chain compound, $N_3P_3Cl_4$[NH-CH_2-$CH(CH_3)$-$OH]_2$ (**5,** 15%); one tri-open chain compound, $N_3P_3Cl_3$[NH-CH_2-$CH(CH_3)$-$OH]_3$ (**6,** 16%); one mono-spiro compound, $N_3P_3Cl_4$[O-$CH(CH_3)$-CH_2-NH] (**4**, 53%); one dispiro compound, $N_3P_3Cl_2$[O-$CH(CH_3)$-CH_2-$NH]_2$ (**7,** 37%,); and one tri-spiro compound, N_3P_3[O-$CH(CH_3)$-CH_2-$NH]_3$ (**8**, 26%). Mono spiro derivative (**4**, 53%) is isolated in larger amount than the other products. Isolated compounds (**3-8**) were characterized by elemental analysis, MS, ^{1}H and ^{31}P NMR spectroscopy and the results are provided as part of the analytical data in the experimental section. Structure of derived compounds are displayed in Figure 2.

2.1. Synthesis and characterization of compounds 3-8.

The selectivity of the substitution reactions of trimer (1) with difunctional regeants is strongly depended on the temperature [25], solvent and the type of nucleophilic regeants [24-25]. Solvent effect plays an important role in determining the stereo and regio sellective control on the cyclophosphazene rings [22-25].

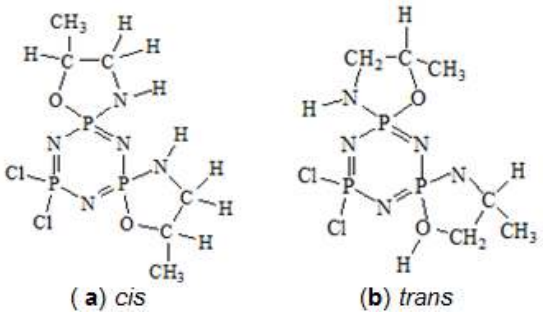
In general, at low temperature with a shorter chain length reagent, the nucleophilic

substitution takes place on different phosphorus atoms and giving rise to open chain products. Here, in our nucleophilic reagent, the amino groups are generally more nucleophilic than hydroxyl groups, so that when an amine and an alcohol (a compound containing a hydroxyl group) are mixed together with a common electrophile in a certain amount, the electrophile almost only enters the reaction with the amine groups. Likewise for compounds containing both an amino group and a hydroxyl group, an electrophile typically reacts at the amine moiety of the molecule.

Reactions at the hydroxyl group is often not possible as long as the amino group is not changed in a separate step using a protecting group to previously react [2]. As noted, it is estimated that the first substitution takes place over the amine group and later on the hydroxyl group. However, the situation is different when working with phosphazenes. Due to the presence of chlorine atoms (Cl or Cl_2) on the phosphorus atoms and since the phosphorus atoms are still open to new substitution reactions after the initial displacement (Cl with amino group), it is possible for hydroxyl group to attack on phosphorus atoms for second substitution. Therefore, we were able to obtain geminal spiro and geminal/non-geminal open chain derivatives. Unless you make a very special changes in reaction conditions, it is unlikely to obtain ansa type cyclic structure with a shorter chain length of nucleophils.

2.2. ^{31}P NMR spectroscopic data

^{31}P NMR spectra of resulting compounds with 1-amino-2-propanol showed the predominance of spiro structures with A_2B, AB_2 and A_3 spin systems, mono-, di-, and tris-spiro derivatives respectively. We can expect to have two different types of isomeric structures from compound **7** which are possible depending on whether the exocyclic nitrogen atoms have a *cis* (**a**) or *trans* (**b**) disposition (see below).



(**a**) *cis* (**b**) *trans*

As mentioned, two structures are possible depending on whether the exocyclic nitrogen atoms have a *cis* or *trans* disposition. Compound **7** is tentatively assigned to the *trans* structure due to its higher TLC R_f value. In general, the TLC R_f value of the *trans-aminochlorocyclo-triphosphazene* derivative is greater than the *cis* analogue [23, 33].

Dispiro derivatives exhibit AB_2 type spectra. Therefore, the ^{31}P {^{1}H} NMR spectrum of compound **7** is AB_2 type and gives rise to very close five line structure. ^{31}P NMR proton-coupled spectrum of the structure allows identification of the lines due to the ≡Pspiro and ≡PCl_2 groups, where spiro group split into further lines. Proton coupling experiments as well as comparison with the analogues diols and diamine derivatives [24, 25] allow precise assignment of the structure.

Compound, $N_3P_3Cl_4$[O-CH(CH_3)-CH_2-NH] (**4**), whose analysis and mass spectrum showed that this can be either mono spiro or its ansa isomer. Previous experience with these two isomers shows that these could have in principle two structures: Spiro or ansa. The ansa compound has an AB_2 type spectrum, while that of the spiro isomer is of the A_2X. ^{31}P (-H) coupling affects the B_2 part of the former and X part of the later giving further splitting on the spectrum. As mentioned above, with a shorter chain lenght nucleophil, we expect to have spiro type stucture and we therefore obtained an A_2X type spin system from this compound and assigned as the mono spiro-cyclic structure.

Compounds (**3**) and (**5**) give rise to A_2X and AB_2 type spin system respectively. Proton

coupling effects the X part of the former and B_2 parts of the later (≡P(NR)Clgroups, where each grouıp split into further lines). The spectra are quite facilitated by looking at the open chain derivatives of diols [36]. We therefore, with confidence assigned them to be open chain derivatives.

In the case of compounds (**6**) and (**8**), where the ^{31}PNMR spectrum is of the A_3 spin type. An A_3 spin system arises, when the phosphorus nuclei have identical or very similar environments. The ≡P(NR), spiro groups and the ≡P(NR)Cl, open chain groups are in identical environments and linked to similar groups in each structure; therefore, one single line is observed at 23.5 and 29.2 ppm for these compounds respectively. ^{31}P NMR data are shown in Table 1 and ^{31}P NMR spectra of compounds **3**, **4**, **5**, **7** and **8** are exhibited in Figures 3, 4 and 5 respectively.

Table 1. Selected ^{31}P NMR parameters (characterisation) of hexachlorocyclotriphosphazene (**1**) derivatives **(3-8**[a]) with 1-amino-2-propanol.

Compound	δPCl_2[b]	δPspiro[b]	δP(NROH)Cl[b]	^2J[Pspiro-PCl_2][c]	^2J[P(NROH)-PCl_2][c]
(**1**) $N_3P_3Cl_6$	19.9				
(**3**) Open chain	24.2		12.1		47.2
(**4**)Mono-spiro	22.9	15.8		44.8	
(**5**) Open chain	25.2		22.2		48.2
(**6**) Open chain			23.5		
(**7**) Dispiro	26.5	18.3		46.9	
(**8**)Tris-spiro		29.2			

[a]In CDCl3 (with respect to 85% phosphoric acid external reference) at 202.38 MHz. [b]In ppm . [c]In Hz.

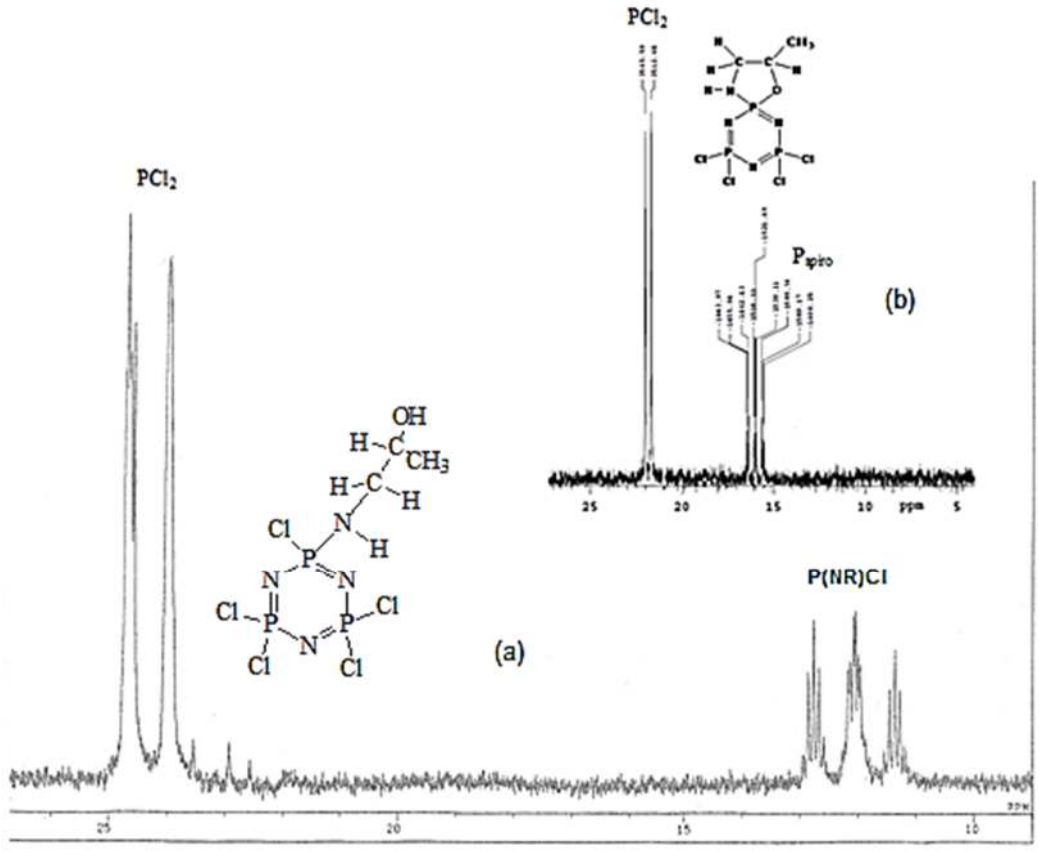


Figure 3. Proton coupled and proton decoupled ^{31}P NMR spectra of compounds **3** (**a**) and **4** (**b**) respectively: in $CDCl_3$, at 202.38 MHz, room temperature, referenced to external 85% H_3PO_4.

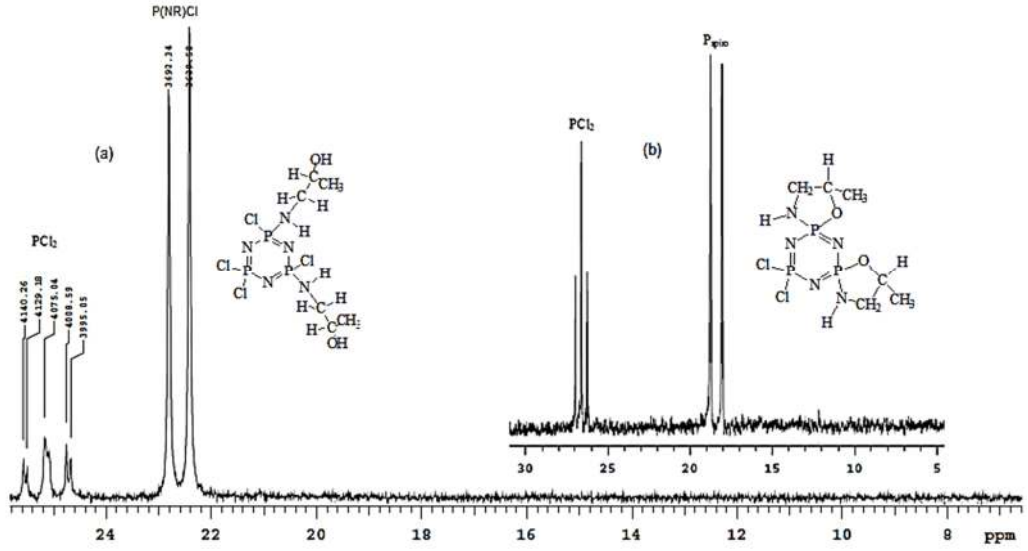


Figure 4. Proton decoupled ^{31}P NMR spectrum of compounds **5** (**a**) and **7** (**b**): in $CDCl_3$ at 202.38 MHz, room temperature, referenced to external 85% H_3PO_4.

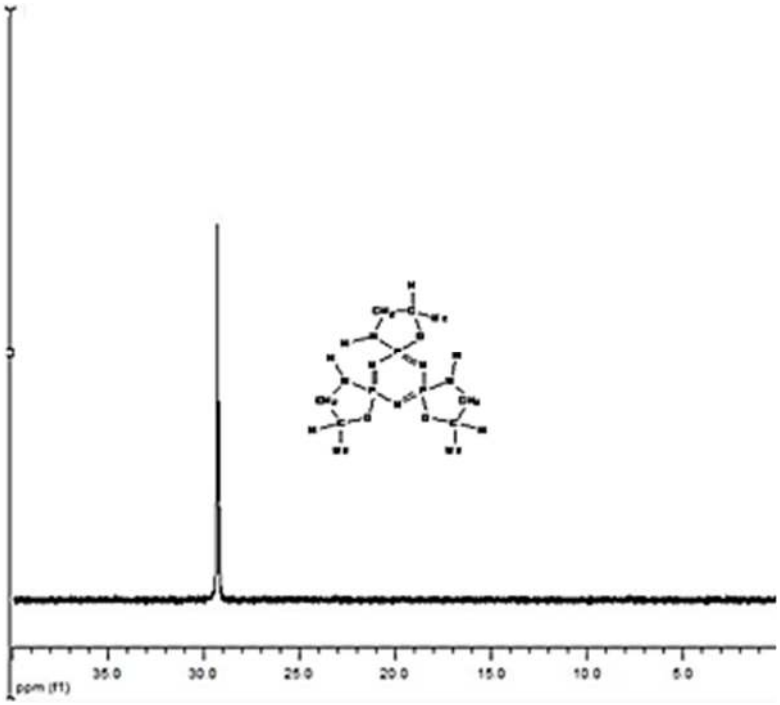


Figure 5. Proton decoupled ^{31}P NMR spectrum of compound **8**: in $CDCl_3$ at 202.38 MHz, room temperature, referenced to external 85% H_3PO_4.

2.3. ^{1}H NMR characterization of compounds 3-8.

The ^{1}H NMR spectra of geminal spiro-cyclic and non-geminal open chain derivatives (**3-8**) are by far the most complex and also the most interesting. The protons of the N<u>H</u>, NC<u>H</u>$_2$, OC<u>H</u> and OC(C<u>H</u>$_3$) groups are non-equivalent due to their being part of a cyclic and open chain moiety and existing in chemically and magnetically in different environments. However, the ^{1}H NMR spectra also reveal a number of interesting properties (shown in Table 2). For compounds **3-8**, the N-<u>H</u> resonance appears as well resolved pairs and the phosphorus ^{2}J(P-H) proton coupling can be measured. For most primary aminocyclophosphazenes, N-<u>H</u> resonances

are seen as absolutely unresolved humps, and binding to phosphorus nuclei is not normally noticeable [20, 21]. Also, intense virtual coupling is observed in the spectrum of Compound **7** (for NCH_2 and OCH signals). The spectra of $N\text{-}CH_2$ and CH protons cannot be resolved because they are very complex and superimposed.

Table 2. Selected ^{1}H NMR parameters of compounds (**3-7**)[a] with 1-amino-2-propanol.

Compound	δPNH[b]	δNCH$_2$[b]	δPOCH[b]	δPOC(CH$_3$)[b]	N-CH$_2$/^{2}J(P-H)[c]
(**3**)	2.68	3.48	4.32	1.23	11.50
(**4**)[d]	2.70	3.35	4.37	0.93	11.60
(**5**)	2.71	3.51	4.30	1.21	11.73
(**6**)	2.64	3.53	4.25	0.91	11.50
(**7**)	2.59	3.38	4.40	1.13	11.50
(**8**)	2.85	3.50	4.26	1.20	11.70

[a]In $CDCl_3$ (referenced to internal TMS) at 199.5 and 399.95 MHz. (room temperature). [b]In ppm. [c]In Hz. [d]In $CDCl_3$ (referenced to internal TMS) at 250.13 MHz (room temperature).

2.4. Calorimetric characterization of compounds (**7** and **8**)

In this study, melting behavior of cyclotriphosphazene derivatives (**7** and **8**) with 1-Amino-2-propanol were obtained in which, the positions and enthalpies of the DSC thermal peaks were assigned at Table 3.

The whole thermogram for the derivatives were shown in the Figures 6 and 7, where the thermal peaks were labeled.

As shown in Figure 6, there is a sharp and almost linear endothermic peak found at 208.25 °C for compound (**7**), corresponding to main phase transition temperature (Tm), indicating total melting event. The enthalpy for this event was calculated as ΔH °**C** 80.7**.** No other peaks including pre-transition peak were detected for this derivative**.** Of note, peak width is a valuable measure of purity, in which impurities lower the melting point, i.e. less pure crystals melt first followed by purer larger crystals [37]. Accordingly, the endothermic and sharp melting peak located at higher temperature (208.25 °C) indicates adequate purity of a compound (**7**). As can be seen from the Figure 7 and Table 3, there are four endothermic and one exothermic thermal peak for compound (**8**). For better resolution of some peaks, 80-100 °C thermal region was given as enlarged panel (Figure 7). Endothermic peaks found at 83.74 (#1), 90.39 (#2) and 96.18 °C(#3) positions with respective enthalpies as ΔH° 0.22, 0.09 and 0.03 were assigned to pre-transition events. However, a sharp and large endothermic melting peak (#5) at 110.80 °C position (ΔH ^{0}**C** 114.9) was considered as main phase transition temperature (Tm), indicating that the compound (**8**) is also pure. Exothermic peak (#4) found at 96.91 °C position with respective enthalpy of ΔH °C 0.05 was assigned to intermediate crystallization event probably occurred due to the recrystallization process just before melting step.

Upon heating the specimen in DSC, so called fusion process, i.e. the passage from crystalline state to the liquid state, can be monitored by the appearance of endothermic transition. Usually the largest endothermic transition in the whole thermogram is encountered as melting event. In addition, enthalpy is a term expressing the heat energy needed for the disruption of crystal cage, which is time-dependently measured by the integrating area of the specific peak. Accordingly, during the scanning below melting point of each substance to a temperature above the melting temperature the changes in enthalpy corresponds to a melting of

crystalline [38]. The melting temperature of a substance, which is the crucial physical parameter can be affected by a number of chemical circumstances such as its stereochemistry, molecular mass, the existence of polar functional groups, configuration and number of double bonds [39]. Since, a clear crystal form corresponds to a sharp and distinguishing melting peak, any shifts in temperature and/or enthalpy can be used to identify whether the compound is pure or not. Endothermic melting peak is observed during the disruption of crystal cage of a compound. If it includes impure or unformed (amorphous) structures, the melting temperature and corresponding enthalpy will be diminished respectively. Furthermore, the relative stability (monotrophy and anisotrophy) of a crystal material can be determined by appearance of endothermic and exothermic peaks on the same DSC thermogram. Actually, thermal profile can be quite intricate, demonstrating both endothermic and exothermic peaks, which can also reflects the fact that a material in a less stable form will convert to a more stable form during heating [40].

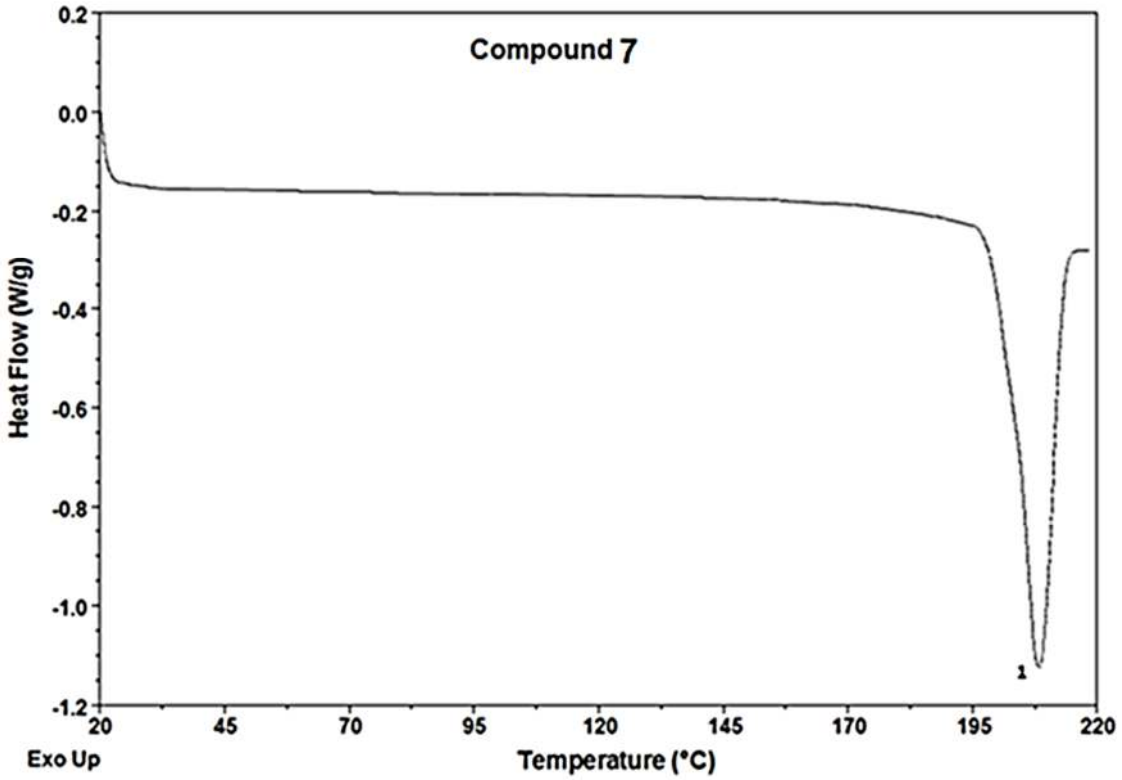


Figure 6. DSC thermogram of compound (**7**).

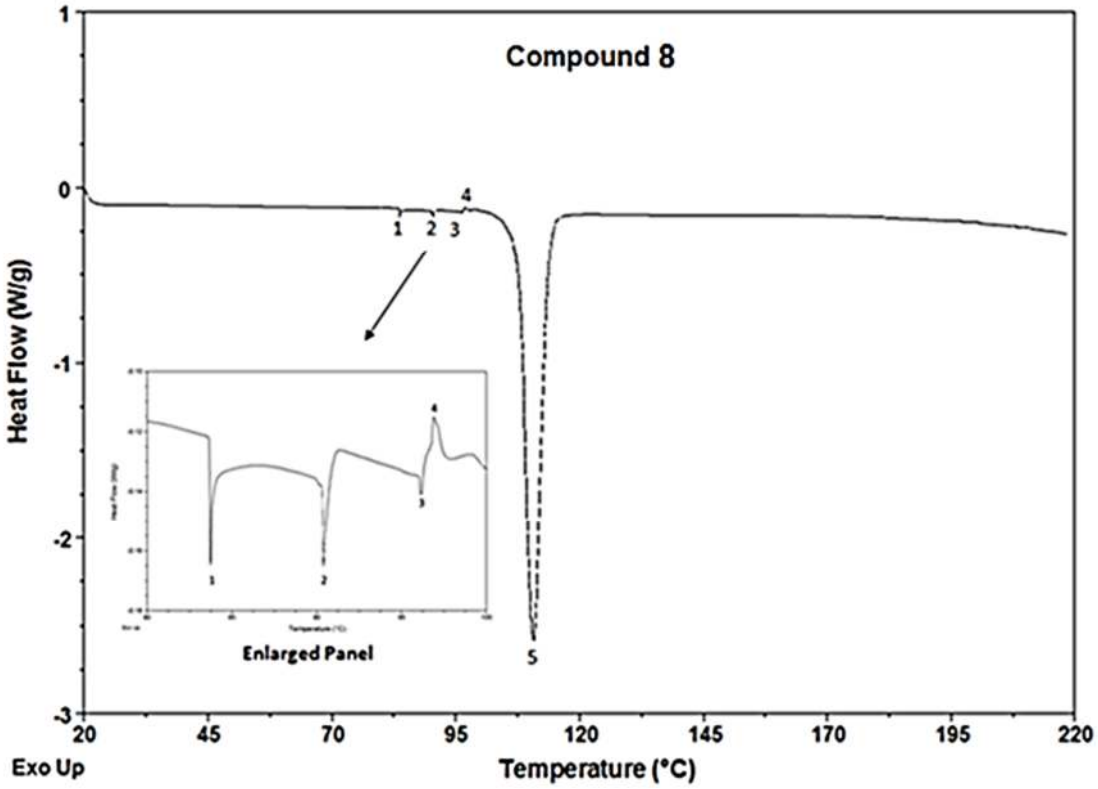


Figure 7. DSC thermogram of compound (**8**).

Table 3. Thermal behaviour of 1-Amino-2-propanol (isopropanolamine) compounds (**7**) and (**8**).

1-Amino-2-propanol (isopropanolamine)	# Peaks	Peak character	Peak position (°C)	EnthalpyΔH °C (J/g)	Phase Transition Events
(**7**)	1	Endothermic	208.25	80.7	Main melting
(**8**)	1	Endothermic	83.74	0.22	Pre-transition
	2	Endothermic	90.39	0.09	Pre-transition
	3	Endothermic	96.18	0.03	Pre-transition
	4	Exothermic	96.91	0.05	Recrystallization
	5	Endothermic	110.80	114.9	Main melting

3. EXPERIMENTAL SECTION

3.1. Materials

Reagent grade solvents were used throughout the work, benzene, light petroleum (bop.40–60 °C), anhydrous diethyl ether, acetonitrile, methanol, butanol, n-hexane (>96%), dichloromethane (>99.0%), chloroform, acetonitrile, dichloromethane, THF, acetone and hexachlorocyclotriphosphazatriene (Sigma Aldrich). Hexachlorocyclotriphosphazene was purified by fractional crystallization from hexane. 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° 254 (silica gel) precoated TLC plates (Merck). The following materials were also obtained from Sigma Aldrich Chemicals: Ninhydridine (0.5% w/v), 1-amino-2-

propanol (**2**) and $NaBH_4$ used as received, 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 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 on 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 ThermoFinnigan Flash 1112 Instrument. ^{1}H NMR spectra were recorded using a Varian INOVA 500 MHz spectrometer and (operating at 499 MHz.), a Bruker DRX 500 MHz spectrometer. Samples were dissolved in $CDCl_3$ and placed in 5mm 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 an external reference. Mass spectra were recorded using a LC/MS (obtained by a Bruker MicrOTOF LC/MS spectrometer using electro spray ionization (ESI) method). Microanalyses were carried out by University of Bilecik, micro analytical service. For DSC analyses samples were prepared in the aluminum hermetic pans and the pans weresealed before the test. An empty pan was sealed and placed in a particular position in DSC device next to the pan containing sample in order to eliminate calorimetric pan effect. Scan was performed at a thermal region from 20 °C to 220 °C with 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 positions in temperature axis (°C) were evaluated for the calculation of the melting temperatures. Enthalpies (ΔH °C J/g) were calculated by linearly dividing the integrating peak area to the sample weight. All the experiments and were carried out using DSC Q2000 instrument (*TA Instruments,* US), while the data analyses were conducted by thermal analysis software (*Universal Analysis 2000, TA Instruments,* US) [41]. Experimental details together with product types and the relative yields of the reported products are summarized in Tables 4 and ^{31}P and ^{1}H NMR data may be found in Tables 1 and 2.

3.3. Synthesis

In this paper, we report on the synthesis and characterisation of spiro-cyclic and open chain phosphazene ligands, along with calorimetric characterisation of compounds **6** and **7**.

Reactions were carried out with one (32 h), two (36 h) and three (26 h) equivalents of 1-amino-2-propanol in excess of NaH, and in THF and acetonitrile solutions.

3.3.1. Addition of one equivalent of 1-amino-2-propanol (2) at room temperature:

Cyclotriphosphazene (**1**), (4 g, 0.0116 mole) and 1-amino-2propanol (0.87 g, 0.0116 mole) were dissolved in 100 mL of THF and mixed in a 250 mL three-necked round-bottom flask. This mixture was stirred approximately for half an hour then two equivalents of NaH (60% oil suspension, 0.557 g, 0.023 mole) in 30 mL of THF was added dropwise to the stirred solution under an argon atmosphere. The mixture was stirred at room temperature (32 h) 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-diethyl ether (3:1) as the eluent. The solvent was removed under reduced pressure and the resulting colorless solids and oils were subjected onto column chromatography using the same solvent system, dichlomethane: diethyl ether (3:1) as the mobile phase. Products were recrystallized from benzene containing a few drops of light petroleum (b.p. 40-60 °C). Two main fractions were synthesized:

(**i**) The first phosphazene derivative was identified as mono-spiro, $N_3P_3Cl_4$ [HN-CH_2-CH-(CH_3)-O] (**4**): m.p. 133-134 °C, yield 1.3 g (53%). For $C_3H_7ON_4P_3Cl_4$: Calculated: C, 10.34; H, 2.01; N, 16.09%; M, 348. Found: C, 10.33; H, 2.05; N, 16.09%; M^+, 349.03.

(**ii**) Second compound was identified as an open chain product, $N_3P_3Cl_5$[NH-CH_2-

CH(CH_3)-OH] (**3**): m.p. 140-142 °C, yield 0.42 g (19%). For $C_3H_8ON_4P_3Cl_5$: Calculated: C, 9.38; H, 2.08; N, 14.58%; M, 384. Found: C, 9.35; H, 2.1; N, 14.58%; M^+, 348.09.

3.3.2. Addition of two equivalents of 1-amino-2-propanol (2) at room temperature:

Reaction procedure as for one equivalent of 1-amino-2-propanol (**2**). In acetonitrile solution, in excess of NaH, at room temperature, stirring time was approximately 36 h.

(**i**) The first phosphazene derivative was identified as, mono-spiro, (**4**): yield 0.7 g (38%).

(**ii**) Second phosphazene derivative was identified as bis open chain product,

$N_3P_3Cl_4$[NH-CH_2-CH(CH_3)-OH]$_2$ (**5**): m.p. 166-169°C, yield 0.32 g (15%). For $C_6H_{16}O_2N_5P_3Cl_4$: Calculated: C, 17.02; H, 3.78; N, 16.55%; M, 423. Found: C, 17.03; H, 3.80;N, 16.55%; M^+, 423.07.

(**iii**) Third compound was identified as bis spiro compound, $N_3P_3Cl_2$[O-HC(CH_3)-CH_2-NH]$_2$ (**7**): m.p. 205-207 °C, yield 0.66 g (37%). For $C_6H_{14}O_2N_5P_3Cl_2$: Calculated: C, 20.5; H, 3.99; N, 19.9%; M, 351. Found: C, 20.61; H, 4.2; N, 19.94%; M^+, 352.01.

3.3.3. Addition of three equivalents of 1-amino-2-propanol (2) at room temperature:

Reaction procedure as for one equivalent of 1-amino-2-propanol (**2**). (**i**) mono-spiro derivative (**4**); yield 0.37 g (18%). (**ii**) dispiro derivative (**7**), yield 0.25 g (12%). (**iii**) tri-open chain derivative, $N_3P_3Cl_3$[NH-CH_2-CH(CH_3)-OH]$_3$ (**6**); m.p. 152-155 °C,yield 0.30 g 16%). For $C_9H_{24}O_3N_6P_3Cl_3$: Calculated: C, 23.38; H, 5.20; N, 18.18%; M, 462. Found: C, 23.37; H, 5.22; N, 18.18%; M^+, 463.01.

3.3.4. Addition of three equivalents of 1-amino-2-propanol (2)under reflux:

Cyclotriphosphazene (**1**) (4 g, 0.0116 mole) and 1-amino-2-propanol (**2**) (2.61 g, 0.034 mole) were dissolved in 100 mL of dry THF and mixed in a 250 mL three-necked round-bottom flask. This mixture was stirred approximately for half an hour at room temperature then six equivalents of NaH (60% oil suspension, 1.67 g, 0.070 mole) was added dropwise to the stirred solution under an argon atmosphere. The solution left stirring for another half an hour. Then the solution was heated for 26 h under reflux. The course of the reaction was followed by TLC with silica gel plates using benzene / dichloromethane (1: 2). Heating was stopped and the mixture was cooled to room temperature. Then the bulk of the reaction mixture was filtered off and the remaining material was removed by column chromatography using a mixture of CH_2Cl_2 / Et_2O (3: 1). For the separation of the individual phosphazenes the mixture was re-chromatographed using benzene / dichloromethane (1: 2) as the eluent. Products were recrystallized from benzene containing a few drops of light petroleum (b.p. 40-60 °C). Three main phosphazene fractions were obtained: (**i**) Mono-spiro

derivative (**4**), in trace amount. (**ii**) Dispiro derivative, (**7**): yield 0.35 g (13%). **(iii)** Tris-spiro derivative, N_3P_3[HN-CH_2-CH-(CH_3)-O]$_3$ (**8**): m.p. 114-116 °C, yield 0.70 g (26%). For $C_9H_{21}O_3N_6P_3$: Calculated: C, 30.5; H, 5.93; N, 23.72%; M, 354. Found: C, 30.63; H, 5.98;N, 23.72%; M^+, 354.09.

Table 4. Elemental analysis and the percentage yields of compounds (**3-8**).

Compound	Elemental analysis								Yields			Melting Point
	Calculated				Found				Mole ratios			
	H (%)	C (%)	N (%)	M	H (%)	C (%)	N (%)	$[M^+H]^+$	1:1	1:2	1:3	°C
3	2.08	9.38	14.58	384	2.10	9.35	14.58	385.1	19			140-142
4	2.01	10.34	16.09	348	2.05	10.33	16.09	349.03		15		166-169
5	3.78	17.02	16.55	423	3.80	17.03	16.55	423.09			16	152-155
6	5.20	23.38	18.18	462	5.22	23.37	18.18	463.01	53	38	18	133-134
7	3.99	20.50	19.94	351	4.20	20.61	19.94	351.01		37	12	205-207
8	5.93	30.50	23.72	354	5.98	30.63	23.72	354.09			26	114-116

4. CONCLUSIONS

Compared to geminal and vicinal (*cis*) compounds, the adjacent trans substitution is less dependent on chain length or cyclization, but is more dependent on the ring stain of the phosphazene. Ring strain breaks the plane of the cyclic phosphazene and reduces "pseudo-resonance", which is different from the "exact resonance" in benzene. The distortion of the phosphazene ring relative to the planarity results in a significant amount of energy to the formation energy of the resulting vicinal (trans) substituted phosphazene. This dominates the reaction energy of the heteroatom chain with phosphazene. As expected, the increased chain length reduces the distortion that promotes the reaction. The energy difference between trans and cis vicinal substituted phosphazenes consists of ring strain and the ability of the chain to reach around the ring. Structural molecules of the cyclophosphazenes with the appropriate orientation of the substituents may exhibit thermosensitivity and thermal properties can be fully controlled by altering the components and types of hydrophilic and hydrophobic substituents.

ACKNOWLEDGEMENTS

We are grateful to Bilecik Seyh Edebali University for their financial support(Grant no: BAP 2016-01.BŞEÜ.04-02). We are indebted to the School of Chemistry, Southampton University and Middle East Technical University for obtaining MS, DSC and NMR measurements. Finally, the authors wishes to express gratitude to Prof. Dr. Simon Coles for his helpful suggestions and insight during this research studies.

REFERENCES

[1] S. B. Lee, S. C. Song, J. Il Jin, and Y. S. Sohn, “Thermosensitive cyclotriphosphazenes [9]”, *Journal of the American Chemical Society*, vol. 122, no. 34. pp. 8315–8316, 2000.

[2] G. Peris and S. J. Miller, “Catalysis: Triumph of a chemical underdog”, *Nature*, vol. 452, no. 7186. pp. 415–416, 2008.

[3] H. R. Allcock and S. Kwon, “An IonicallyCross-Linkable Polyphosphazene: Poly[bis(carboxylatephenoxy)phosphazene] and Its Hydrogels and

Membranes", *Macromolecules*, vol. 22, no. 1, pp. 75–79, 1989.

[4] H. R. Allcock and M. L. Turner, "Ring Expansion and Polymerization of Transannular Bridged Cyclotriphosphazenes and Their Spirocyclic Analogues", *Macromolecules*, vol. 26, no. 1, pp. 3–10, 1993.

[5] H. R. Allcock and G. K. Dudley, "Lower critical solubility temperature study of alkyl ether based polyphosphazenes", *Macromolecules*, vol. 29, no. 4, pp. 1313–1319, 1996

[6] D. B. Davies et al., "Chiral configurations of cyclophosphazenes", *J. Am. Chem. Soc.,* vol. 122, no. 50, pp. 12447–12457, 2000.

[7] P. I. Richards and A. Steiner, "Cyclophosphazenes as Nodal Ligands in Coordination Polymers", *Inorg. Chem.,* vol. 43, no. 9, pp. 2810–2817, 2004.

[8] H. R. Allcock and E. C. Kellam, "Incorporation of cyclic phosphazene trimers into saturated and unsaturated ethylene-like polymer backbones", *Macromolecules,* vol. 35, no. 1, pp. 40–47, 2002.

[9] M. Breza, "The electronic structure of planar phosphazene rings", *Polyhedron*, vol. 19, no. 4, pp. 389–397, 2000.

[10] A. B. Chaplin, J. A. Harrison, and P. J. Dyson, "Revisiting the electronic structure of phosphazenes", *Inorg. Chem.*, vol. 44, no. 23, pp. 8407–8417, 2005.

[11] R. C. Haddon, "Theoretical study of the cyclotriphosphazenes importance of phosphorus d orbitals", *Chem. Phys. Lett.*, vol. 120, no. 4–5, pp. 372–374, 1985.

[12] H. R. Allcock, M. L. Turner, and K. B. Visscher, "Synthesis of transannular- and spiro-substituted cyclotriphosphazenes: x-ray crystal structures of 1,1-[$N_3P_3(OCH_2CF_3)_4\{O_2C_{12}H_8\}$], 1,3-[$N3P_3(OCH_2CF_3)_4\{O_2C_{12}H_8\}$], 1,1-[$N_3P_3(OCH_2CF_3)_4\{O_2C_{10}H_6\}$], and 1,3-[$N_3P_3(OCH_2CF_3)_4\}O_2C_{10}H_6\}$]", *Inorg. Chem.*, vol. 31, no. 21, pp. 4354–4364, 1992.

[13] H. R. Allcock, "Recent advances in phosphazene (phosphonitrilic) chemistry", *Chem. Rev.,* vol. 72, no. 4, pp. 315–356, 1972.

[14] H. R. Allcock, J. S. Rutt, and M. Parvez, "Synthesis of Cyclic Phosphazenes with Isothiocyanato, Thiourethane, and Thiourea Side Groups: X-ray Crystal Structure of $N_3P_3(NMe_2)_3(NCS)_3$", *Inorg. Chem.,* vol. 30, no. 8, pp. 1776–1782, 1991.

[15] C. W. Allen, "Regio- and Stereochemical Control in Substitution Reactions of Cyclophosphazenes", *Chem. Rev.,* vol. 91, no. 2, pp. 119–135, 1991.

[16] E. E. Ilter *et al.*, "Phosphorus-nitrogen compounds. 14. Synthesis, stereogenism, and structural investigations of novel N/O spirocyclic phosphazene derivatives", *Inorg. Chem.*, vol. 46, no. 23, pp. 9931–9944, 2007.

[17] K. Muralidharan, P. Venugopalan, and A. J. Elias, "Ansa versus spiro substitution of cyclophosphazenes: Is fluorination essential for ansa to spiro transformation of cyclophosphazenes?", *Inorg. Chem.*, vol. 42, no. 10, pp. 3176–3182, 2003.

[18] A. J. Elias, B. Twamley, and J. M. Shreeve, "Syntheses and Experimental Studies on the Relative Stabilities of Spiro, Ansa , and Bridged Derivatives of Cyclic Tetrameric Fluorophosphazene", *Inorg. Chem.*, pp. 2120–2126, 2001.

[19] ChemicalComputingGroupInc., "Molecular Operating Environment (MOE)", *Sci. Comput. Instrum.*, vol. 22, no. 1, p. 32, 2004.

[20] D. J. Lingley, R. A. Shaw, M. Woods, and S. S. Krishnamurthy, "Studies of phosphazenes. part vi. [1] the preparation of the isomeric

tetrachlorobis-isopropylaminocyclotriphosphazatrienes", *Phosphorus Sulfur Relat. Elem.*, vol. 4, no. 3, pp. 379–382, 1978.

[21] S. S. Krishnamurthy, K. Ramachandran, and M. Woods, "Studies of Phosphazenes, Part Xi. Syntheses and Structures of Bis(Primary Amino)Hexachlorocyclotetraphosphazenes and Their Dimethylamino Derivatives", *Phosphorus Sulfur Relat. Elem.*, vol. 9, no. 3, pp. 323–328, 1981.

[22] S. Beşli *et al.*, "Crystallographic proof of double Walden inversion in nucleophilic substitution reactions of macrocyclic cyclotriphosphazene derivatives", *Eur. J. Inorg. Chem.*, no. 5, pp. 959–966, 2005.

[23] S. Beşli, S. J. Coles, D. B. Davies, M. B. Hursthouse, A. Kiliç, and R. a Shaw, "A spiro to ansa rearrangement in cyclotriphosphazene derivatives.", *Dalton Trans.*, no. 26, pp. 2792–2801, 2007.

[24] D. Davarci, S. Beşli, and F. Yuksel, "Reactions of cyclotriphosphazene with 1,6-diaminohexane and 1,8-diaminooctane: Mono-ansa, double- and triple-bridged derivatives", *Polyhedron*, vol. 68, pp. 10–16, 2014.

[25] S. Beşli, S. J. Coles, D. Davarci, D. B. Davies, and F. Yuksel, "Effect of chain length on the formation of intramolecular and intermolecular products: Reaction of diols with cyclotriphosphazene", *Polyhedron*, vol. 30, no. 2, pp. 329–339, 2011.

[26] K. K. Jin, U. S. Toti, R. Song, and S. S. Youn, "A macromolecular prodrug of doxorubicin conjugated to a biodegradable cyclotriphosphazene bearing a tetrapeptide", *Bioorganic Med. Chem. Lett.,* vol. 15, no. 15, pp. 3576–3579, 2005.

[27] Y. J. Jun *et al.*, "Thermoresponsive micelles from oligopeptide-grafted cyclotriphosphazenes", *Angew. Chemie - Int. Ed.*, vol. 45, no. 37, pp. 6173–6176, 2006.

[28] P. Castera *et al.*, "An answer to the SPIRO versus ANSA dilemma in cyclophosphazenes. Part VII. Neither SPIRO nor ANSA: the BINOdicyclotriphosphazenes, $N_3P_3Cl_5$ $[HN(CH_2)_nNH]Cl_5P_3N_3$", *Inorganica Chim. Acta*, vol. 108, no. 1, pp. 29–33, 1985.

[29] X. Q. Sournies, F., Labarre, J. F., Spreafico, F., Filippeschi, S., & Jin, "Atempts at the production of more selective antitumourals part ii. The antineoplastic activity of cyclophosphazenes linked to spermine, *Bioorganic Med. Chem. Lett.* vol. 147, pp. 161–173, 1986.

[30] H. R. Allcock, U. Diefenbach, and S. R. Pucher, "New Mono- and Trispirocyclotriphosphazenes from the Reactions of (NPCl2)3 with Aromatic Ortho Dinucleophiles", *Inorg. Chem.*, vol. 33, no. 14, pp. 3091–3095, 1994.

[31] K. Brandt et al., "Host-guest complex dependent regioselectivity in substitution reactions of chlorocyclotriphosphazene-containing PNP-crowns with alkylenediamines", *J. Am. Chem. Soc.,* vol. 119, no. 5, pp. 1143–1144, 1997.

[32] (a) El Murr, N.; Lahana, R.; Labarre, J. F.; Declercq, J. P., "Phosphorus-Nitrogen compounds. Spectroscopic investigation of cyclophosphazenes" *J Mol Struct*, 117, 73-85, 1984.

(b) J. F. Labarre,. "Spectroscopic investigation of cyclophosphazenes", *Top Curr. Chem.*, 129, 173–230, 1985.

[33] (a) R. A. Shaw, "The Phosphazenes–Structural Parameters and Their Relationships To Physical and Chemical Properties", *Phosphorous Sulfur Relat. Elem*., vol. 28, no. 1–2, pp. 99–128, 1986. (b) R. A. Shaw, "The reactions of phosphazenes with difunctional and polyfunctional

nucleophilic reagents, "*Phosphorus Sulfur and Silicon and the Related Elements*, vol. 45, no. 1-2, pp, 103-136, 1989.

[34] H. Alkubaisi, H. G. Parkes, and R. A. Shaw, "Phosphorus-nitrogen compounds. Part 58. The reactions of hexachlorocyclotriphosphazatriene with ethane-, 1,3-propane- and 1,4-butane-diols. Spiro, ansa, bridged and dangling derivatives and their 31P and 1H nuclear magnetic resonance spectra", *Heterocycles,* vol. 28, no. 1, pp. 347–358, 1989.

[35] I. Porwolik-Czomperlik, K. Brandt, T. A. Clayton, D. B. Davies, R. J. Eaton, and R. A. Shaw, "Diastereoisomeric singly bridged cyclophosphazene-macrocyclic compounds", *Inorg. Chem.*, vol. 41, no. 19, pp. 4944–4951, 2002.

[36] S. Ture, "Phosphorus-nitrogen compounds: Reinvestigation of the reactions of hexachlorocyclo-triphosphazene with 1,4-butane- and 1,6-hexane-diols—NMR studies of the products", *Phosphorous Sulfur Relat. Elem*., vol.191, no. 8, pp. 1174 -1182, 2016.

[37] C. Plato and A. R. Glasgow, "Differential Scanning Calorimetry as a General Method for Determining the Purity and Heat of Fusion of High-Purity Organic Chemicals. Application to 95 Compounds", *Anal. Chem.*, vol. 41, no. 2, pp. 330–336, 1969.

[38] R. B. Cassel and R. Behme, "A DSC method to determine the relative stability of pharmaceutical polymorphs", *Am. Lab.*, vol. 36, no. 16, pp. 0–2, 2004.

[39] G. Knothe and R. O. Dunn, "A Comprehensive Evaluation of the Melting Points of Fatty Acids and Esters Determined by Differential Scanning Calorimetry", *J Am Oil Chem Soc*, vol. 86, pp. 843–856, 2009.

[40] Particle Analytical, "Differential Scanning Calorimetry (DSC) theory." [Online]. Available: *http://particle.dk/methods-analytical-laboratory/dsc-differential-scanning-calorimetry-2/dsc-theory/.* [Accessed: 16-Nov-2017].

[41] R. Gurbanov and F. Yıldız, "Molecular profile of oral probiotic bacteria to be used with functional foods", *J. Food Heal. Sci.*, vol. 3, pp. 117–131, 2017.