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NMR and DSC studies on the reactions of pentanedioxy spiro-ansa cyclochlorotriphosphazene and pentanedioxy triple-bridged cylochlorotriphosphazene with monofunctional nucleophiles

Rafig Gurbanov[1]*[2], Murat Tuna[3], Sedat Türe[4]

Abstract

In this study, the reactions of 2-(2-hydroxyethyl) thiophene (**2**) and benzyl alcohol (**3**) with pentanedioxycyclochlorotriphosphazene (**1**) and pentanedioxy triple-bridged cylochlorotriphosphazene (**6**) were studied. The novel cyclotriphosphazene compounds: two di-substituted spiro-ansa, $N_3P_3[O(CH_2)_5O]$-$(C_6H_7OS)]_2$ (**4**) and $N_3P_3[O(CH_2)_5O$-$(C_6H_5CH_2O)]_2$ (**5**); and two fully substituted triple-bridged, $N_3P_3[O(CH_2)_5O]_3$-$(C_6H_7OS)_6N_3P_3$ (**7**) and $N_3P_3[O(CH_2)_5O]_3$-$(C_6H_5CH_2O)_6N_3P_3$ (**8**) derivatives were formed in THF solvent by using NaH base at ambient conditions. Because of their variety of applications, there is a great deal of interest in the preparation of aromatic macrocyclic derivatives of cyclophosphazenes. The main purpose of these studies is to develop bioactive cyclophosphazene derivatives in the search for new effective drug candidates for the treatment of various diseases, in particular, anticancer and antimicrobials. The synthesized compounds (**4, 5, 7, 8**) were defined using analytical techniques namely Element analysis, TLC/MS system, and NMR spectroscopy. Thermal stabilities, crystal purity, and recrystallization properties and corresponding enthalpies of synthesized derivatives were analyzed in the course of heating and cooling cycles of DSC.

Keywords: Cyclophosphazene, spiro-ansa compounds, triple-bridged compounds, monofunctional nucleophilic reagents, Nuclear magnetic resonance spectroscopy, Differential scanning calorimetry

1. INTRODUCTION

Cyclic phosphazene compounds demonstrate unique thermal features which are composed of interspersing phosphorus and nitrogen atoms with two substituents attached to the phosphorus atoms [1]. Alongside, cyclotriphosphazene-based materials are of special interest not only because of their stable chemical properties but also due to their flame-retardant features [1]. Due to these properties, there are military programs carrying out basic research on the synthesis and properties of polyphosphazenes and phosphazene fluids for the army, navy, other governmental, and commercial applications [2].

The biological activities of phosphazene derivatives are also at the target of current research due to their medicinal applications in the therapy of microbial, fungal and oncological diseases [3]–[7]. In this, special attention should be again given to cyclophosphazene ring carrying various groups of atoms, since they demonstrate antitumor features [8], [9]. The cytotoxicity of cyclotriphosphazenes against blood, lung, cervix, larynx, colon, bladder, prostate, and breast cancer cell lines have been shown in many studies [9]–[13].

Valuable molecular information on different cyclotriphosphazene derivatives can be extracted using thermo-analytical and spectroscopic

characterization techniques [14]–[19]. In brief, DSC presents quantitative and qualitative information about endothermic and exothermic chemical processes, by directly measuring the melting behavior of compound [14], [20], [21]. On the other hand, spectroscopic techniques yield a spectrum representing the unique molecular fingerprint of any substance [22].

The hexachlorocyclophosphazatrienes (**1**) reacting with functional substitutive atoms are of special interest [23]–[32]. In this, the diols are seemed to be the most important [13], [27], [33]–[38], in which spiro, ansa, linear, and bridged chain molecules were identified. The previous studies have shown the heat-induced conversion of bridged-chain fluorophosphazine into a spiro form along with the catalyst-induced remodeling of eight-membered ansa derivatives into six-membered spiro isomers [23], [39], [40]. The mentioned findings are in agreement with the evidence pronouncing the thermodynamic stability of spiro compounds over bridged-chains and/ or ansa ones [41], [42].

The aim of this work was to probe the arrangement profiles of spiro-ansa replaced cyclophosphazene compounds (**1**) with monofunctional nucleophiles. The expansion of the presented work in terms of the antitumor and antimicrobial activities will be executed in the short run.

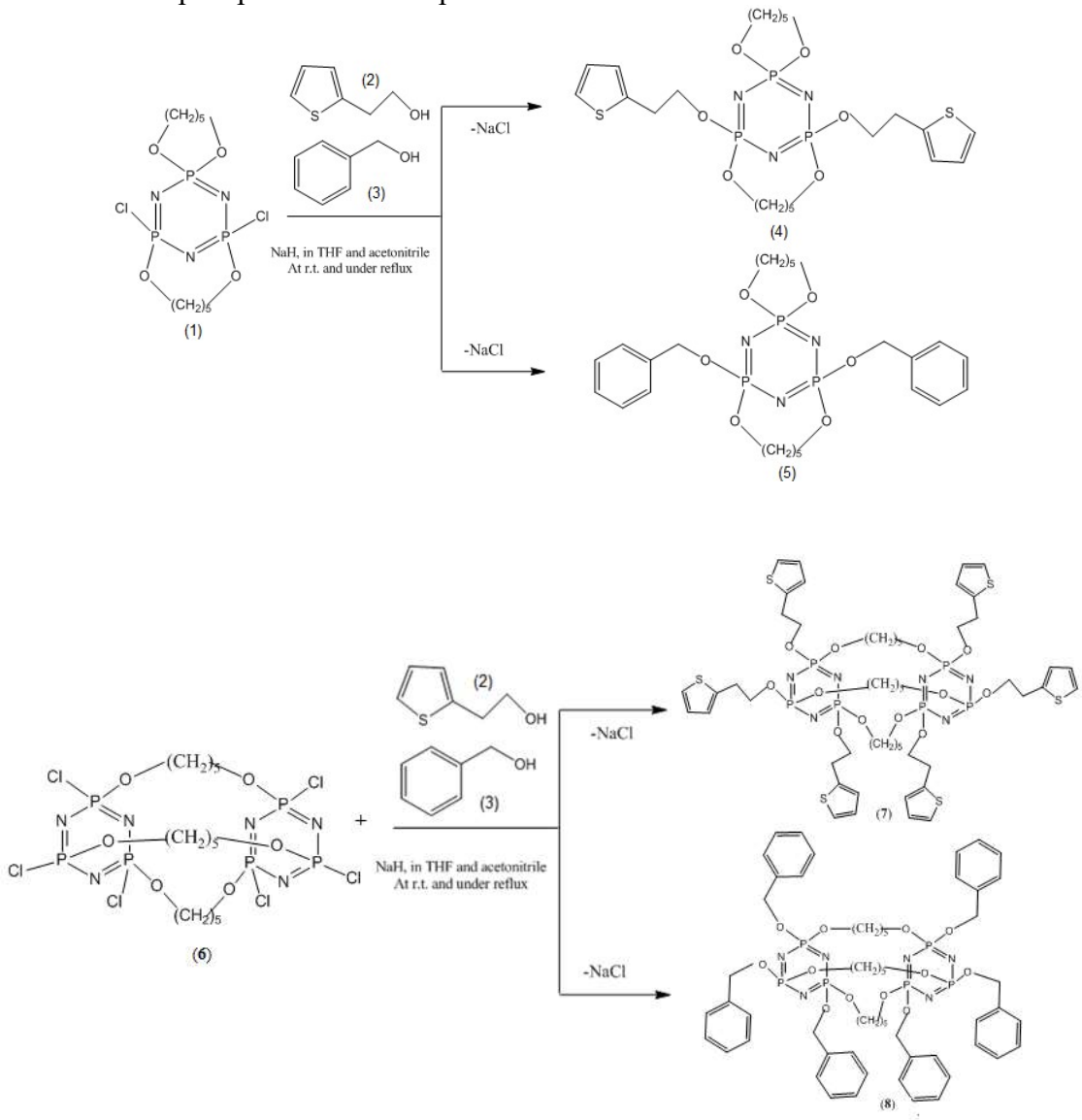

Figure 1. Chemical reaction flowchart for derived products (**4, 5, 7, 8**).

2. EXPERIMENTAL

2.1. Materials

Reagent-grade solvents; THF, dichloromethane, diethyl ether, chloroform, benzene, petroleum (b.p. 40-60^0 C) were obtained from May & Baker Ltd., UK. Deuterated $CDCl_3$ (using as an NMR lock) for NMR spectroscopy, benzyl alcohol, 2-thiophenethanol, 1,4-butanediol, and 1,5-pentanediol were obtained from Aldrich Chem. Co. Ltd. Chemicals leftover from our previous works: $NaBH_4$/NaH and hexachlorocyclotriphosphazatriene were obtained from Sigma & Aldrich Chem. Co. Ltd. TLC plates and silica gel (60, 0.063–0.200 mm), for chromatographic applications, were acquired from Merck Merck & Co., Inc., Solvents were dried by known basic methods. Dichloromethane and THF were distilled on a sodium-potassium alloy under a dry argon atmosphere. Hexachlorocyclotriphosphazene was purified by fractional crystallization technique from n-hexane.

2.2. Methods

Reactions were followed up by using Kieselgel 60^0 254 with pre-coated TLC plates and sprayed with Ninhydrin (0,5% w/v) in a butanol solution and elaborated about at 130^0 C.

The products were separated by column chromatography using Kieselgel 60 (Merck 60, 0.063–0.200 mm). Melting points were established with a Hot Stage Microscopy connected to an FP 800 central processor attached to a polarizing microscope. Elemental analyses were achieved by using a Thermo Finnigan Flash 1112 Instrument. Mass spectra were recorded using a TLC/MS Advion Mass Spectrometer.

^{1}H NMR spectra were recorded using a Varian INOVA 500 MHz and a Bruker DRX spectrometer operating at 499 MHz. and at 500 MHz. respectively. Measurements were performed by using a $CDCl_3$ lock, TMS was used as an internal reference in sample concentrations of 15-20 mg cm^3. ^{31}P NMR spectra were performed by using a Bruker AVII and AVIIIHD 400 MHz spectrometer, operating at 161.97 MHz. (measurements were carried out in $CDCl_3$ using 85%, H_3PO_4 as an external reference.

For thermal analysis, Differential Scanning Calorimetry (DSC) was used according to our previous study [43]. The compounds in crystal form were placed in special DSC containers (aluminum hermetic pans) and sealed using Sample Encapsulating Press. The experiment was conducted through heating and cooling cycles, in which the specimen was heated from -30 °C to 250 °C and then cooled down with a ramp of 5 °C/min. The melting and crystallization events were identified on the basis of corresponding peak locations. The integrated peak area was divided linearly to the specimen mass to determine the enthalpy changes (ΔH° J/g) were calculated by dividing the integrating peak area to the sample weight.

Experimental details together with product types and the relative yields are summarized in Table 1, whereas the NMR data may be found in Tables 2 and 3. The calorimetric characterization of compounds (**4, 5, 7, and 8**) is illustrated in Table 4.

2.3. Synthesis

(**a**) The reactions of pentanedioxycyclochlorotriphosphazene (**1**) with 2-Thiophen ethanol (**2**): Two equivalents of **2**, in excess of NaH, in THF at room temperature: Pentanedioxycyclochlorotriphosphazene (**1**, 0.5 g, 1.2 mmol) was dissolved in dry chloroform (30 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. NaH (0.115 g, 4.8 mmol) was dissolved in chloroform (10 mL) and the reaction mixture was stirred for half an hour on a magnetic stirrer. After, 2-Thiophen ethanol (**2**, 0.30 g, 2.4 mmol) was dissolved in dry chloroform (20 mL) added dropwise into the stirred solution under an argon atmosphere. Then the reaction mixture was kept stirring for about 48 h at room temperature.

The reaction was followed by TLC silica gel plates using dichloromethane-diethyl ether (5:1) as the eluent for completion of the reaction. Except in small quantity of starting material (**1**) one spot was observed on TLC, using dichloromethane-diethyl ether (5:1) as the mobile phase. The reaction mixture was filtered to remove the NaCl salts and some other insoluble balky materials. The solvent was removed from

the reaction mixture under reduced pressure and the resulting white-colored solid was subjected to column chromatography using the same solvent system as described above. Di-substituted spiro-ansa, $N_3P_3[O(CH_2)_5O]$-$(C_6H_7OS)]_2$ (**4**) derivative was synthesized and characterized. Yield 0.34 g, 78%, m.p.109 °C. Anal. Calc. for $N_3P_3C_{22}H_{34}O_6S_2$: C, 44.52; H, 5.77; N, 7.08, M, 593.505. Found: C, 44.51; H, 5.80; N, 7.08, M^+, 594.39.

(**b**) The reactions of pentanedioxycyclochlorotriphosphazene (1) with Benzyl alcohol (**2**). Two equivalents of **3**, in excess of NaH, in THF at room temperature: Pentanedioxycyclochlorotriphosphazene (1, 0.5 g, 1.2 mmol) was dissolved in dry chloroform (30 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. NaH (0.115 g, 4.8 mmol) was dissolved in chloroform (10 mL) and the reaction mixture was stirred for half an hour on a magnetic stirrer. After, Benzyl alcohol (**3**, 0.25 g, 2.4 mmol) was dissolved in dry chloroform (20 mL) and added dropwise into the stirred solution under an argon atmosphere. Then the reaction mixture was kept stirring for about 48 h at room temperature.

For completion of the reaction, the reaction was followed by TLC silica gel plates using dichloromethane-diethyl ether (3:1) as the eluent. Except in small quantity of starting material (**1**) one spot was observed on TLC, using dichloromethane-hexane (3:1) as the mobile phase. The reaction mixture was filtered to remove the NaCl salts and some other insoluble balky materials. The solvent was removed from the reaction mixture under reduced pressure and the resulting white-colored solid was subjected to column chromatography using the same solvent system as described above. Except for some glue type insoluble resinous materials, di-substituted spiro-ansa, $N_3P_3[O(CH_2)_5O$-$(C_6H_5CH_2O)]_2$ (**5**) was synthesized and characterized. Yield 0.40 g, 82%, m.p.109 °C. Anal. Calc. for $N_3P_3C_{24}H_{34}O_6$: C, 52.08; H, 6.19; N, 7.59, M, 553.407. Found: C, 53.0; H, 6.23; N, 7.59, M^+, 554.43.

(**c**) The reactions of pentanedioxy triple-bridged cylochlorotriphosphazene (**6**) with 2-Thiophen ethanol (**2**). Six equivalents of **2**, in excess of NaH, in chloroform at room temperature: pentanedioxy triple-bridged cylochlorotriphosphazene (**6**, 0.5 g, 0.6 mmol) was dissolved in dry chloroform (40 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. NaH (0.172 g, 7.2 mmol) was dissolved in 10 mL of the above-mentioned solvent system and the reaction mixture was stirred for half an hour on a magnetic stirrer. After, 2-Thiophen ethanol (**2**, 0.46 g, 3.6 mmol) was dissolved in dry chloroform (20 mL) and added dropwise into the stirred solution under an argon atmosphere. Then the reaction mixture was kept stirring for about 96 h at room temperature. The reaction was followed by TLC silica gel plates using dichloromethane-hexane (2:1) as the eluent. One spot was observed on TLC, using dichloromethane-hexane (2:1) as the mobile phase. The reaction mixture was filtered to remove the NaCl salts and some other insoluble balky materials. The solvent was removed from the reaction mixture under reduced pressure and the resulting white-colored solid was subjected to column chromatography using the same solvent system as described above. The synthesized product was recrystallized from benzene-hexane (1:5) to give white crystals of Hexa-substituted tripel-bridged, $N_3P_3[O(CH_2)_5O]_3$-$(C_6H_7OS)_6N_3P_3$ (**7**) derivative, yield 0.30 g, 71%, m.p. 206 °C. Anal. Calc. for $N_6P_6C_{51}H_{72}O_{12}S_6$: C, 45.73; H, 5.41; N, 6.27, M, 1339.239. Found: C, 45.75; H, 5.46; N, 6.27, M^+, 1340.29.

(**d**) The reactions of hexachlorocyclotriphosphazatriene (1) with Benzyl alcohol (**2**). Six equivalents of **3**, in excess of NaH, in Chloroform at room temperature: Cyclotriphosphazene (**1**, 0.5 g, 0.6 mmol) was dissolved in dry chloroform (40 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. NaH (0.172 g, 7.2 mmol) was dissolved in 10 mL of the above-mentioned solvent system and the reaction mixture was stirred for half an hour on a magnetic stirrer. After, Benzyl alcohol (**3**, 0.38 g, 3.6 mmol) was dissolved in dry chloroform (20 mL) and added dropwise into the stirred solution under an argon atmosphere. Then the reaction mixture was kept stirring for about 96 h at room temperature. The reaction was followed by TLC silica gel

plates using dichloromethane-diethyl ether (3:1) as the eluent for completion of the reaction. Except in small quantity of starting material (**6**) one spot was observed on TLC, using dichloromethane-diethyl ether (3:1) as the mobile phase. The reaction mixture was filtered to remove the NaCl salts and some other insoluble resinous materials. The solvent was removed under reduced pressure and the resulting white-colored solid was subjected to column chromatography using the same solvent system as described above. The product was recrystallized from benzene-hexane (1:6) to give white crystals of Hexa substituted tripel-bridged, $N_3P_3[O(CH_2)_5O]_3$-$(C_6H_5CH_2O)_6N_3P_3$ (**8**) derivative. Yield 0.32 g, 83%, m.p. 208 °C. Anal. Calc. for $N_6P_6C_{57}H_{72}O_{12}$: C, 48.49; H, 5.14; N, 5.95, M, 1411.785. Found: C, 48.51; H, 5.17; N, 5.95, M^+, 1412.81.

Table 1. Elemental analysis and the percentage yields of compounds (**4, 5, 7, 8**).

Classification (%)	**Calculated**				**Found**			
Compound	H (%)	C (%)	N (%)	M	H (%)	C (%)	N (%)	$[M^+H]^+$
4 (78%)	5.77	44.52	7.08	593.505	5.80	44.51	7.08	594.39
5 (82%)	6.19	52.08	7.59	553.407	6.23	53.00	7.59	554.43
7 (71%)	5.41	45.73	6.27	1339.239	5.46	45.75	6.27	1340.29
8 (83%)	5.14	48.49	5.95	1411.785	5.17	48.51	5.95	1412.81

3. RESULTS AND DISCUSSION

The interaction between pentanedioxycyclochlorotriphosphazene (**1**) and pentanedioxy triple-bridged cylochlorotriphosphazene (**6**) and 2-(2-hydroxyethyl) thiophene (**2**) and benzyl alcohol (**3**) gave rise to 4 novel synthesized products: two di-substituted spiro-ansa, $N_3P_3[O(CH_2)_5O]$-$(C_6H_7OS)]_2$ (**4**, 78%), and $N_3P_3[O(CH_2)_5O$-$(C_6H_5CH_2O)]_2$ (**5**, 82%); and two hexa-substituted tripel-bridged, $N_3P_3[O(CH_2)_5O]_3$-$(C_6H_7OS)_6N_3P_3$ (**7**, 71%), and $N_3P_3[O(CH_2)_5O]_3$-$(C_6H_5CH_2O)_6N_3P_3$ (**8**, 83%) derivatives.

Analytical techniques namely, Elemental analysis, TLC-MS, ^1H, and ^{31}P NMR spectroscopy were utilized for the characterization of synthesized derivatives. Thermal properties, such as thermal stabilities, crystal purity, and crystallization features were determined using DSC technique. All of the synthesized compounds are thermally stable and water-soluble. The structures of the derived compounds (**4, 5, 7, 8**) are shown in Figure 1.

The spiro-ansa compounds (**4**) and (**5**) replaced with 2-thiophene ethanol and benzyl alcohol, respectively displayed A_2X type NMR spectra. Because of the ≡P spiro and ≡P(OR)OR groups, the ^{31}P NMR spectrum of spiro-ansa derivative permitted characterization of the lines, where each group divide into further lines. Comparison of the results with the previous findings on spiro-ansa structures [44], provided clear identification of the derivatives. The yield proportions of the substances are discussed above.

The spectra of the triple-bridged derivatives (**7** and **8**), were found as spin A_3 type emerging from equal or resembling surroundings at the end of bridges among phosphorus nuclei. One single line is identified for these derivatives, due to the similar nature of the bounded groups and chemically and magnetically identical surroundings of ≡P(OR)OR groups.

The spectra of compound **4**, $N_3P_3[O(CH_2)_5O]$-$(C_6H_7OS)]_2$ is illustrated in Figure 2. Whereas, Table 2 shows the selected criteria (chemical shifts and coupling constants).

Table 2. ^{31}P NMR spectral data from the synthesized derivatives (**4, 5, 7, 8**)[a]

Compound	δP(OR)$_2$[b]	δP(OR)OR[b]	^2J[P(OR)$_2$-P(OR)OR][c]	
(**1**)				[44]
(**6**)				[44]
(**4**)	17.73	25.11	63.72	
(**5**)	18.40	24.60	64.13	
(**7**)		17.73		
(**8**)		17.90		

[a]In $CDCl_3$, relative to 85% H_3PO_4 standard at 161.97 MHz
[b]In ppm
[c]In Hz

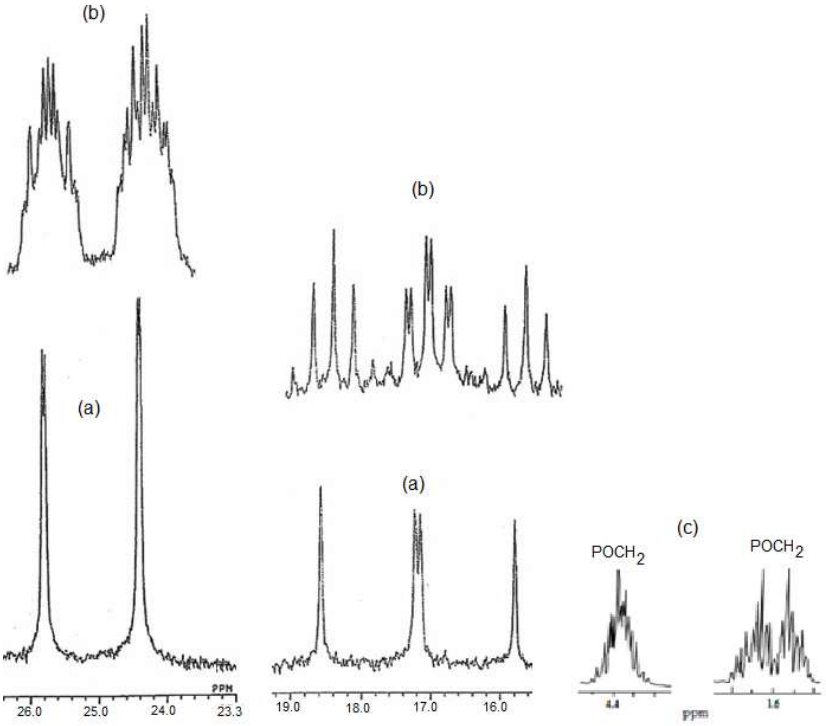

Figure 2. ^{31}P NMR proton decoupled (a) and coupled (b) spectra of compound (**4**): in $CDCl_3$, at 161.97 MHz, ambient temperature and relative to 85% H_3PO_4; and (c) its ^{1}H NMR spectrum, at ambient temperature, in $CDCl_3$ (TMS as internal reference) and at 399.95 MHz.

The α- and β- or aromatic ring protons of methylene may appear in various chemical surroundings depending on their positions relative to the oxygen atoms and aromatic rings. Because of the disproportional locations of the protons, the ^{1}H NMR spectra of compounds **4**, **5**, **7** and **8** demonstrate intricate spectra. The findings are compatible with earlier reported 2-thiophene and benzyl alcohol-substituted ansa derivatives [34]. The interplay between the interchangeable protons in particular groups causes the formation of multiplets specifically AB quartet. This pattern will be future cleaved/ segmented by the adjacent protons and phosphorus nuclei causing the formation of the intricate NMR spectrum. Consequently, different overlapping multiplets may be seen for the protons of $POCH_2$ and the $POCCH_2$. ^{1}H NMR spectral measurements are shown in Table 3 and ^{1}H NMR spectra of α- and β methylene protons of compound **4** are shown in Figure 2.

Table 3. ^{1}H NMR spectral data from the synthesized derivatives (**4, 5, 7, 8**)[a]

Compound		δPOC$\underline{H}_2$[b]	δPCC$\underline{H}_2$[b]		
δPCCC$\underline{H}_2$[b]		^{3}J($\underline{PH}$)[c]			
(**1**)		[44]			
(**6**)		[44]			
(**4**)	Spiro	4.44/4.35	1.75/1.68	1.34	10.90
	Ansa	4.26/4.17	1.59/1.54	1.27	10.60
(**5**)	Spiro	4.38/4.30	1.74/1.67	1.34	13.05
	Ansa	4.25/4.13	1.62/1.55	1.26	13.70
(**7**)		4.29	1.66	1.20	13.01
(**8**)		4.26	1.63	1.23	13.55

δBenzyl-H: 7.30-7.45
δThiophen-H: 6.75-6.90

[a]In $CDCl_3$ (with reference to internal TMS) at 399.95 MHz.
[b]In ppm. [c]In Hz.

In this study, thermal characteristics, i.e. thermal stabilities, crystal purity and recrystallization properties of synthesized derivatives were analyzed in the course of heating and cooling cycles. DSC thermograms have been shown in Figures 3-4. The obtained thermal peaks were numbered and thermal properties of these peaks were characterized in Table 4. Figure 3A and 3B represent the thermograms of compounds **4** and **5**, respectively. For both compounds, two endothermic (1 and 2) and one exothermic peak (1) were found during the heating and cooling cycles, respectively. In the course of heating cycles, endothermic peaks at 109 °C (compound 4 ΔH° 079, compound 5 ΔH° 054) position was assigned to the main melting process for both compounds. Additional melting events happened in these compounds at 205 °C (ΔH° 001) and 231 °C (ΔH° 002) positions, respectively. Recrystallization events occurred at 65 °C (ΔH° 008) and 85 °C (ΔH° 042) positions during the cooling cycles in both compounds (Figure 3A and 3B, Table 4).

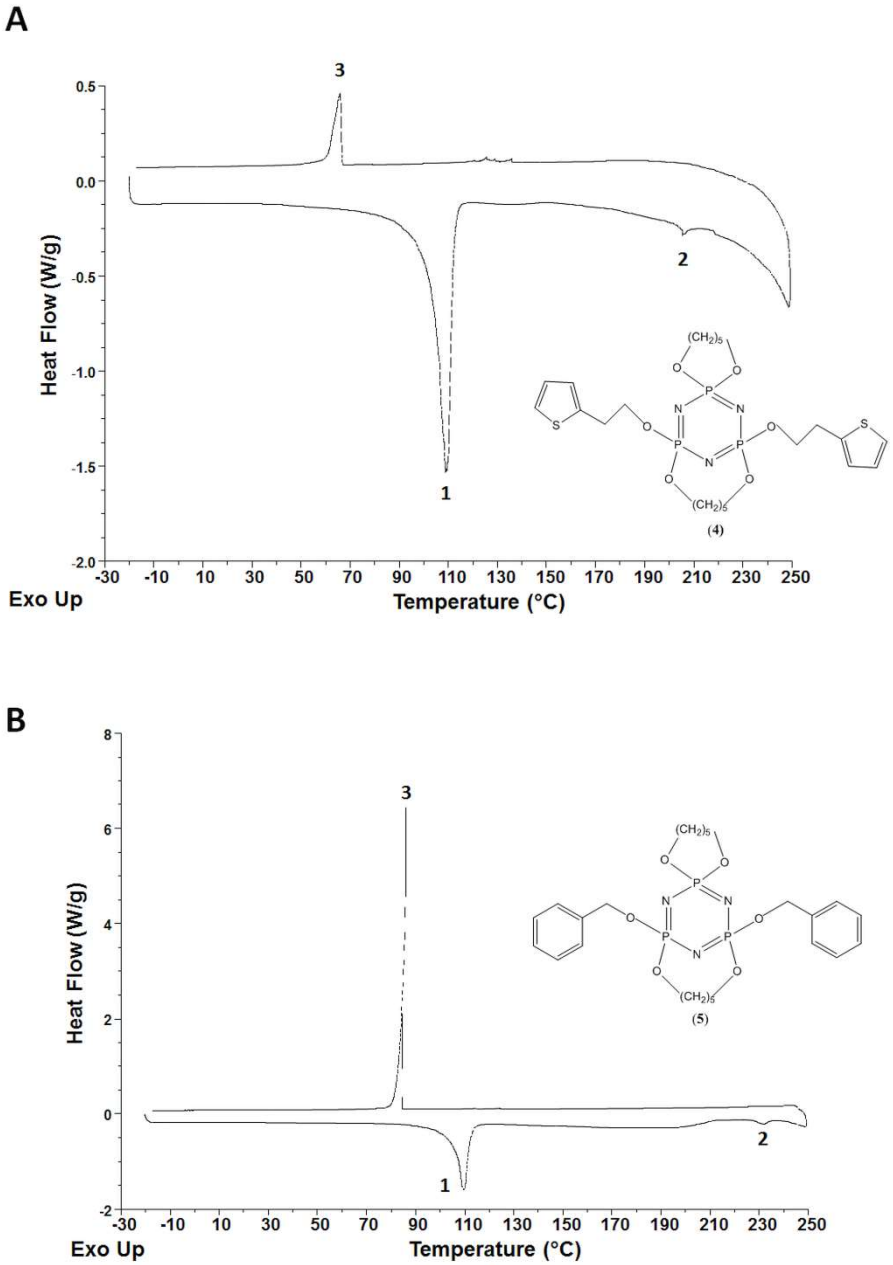

Figure 3. DSC thermograms of compounds **4** (A) and **5** (B).

Thermograms for compounds **7** and **8** have been shown in Figure 4A and 4B, respectively. During the heating cycle, compound **7** gave totally three peaks at positions of 161 °C (ΔH° 097), 206 °C (ΔH° 147), and 213 °C (ΔH° 050), respectively. In this figure, the first exothermic peak (1) was due to the crystallization event, while the other two endothermic peaks (2 and 3) were identified as an indicator of melting events. No thermal event was encountered during the cooling cycle (Figure 4A, Table 4). In total, three peaks appeared again for compound **8**. These peaks were measured in the course of heating and cooling cycle at positions of 195 °C (ΔH° 009), 208 °C (ΔH° 018), and 246 °C (ΔH° 037), respectively. Over the heating cycle, exothermic peak (1) has arisen as a result of crystallization event, while the endothermic one (2) was assigned to the main melting process. Throughout the cooling cycle, a single exothermic peak (3) was assigned to the recrystallization event (Figure 4B, Table 4).

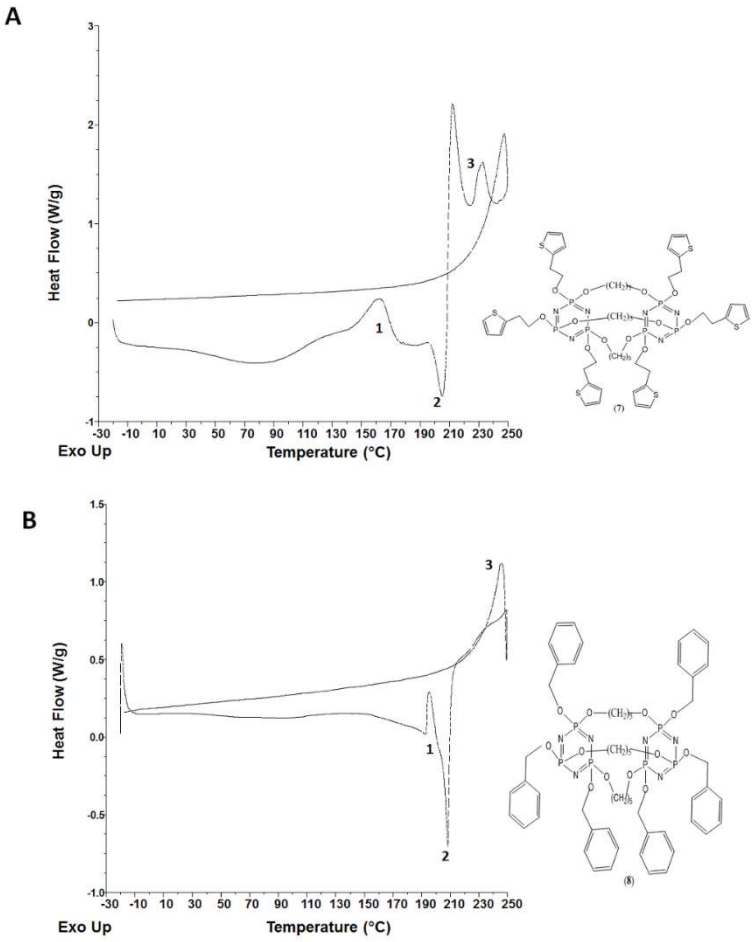

Figure 4. DSC thermograms of compounds **7** (A) and **8** (B).

Table 4. Calorimetric characterization of compounds (**4, 5, 7, 8**).

Compound	Cycle	# Peak	Peak character	Peaks (°C)	Enthalpy ΔH° (J/g)	Phase Transitions
(4)	Heating	1	Endothermic	109	079	Main melting p.
		2	Endothermic	205	001	Melting p.
	Cooling	3	Exothermic	065	008	Recrystallization p.
(5)	Heating	1	Endothermic	109	054	Main melting p.
		2	Endothermic	231	002	Melting p.
	Cooling	3	Exothermic	085	042	Recrystallization p.
(7)	Heating	1	Exothermic	161	097	Crystallization p.
		2	Endothermic	206	147	Main melting p.
		3	Endothermic	213	050	Melting p.
(8)	Heating	1	Exothermic	195	009	Crystallization p.
		2	Endothermic	208	018	Main melting p.
	Cooling	3	Exothermic	246	037	Recrystallization p.

4. CONCLUSIONS

All 2-thiophene ethanol and benzyl alcohol-replaced spiro-ansa and triple-bridged cyclotriphosphazene derivatives were purified using column chromatography and illuminated by several independent analytical tools. Thermal properties such as crystallization and melting behavior and corresponding enthalpies were identified by the DSC technique. Neutral 2-thiophene ethanol and benzyl alcohol with anionic reagents (NaH or $NaBH_4$) were used as the hydrogen chloride acceptor, and the reaction in THF and at room temperature was accomplished. The relatively large and virtually identical yields of spiro-ansa and triple-bridged entities were noted. The novel synthesized cyclophosphazene derivatives (**4, 5, 7, 8**) with aromatic reagents is very important due to their antimicrobial and antitumor activities.

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