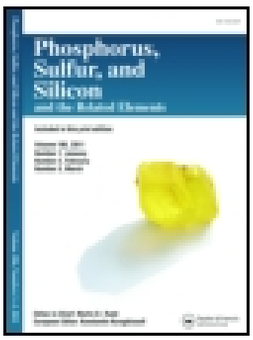

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Synthesis, characterization, and photophysical properties of paraben substituted cyclotriphosphazenes with hydrophilic side groups

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ABSTRACT

In this study, five new paraben substituted cyclotriphosphazene compounds containing hydrophilic glycol groups were successfully synthesized. All synthesized cyclotriphosphazene compounds **1-10** were fully characterized via general spectroscopic techniques such as ^{1}H, ^{31}P NMR and MALDI-TOF mass spectrometry. In addition, the investigations of the UV-vis absorption and fluorescence emission properties of the **1-10** carried out via absorption and fluorescence spectroscopies in different solvents. The absorbance bands of the all synthesized compounds **1-10** were observed at about 230–300 nm in all solvents studied. Furthermore, the highest fluorescence emission intensity of the compounds **1-10** was observed in tetrahydrofuran at about 312 nm and the lowest emission intensity was observed in chloroform. The synthesized molecules can be used as custom designed molecules to investigate the DNA binding properties in automatic biosensor device in our laboratories, since they carry hydrophilic glycol units for water solubility and paraben derivatives for DNA effecting properties.

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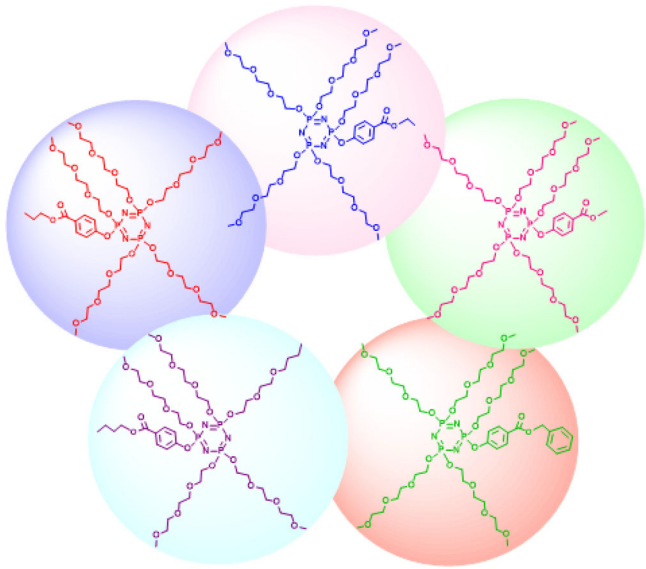
Paraben; cyclotriphosphazene; hydrophilic tails; UV-vis absorption; fluorescence

GRAPHICAL ABSTRACT



1. Introduction

Phosphazenes are an important class of inorganic chemistry. Hexachlorocyclotriphosphazene, trimer, ($N_3P_3Cl_6$), is a member of cyclophosphazene family. As a result of substitution reaction of cyclotriphosphazene with different nucleophilic reagents, cyclotriphosphazene derivatives having a variety features, can be synthesized.[1,2] The versatile chemistry of cyclotriphosphazenes enable designing materials with particular properties.[3,4] In this regard, diverse strategies to constitute rationally designed cyclotriphosphazene systems emerged to develop materials with useful chemical and physical properties.[5] These properties of cyclotriphosphazene derivatives lead to a wide range of application areas of these compounds as well as to differences in the application at the same time. Examples of these applications include such as biomedical materials, liquid crystals, flame retardants, organic light-emitting diodes, photophysical materials, and fluorescence chemosensor.[6–13] In particular, the

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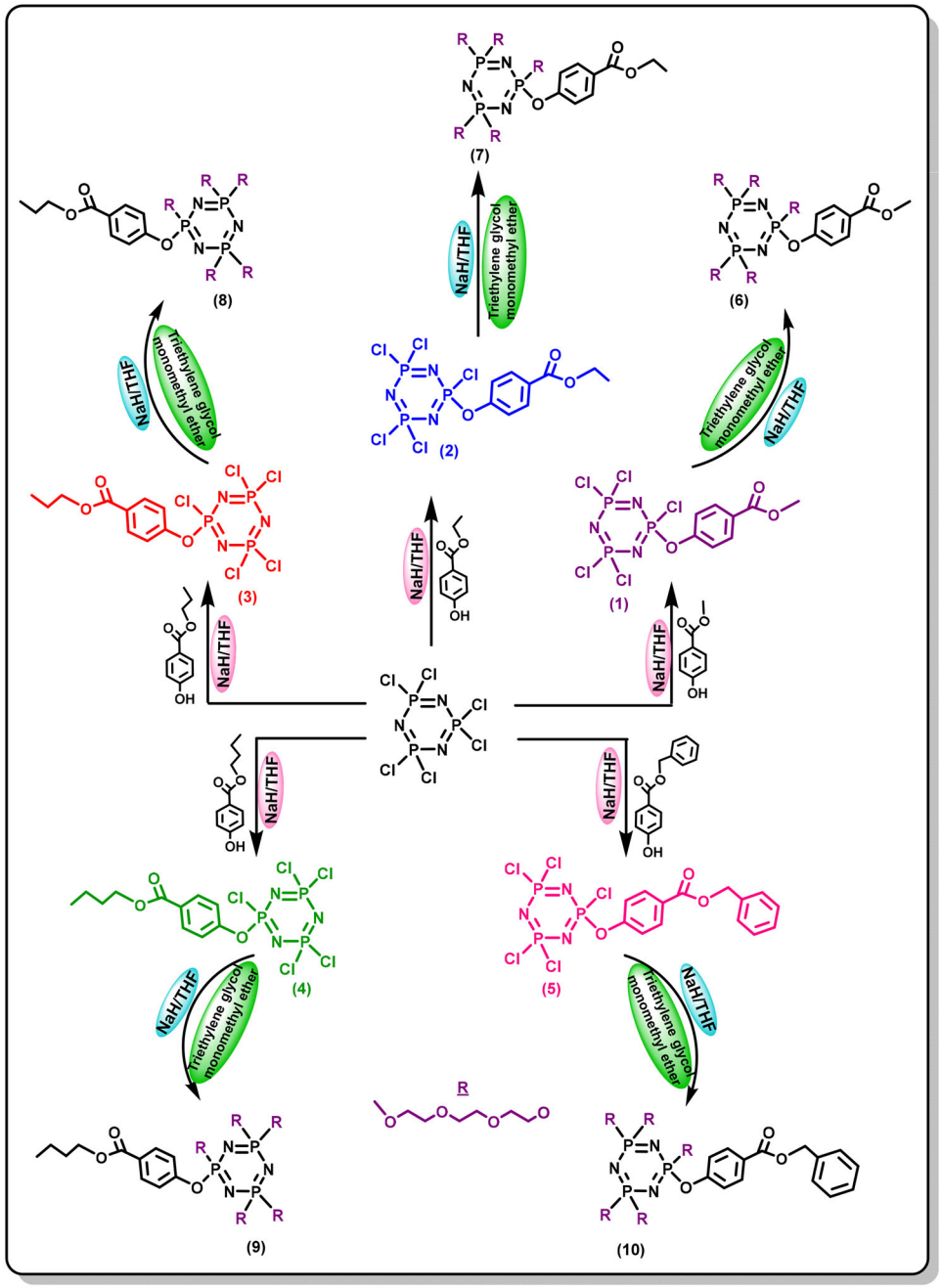

Scheme 1. Synthesis of the cyclotriphosphazene derivatives **1-10**.

biological applications of cyclotriphosphazenes have attracted the attention of researchers in recent years and studies in this area have increased. Especially, organocyclotriphosphazenes were studied as a potential anti-cancer agent.[14–16] The side groups such as spermine, chalcone, and parabens on the cyclotriphosphazene core were reported to maintain cytotoxicity to these potential drug candidates.[17–20]

Parabens are known antimicrobial agents, that have been utilized in numerous daily use products thanks to their broad antimicrobial spectrum.[21–23] Studies also concluded the effect of parabens on DNA which empowered synthesis of novel genotoxic compound.[20,24,25] Furthermore, tailor-made decorated cyclotriphosphazene frameworks with hydrophilic glycol units does provide interaction with water which is valuable for biocompatibility and in applications which needs to stimulate biological environment.[26–29] In previous studies made by our group, paraben derivatives of cyclotriphosphazene and cyclotetraphosphazene were synthesized and their DNA effects were investigated as potential drug candidates.[20,24,25] In biological applications, workability in water or in aqueous environments is an important factor. Therefore, it is very significant for biological and other applications that synthesized compounds to be soluble in these solvents. To expedite hydrophilicity, in the current study paraben derivatives with different side groups and glycol moieties were introduced in a single molecule (Scheme 1). The paraben cyclotriphosphazene compounds

Table 1. ^{31}P $\{^{1}H\}$ NMR parameters for compounds **1-10** in $CDCl_3$.

	$\delta(^{31}P$ NMR) [ppm]					^{2}J(PP) [Hz]		
Comp.	P (R_1Cl)	$P(R_2)_2$	$P(Cl)_2$	$P(R_1)(R_2)$	Spin system	$^{2}J_{AX}$	$^{2}J_{AB}$	MS (MALDI-TOF)
1	11.95	–	22.50	–	A_2X	61.89	–	464.46 $[M+H]^+$
2	11.93	–	22.49	–	A_2X	61.89	–	478.81 $[M+H]^+$
3	11.88	–	22.51	–	A_2X	62.06	–	491.50 $[M]^+$
4	11.87	–	22.51	–	A_2X	62.0	–	505.49 $[M]^+$
5	11.89	–	22.52	–	A_2X	62.03	–	539.31 $[M]^+$
6	–	17.30	–	14.35	A_2B	–	85.54	1102.46 $[M]^+$
7	–	17.27	–	14.27	A_2B	–	85.33	1085.54 $[M\text{-}C_2H_5]^+$
8	–	17.29	–	14.07	A_2B	–	85.28	1086.95 $[M\text{-}C_3H_7]^+$
9	–	17.25	–	14.37	A_2B	–	85.41	1144.37 $[M]^+$
10	–	17.24	–	14.16	A_2B	–	85.21	1085.58 $[M\text{-}C_7H_9]^+$

R_1: paraben, R_2: hydrophilic side groups.

with hydrophilic side groups were characterized by mass spectrometry (MALDI-TOF) and ^{1}H and ^{31}P NMR spectroscopy. In addition, UV-vis absorption and fluorescence emission behaviors of the compounds **1-10** were investigated in seven different solvent systems and the results obtained were compared. The potential biological activity properties of the parabens and the water solubility enhancement properties of the hydrophilic groups are known. In the next phase of the study, the DNA binding properties of the synthesized paraben-cyclotriphosphazene derivatives carrying hydrophilic group will be investigated with automatic biosensor device in our laboratories.

2. Result and discussion

2.1. Synthesis and NMR characterization of parabene substituted cyclotriphosphazenes

In the present work, paraben substituted cyclotriphosphazene compounds **1-5** and paraben functionalized cyclotriphosphazenes with hydrophilic side group **6-10** were successfully synthesized and their synthesis strategies were summarized in Scheme 1. Compounds **1** and **2** were synthesized according to the literature where compounds **3-5** were synthesized first time in this study by employing the literature method. In these frameworks, firstly, reactions of hexachlorocyclotriphosphazene with methylparaben, ethylparaben, propylparaben, butylparaben and benzylparaben were performed in the presence of THF/NaH to obtain compounds **1-5**, respectively. Then, the novel compounds **6-10**, containing hydrophilic side group cyclotriphosphazenes were synthesized from the substitution reaction of mono paraben substituted cyclotriphosphazene compounds **1-5** with triethylene glycol monomethyl ether (Scheme 1). Each of the synthesized compounds **1-10** was characterized by mass (MALDI-TOF), ^{1}H and ^{31}P NMR spectroscopy. The structure analysis data (mass, ^{1}H and ^{31}P NMR results) of the compounds were presented in the experimental section. Also, the ^{31}P NMR chemical shifts and phosphorus–phosphorus coupling constants and mass spectrum values of synthesized compounds **1-10** were summarized in Table 1. The proton decoupled ^{31}P NMR spectrum of compounds **1-5** were observed as A_2X spin system due to the different environments of the two different phosphorus nuclei on the cyclotriphosphazene ring. As an example, the proton decoupled ^{31}P NMR spectrum of compounds **3** and **8** were shown in Figure 1a,b, respectively. The signals include one triplet for the -PCl_2 groups in the chemical shift range of $\delta = 11.87$–11.65 ppm and a doublet for the –$P(R_1Cl)$ (R_1 = paraben) groups in the range of $\delta = 22.49$–22.52 ppm (phosphorus-phosphorus coupling constants are average of about $^{2}J_{PP} = 62$ Hz, Table 1). The proton decoupled ^{31}P NMR spectrum of compounds **6-10** exhibited A_2B spin systems, as expected since the two different phosphorus nuclei of the cyclotriphosphazene ring have close chemical shifts (Table 1). For example for compound **8** the signals were seen as one doublet of doublets for the -$P(R_2)_2$ (R_2 = hydrophilic side groups) group ($\delta = 17.29$ ppm, $^{2}J_{PP} = 85.28$ Hz) and one doublet for the -$P(R_1)(R_2)$ (R_1 = Paraben, R_2 = hydrophilic side groups) group ($\delta = 14.07$ ppm, $^{2}J_{PP} = 85.28$ Hz) in the spectrum, respectively (Figure 1b). Besides, when the proton coupled ^{31}P NMR spectrum of compound **8** was examined, the $\delta = 17.29$ ppm and $\delta = 14.07$ ppm signals were seen as split/broad multiplet peaks due to the -CH_2 protons (Figure 1c).

In addition, the ^{1}H NMR chemical shifts and coupling constants of all protons in the experimental section confirmed the structures of synthesized compounds **1-10**. While the aromatic protons for the paraben substituted cyclotriphosphazene compounds **1-5** and paraben derivative cyclotriphosphazene compounds containing hydrophilic side groups **6-10** were observed between 8.16–7.14 ppm, aliphatic protons of paraben groups were observed between 5.39–0.81 ppm. In cyclotriphosphazene compounds containing hydrophilic side groups **6-10**, in addition to these paraben aliphatic protons, the -OCH_3 and -OCH_2 protons were observed as single peaks at approximately 3.35 ppm and as multiple peaks in the range of 3.80-3.40 ppm, respectively (e.g., Figure 2a for comp. 3 and 2b for comp. 8).

2.2. Ground state electronic absorption and fluorescence properties

The photophysical properties paraben substituted cyclotriphosphazene compounds **1-5** and paraben derivative cyclotriphosphazene compounds containing hydrophilic side groups **6-10** were investigated using UV-vis and fluorescence spectroscopy. The ground state electronic absorption and fluorescence emission behaviors of compounds were evaluated in a variety of solvents such as tetrahydrofuran, acetonitrile, dichloromethane, chloroform, dimethylsulfoxide,

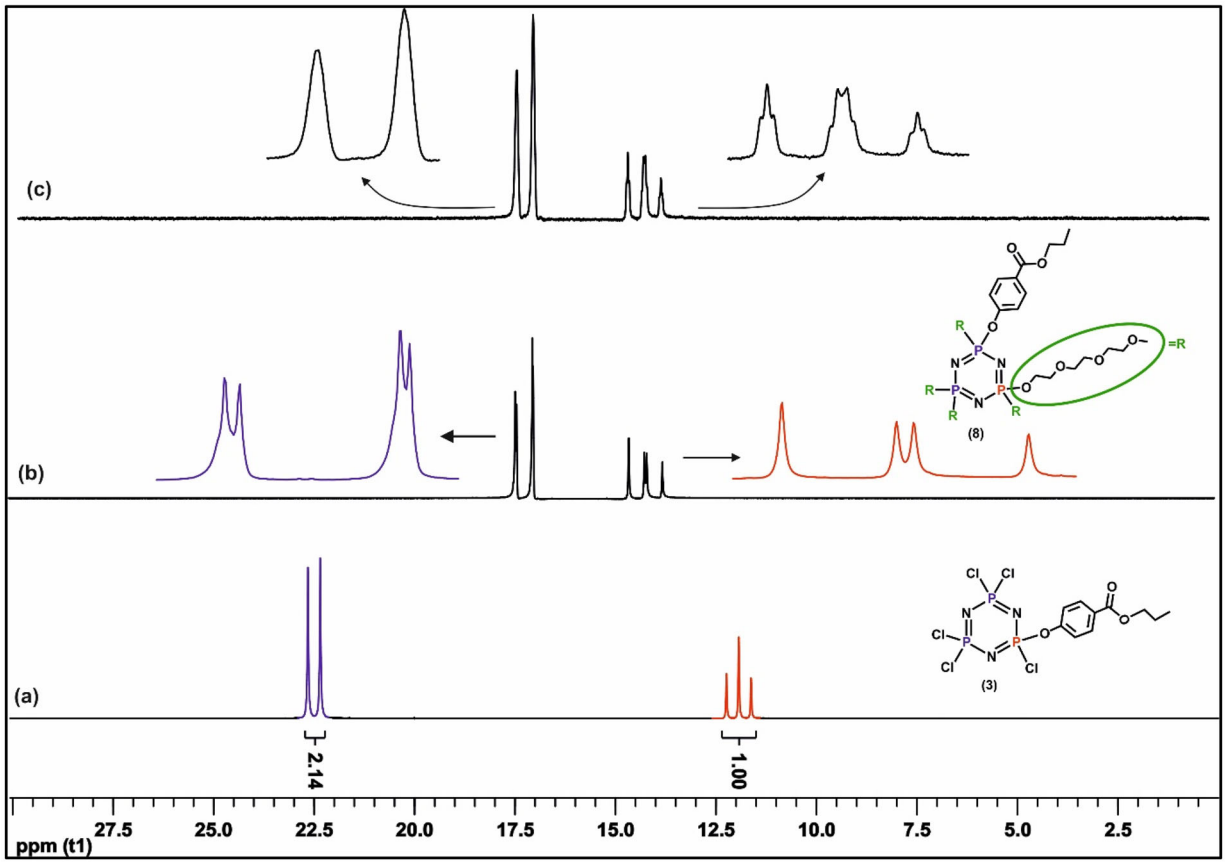

Figure 1. (a) The proton decoupled ^{31}P NMR spectrum of **3**, (b) the proton decoupled ^{31}P NMR spectrum of **8**; (c) the proton coupled ^{31}P NMR spectrum of **8** in $CDCl_3$ solution.

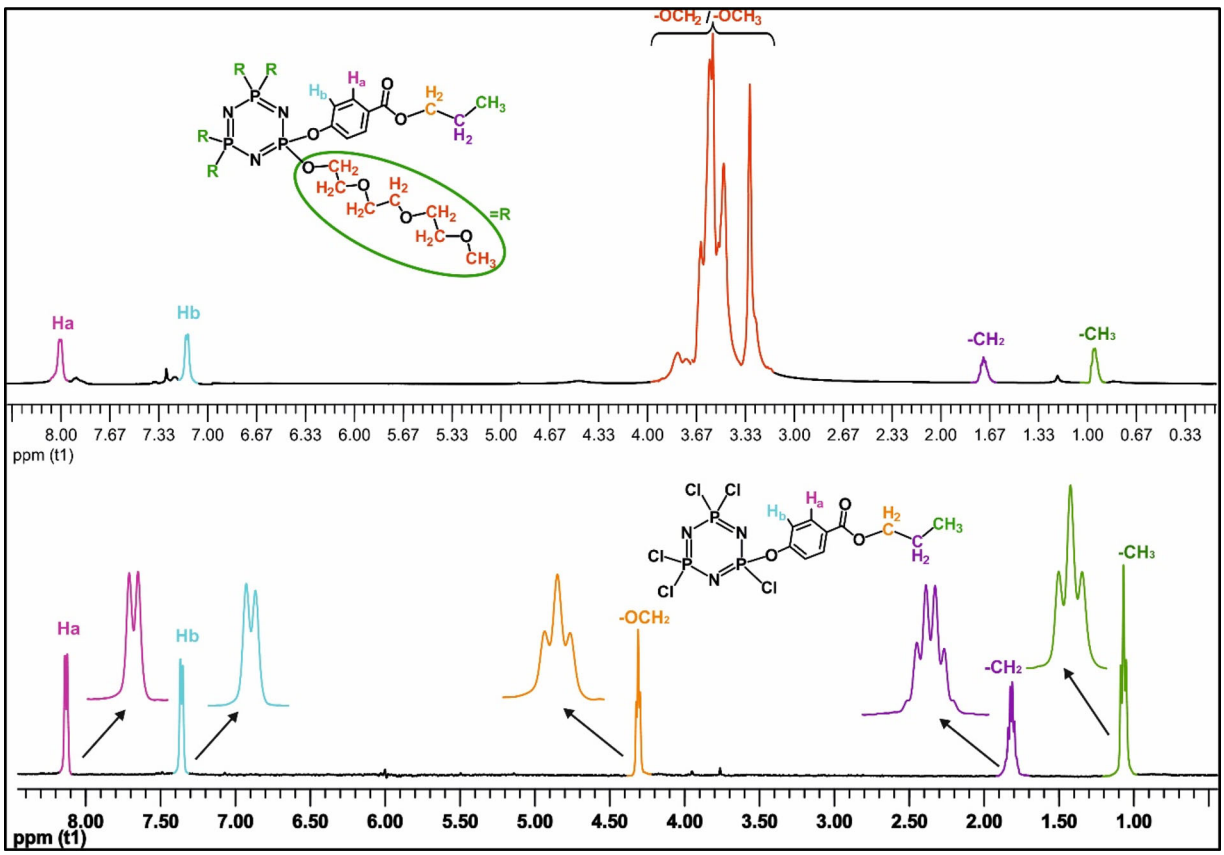

Figure 2. (a) The ^1H NMR spectrum of **3** and (b) the ^1H NMR spectrum of **8** in $CDCl_3$ solution.

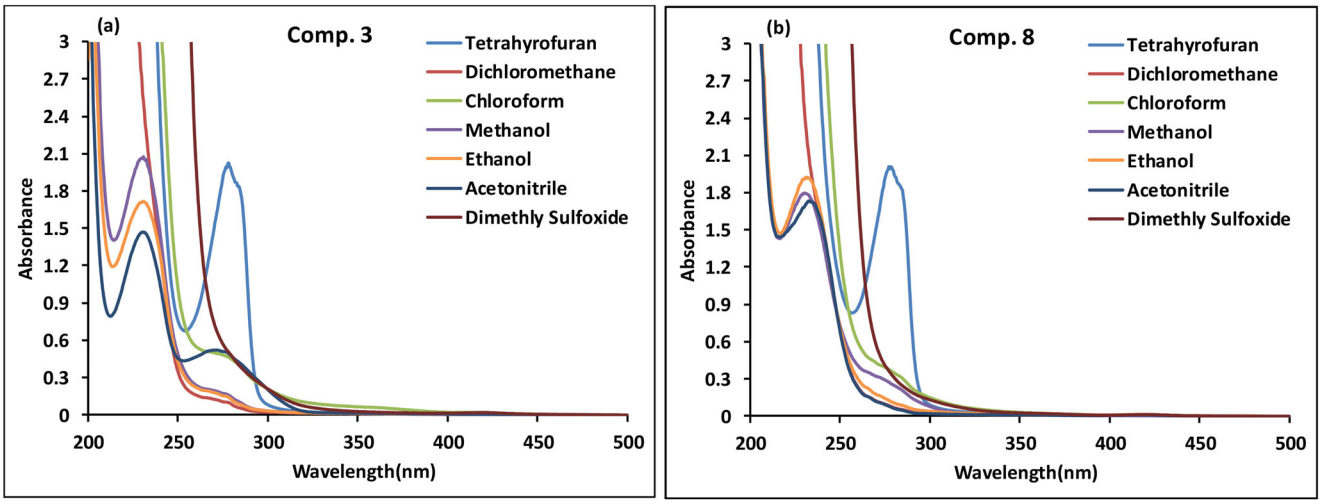

Figure 3. Absorbance spectra of (a) **3** and (b) **8** (100 μM) in different solvents.

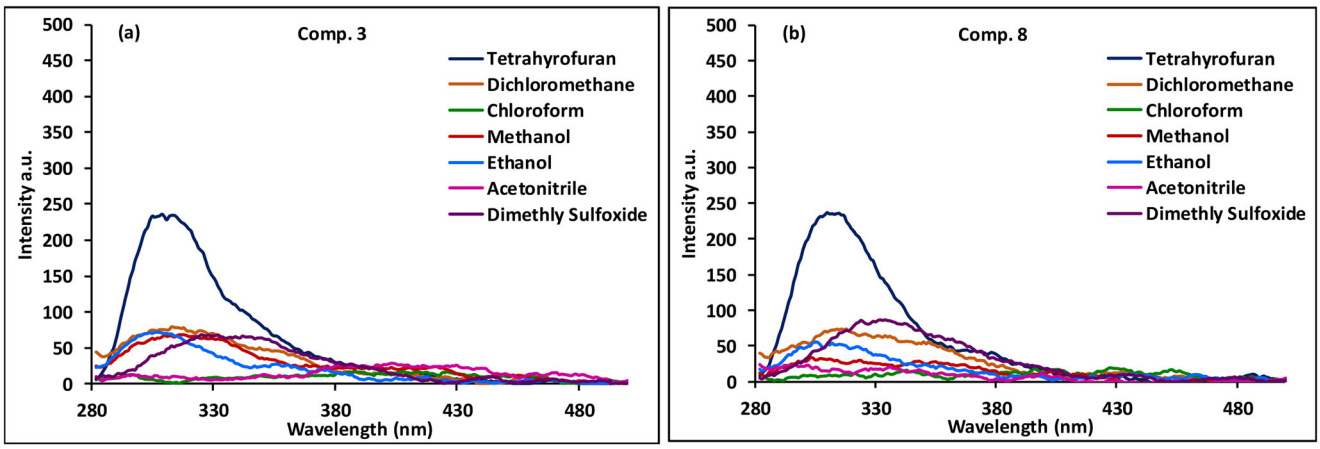

Figure 4. Fluorescence spectra of (a) **3** and (b) **8** (100 μM) in different solvents ($\lambda_{exc.}$=270 nm).

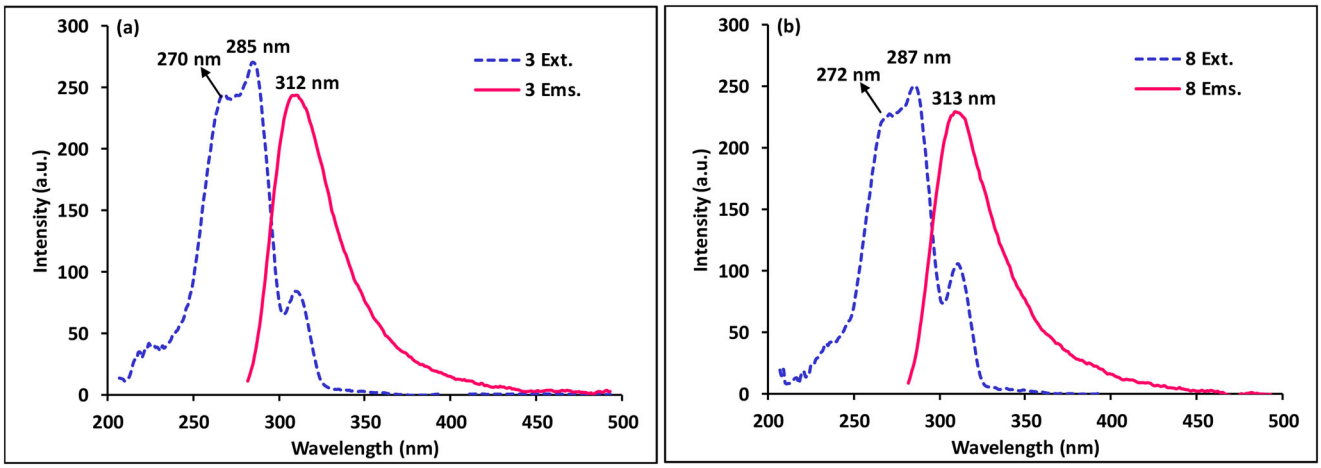

Figure 5. Excitation (dashed lines) and emission spectra (solid lines) of (a) for **3**, (b) for **8** in tetrahydrofuran, $\lambda_{exc.}$ = 270 nm (C = 100 μM).

methanol and ethanol (Figures 3–5 and Supporting Information Figures S26–S33). When the absorbance of the compounds in different solvents was investigated, it was found that the absorbance bands were not changed even if the absorbance intensity of the compounds changed with the solvent effect (Figure 3 and Supporting Information Figures S26 and S27). In general, absorbance bands were observed in the range of 230–300 nm as broad bands for compounds **1-10** in all the studied solvents. These absorbance bands observed for compounds can be attributed to π-π* and n-π* transitions.[30–33] In addition, the ground state absorption spectra of the compounds in acetonitrile

Table 2. Photophysical properties of cyclotriphosphazene derivatives (**1–10**).

Comp.	C (μM)	[a]λ_{ab} (nm)	λ_{em} (nm)	$\epsilon^{a,b}$, 10^4 $M^{-1}.cm^{-1}$	[c]Δ_{Stokes}, max., min. (nm)
1	100	230, 268, 277	$310_{(THF)}$, $330_{(DMSO)}$	2.10	42, 25
2	100	230, 270, 279	$312_{(THF)}$), $338_{(DMSO)}$	1.92	43, 26
3	100	230, 271, 280	$312_{(THF)}$, $340_{(DMSO)}$	1.50	42, 27
4	100	230, 267, 281	$310_{(THF)}$, $340_{(DMSO)}$	1.74	42, 25
5	100	230, 271, 279	$312_{(THF)}$, $335_{(DMSO)}$	1.48	42, 27
6	100	234, 269, 278	$312_{(THF)}$, $336_{(DMSO)}$	2.21	40, 23
7	100	236, 270, 287	$310_{(THF)}$, $337_{(DMSO)}$	1.61	41, 26
8	100	235, 268, 281	$313_{(THF)}$, $336_{(DMSO)}$	2.10	41, 26
9	100	235, 271, 282	$310_{(THF)}$, $348_{(DMSO)}$	1.65	41, 24
10	100	232, 272, 282	$310_{(THF)}$, $335_{(DMSO)}$	1.82	43, 26

[a]Acetonitrile.
[b]Molar extinction coefficients.
[c]Tetrahydrofuran.

were obtained at different concentrations. From these spectra, the molar extinction coefficients of the compounds (**1-10**) were calculated according to Beer-Lambert law (Supporting Information Figures S28 and S29). The solvent effect in the fluorescence emission spectrum of compounds (**1-10**) was also examined. According to fluorescence emission spectra, the highest emission intensity of the compounds (**1-10**) was observed at about 312 nm in tetrahydrofuran. The lowest emission intensity for all compounds was observed in chloroform. Also, there was no significant shift in the fluorescence wavelength of the compounds (**1-10**) in the other solutions except dimethylsulfoxide (Figure 4, Supporting Information Figures S30 and S31). Depending on the solvent effect, a red shift of approximately 25 nm relative to the other solvents was observed at the fluorescence emission wavelength of all compounds (**1-10**) in DMSO (Table 2). This shift can be due to non-covalent intermolecular interactions between compounds and aromatic solvents. The emission and excitation spectrum of compounds (**1-10**) in tetrahydrofuran are shown in Figure 5 and Supporting Information Figures S32 and S33. Fluorescence emission maxima values of the compounds were recorded in the range of 310-313 nm in THF (Table 2). Stokes shift, which is known as the distance between maximum excitation and emission wavelength, is important for fluorescence measurements. The Stokes Shift values of the compounds (**1-10**) were observed in the range of approximately 23–43 nm measurements in tetrahydrofuran (Table 2).

3. Experimental

3.1. General material and methods

General material and methods were given in Supporting Information.

3.1.1. Synthesis of compound 1 and 2

Compound **1** and **2** were synthesized according to the literatures[34,35] and spectral data of all compounds (**1-10**) were given in the supporting file (Supporting Information Figures S1–S25).

3.1.2. Synthesis of compound 3 (propyl 4-((2,4,4,6,6-pentachloro-1,3,5,2λ^5,4λ^5,6λ^5-triazatriphosphinin-2-yl)oxy)benzoate)

Hexachlorocyclotriphosphazene (1.0 g, 2.80 mmol) and NaH (60% oil suspension, 0.056 g, 2.33 mmol) were dissolved in dry THF (40 mL) under an argon atmosphere in a 250 mL three-necked round-bottomed flask. The reaction mixture was cooled in an ice bath and propyl 4-hydroxybenzoate (0.504 g, 2.8 mmol) in dry THF (10 mL) was added to this stirred solution under an argon atmosphere. The reaction mixture was stirred for 3 days at room temperature by control with TLC. The reaction mixture was filtered to remove the formed sodium chloride and the solvent was removed under reduced pressure. Compound **3** (260 mg, 20%, white oil) was isolated from the reaction mixture in silica gel (70-230 mesh) column, using the *n*-hexane-DCM (1:1) system as the driving phase. Spectral data of compound **3:** MS (MALDI-TOF) (DIT) *m*/*z* (%): Calcd. for ($C_{10}H_{11}Cl_5N_3O_3P_3$): 491.39; found 491.50 $[M]^+$. ^{31}P NMR decoupled to (202 MHz, $CDCl_3$, 298 K), $P(Cl)_2$ $\delta = 22.51$ ppm (2P, $^2J_{P\text{-}P} = 62.06$ Hz); $P(R_1Cl)$ $\delta = 11.88$ ppm (1P, $^2J_{P\text{-}P} = 62.06$ Hz) Spin system: A_2X (Supporting Information Figure S5). ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ ppm, 8.13, d, 2H, H_a ($^3J_{HH}$ = 8.48 Hz); 7.36, d, 2H, H_b ($^3J_{HH}$ = 8.48 Hz); 4.31, t, 2H, (-OCH_2), ($^3J_{HH}$ = 6.70 Hz); 1.82, m, 2H (CH_2); 1.06, t, 3H (-CH_3), ($^3J_{HH}$ = 7.38 Hz) (Supporting Information Figure S6).

3.1.3. Synthesis of compound 4 (butyl 4-((2,4,4,6,6-pentachloro-1,3,5,2λ^5,4λ^5,6λ^5-triazatriphosphinin-2-yl)oxy)benzoate)

Hexachlorocyclotriphosphazene (1.0 g, 2.80 mmol) and NaH (60% oil suspension, 0.056 g, 2.33 mmol) were dissolved in dry THF (40 mL) under an argon atmosphere in a 250 mL three-necked round-bottomed flask. The reaction mixture was cooled in an ice bath and butyl 4-hydroxybenzoate (0.544 g, 2.8 mmol) in dry THF (10 mL) was added to this stirred solution under an argon atmosphere. The reaction mixture was stirred for 3 days at room temperature by control with TLC. The reaction mixture was filtered to remove the formed sodium chloride and the solvent was removed under reduced pressure. Compound **4** (283 mg, 20%, white oil) was isolated from the reaction mixture in silica gel (70-230 mesh) column, using the *n*-hexane-DCM (1:1) system as the driving phase. Spectral data of compound **4:** MS

(MALDI-TOF) (DHB) *m/z* (%): Calcd. for ($C_{11}H_{13}Cl_5N_3O_3P_3$): 505.41; found 505.49 $[M]^+$. ^{31}P NMR decoupled to (202 MHz, $CDCl_3$, 298 K), $P(Cl)_2$ $\delta = 22.51$ ppm (2P, $^2J_{P\text{-}P} = 62.0$ Hz); $P(R_1Cl)$ $\delta = 11.87$ ppm (1P, $^2J_{P\text{-}P} = 62.0$ Hz) Spin system: A_2X (Supporting Information Figure S7). ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ ppm, 8.12, d, 2H, H_a ($^3J_{HH} = 8.33$ Hz); 7.36, d, 2 H, H_b ($^3J_{HH} = 8.33$ Hz); 4.35, t, 2 H, (-OCH_2), ($^3J_{HH} = 6.60$ Hz); 1.78, m, 2H (CH_2); 1.50, m, 2H (CH_2); 1.00, t, 3H (-CH_3), ($^3J_{HH} = 7.34$ Hz) (Supporting Information Figure S8).

3.1.4. Synthesis of compound 5 (benzyl 4-((2,4,4,6,6-pentachloro-1,3,5,2λ^5,4λ^5,6λ^5-triazatriphosphinin-2-yl)oxy) benzoate)

Hexachlorocyclotriphosphazene (1.0 g, 2.80 mmol) and NaH (60% oil suspension, 0.056 g, 2.33 mmol) were dissolved in dry THF (40 mL) under an argon atmosphere in a 250 mL three-necked round-bottomed flask. The reaction mixture was cooled to an ice bath and benzyl-4-hydroxybenzoate (0.544 g, 2.8 mmol) in dry THF (10 mL) was added to this stirred solution under an argon atmosphere. The reaction mixture was stirred for 3 days at room temperature by control with TLC. The reaction mixture was filtered to remove the formed sodium chloride and the solvent was removed under reduced pressure. Compound **5** (330 mg, 22%, white oil) was isolated from the reaction mixture in silica gel (70-230 mesh) column, using the *n*-hexane-DCM (1:1) system as the driving phase. Spectral data of compound **5:** MS (MALDI-TOF) (DIT) *m/z* (%): Calcd. for ($C_{14}H_{11}Cl_5N_3O_3P_3$): 539.43; found 539.31 $[M]^+$. ^{31}P NMR decoupled to (202 MHz, $CDCl_3$, 298 K), $P(Cl)_2$ $\delta = 22.52$ ppm (2P, $^2J_{P\text{-}P} = 62.03$ Hz); $P(R_1Cl)$ $\delta = 11.89$ ppm (1P, $^2J_{P\text{-}P} = 62.03$ Hz) Spin system: A_2X (Supporting Information Figure S9). ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ ppm, 8.16, d, 2H, H_a ($^3J_{HH} = 8.59$ Hz); 7.47, d, 2H, H_c ($^3J_{HH} = 7.19$ Hz); 7.42, t, 2H, H_d ($^3J_{HH} = 7.15$ Hz); 7.38, d, 1H, H_e; 7.36, d, 2H, H_b ($^3J_{HH} = 8.59$ Hz); 5.39, s, 2 H (-OCH_2) (Supporting Information Figure S10).

3.1.5. Synthesis of compound 6 (methyl 4-((2,4,4,6,6-pentakis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)−1,3,5,2λ^5, 4λ^5,6λ^5-triazatriphosphinin-2-yl)oxy)benzoate)

Triethylene glycol monomethyl ether (190 mg, 1.17 mmol) was dissolved in dry THF (50 mL) in a 250 mL round-bottomed three-necked flask in an argon atmosphere. NaH (47 mg, 1.17 mmol (60%)) solid was added to the reaction medium and heated at reflux temperature of THF under reflux for 2 h. After cooling the reaction mixture to room temperature, the outdoor was cooled to about −10 °C in an ice-salt bath. Compound **1** (100 mg, 0.22 mmol) was slowly added to the reaction mixture by dissolving in dry THF (100 mL). The reaction was allowed to warm to room temperature and stirred at room temperature for 2 days by control with TLC. The reaction mixture was filtered through a sintered filter to remove the sodium chloride salt. The solvent of the filtrate was removed in vacuum using a rotary evaporator. Compound **6** (120 mg, 50%, white oil) was isolated from the reaction mixture in silica gel (70-230 mesh) column, using the *n*-hexane-DCM (2: 3) system as the driving phase. Spectral data of compound **6:** MS (MALDI-TOF) (DHB) *m/z* (%): Calc. for ($C_{43}H_{82}N_3O_{23}P_3$): 1102.05; found 1102.46 $[M]^+$. ^{31}P NMR decoupled to (202 MHz, $CDCl_3$, 298 K), $P(R_2)_2$ $\delta =$ 17.30 ppm (2 P, $^2J_{P\text{-}P} = 85.54$ Hz); $P(R_1)(R_2)$ $\delta =$ 14.35 ppm (1P, $^2J_{P\text{-}P} = 85.54$ Hz) Spin system: A_2B (Supporting Information Figures S11 and S12). ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ ppm, 8.06, d, 2H, H_a ($^3J_{HH} = 7.50$ Hz); 7.24, d, 2H, H_b ($^3J_{HH} = 7.50$ Hz); 3.76–3.50, m, 60 H (-OCH_2); 3.33, s, 18 H, (-OCH_3) (Supporting Information Figure S13).

3.1.6. Synthesis of compound 7 (ethyl 4-((2,4,4,6,6-pentakis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)−1,3,5,2λ^5, 4λ^5,6λ^5-triazatriphosphinin-2-yl)oxy)benzoate)

Triethylene glycol monomethyl ether (206 mg, 1.26 mmol) was dissolved in dry THF (50 mL) in a 250 mL round-bottomed three-necked flask in an argon atmosphere. NaH (56 mg, 1.4 mmol (60%)) solid was added to the reaction medium and heated at reflux temperature of THF under reflux for 2 h. After cooling the reaction mixture to room temperature, the outdoor was cooled to about −10 °C in an ice-salt bath. Compound **2** (100 mg, 0.21 mmol) was slowly added to the reaction mixture by dissolving in dry THF (100 mL). The reaction was allowed to warm to room temperature and stirred at room temperature for 2 days by control with TLC. The reaction mixture was filtered through a sintered filter to remove the sodium chloride salt. The solvent of the filtrate was removed in vacuum using a rotary evaporator. Compound **7** (110 mg, 47%, white oil) was isolated from the reaction mixture in silica gel (70-230 mesh) column, using the *n*-hexane-DCM (2: 3) system as the driving phase. Spectral data of compound **7:** MS (MALDI-TOF) (DIT) *m/z* (%): Calcd. for ($C_{44}H_{84}N_3O_{23}P_3$): 1116.05; found 1085.54 $[M\text{-}C_2H_5]^+$. ^{31}P NMR decoupled to (202 MHz, $CDCl_3$, 298 K), $P(R_2)_2$ $\delta = 17.27$ ppm (2P, $^2J_{P\text{-}P} = 85.33$ Hz); $P(R_1)(R_2)$ $\delta = 14.27$ ppm (1P, $^2J_{P\text{-}P} = 85.33$ Hz) Spin system: A_2B (Supporting Information Figures S14 and S15). ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ ppm, 8.04, d, 2H, H_a ($^3J_{HH} = 6.63$ Hz); 7.21, d, 2H, H_b ($^3J_{HH} = 6.63$ Hz); 3.75–3.45, m, 62 H (-OCH_2); 3.33, s, 15H, (-OCH_3); 1.33–1.16, m, 3 H, (-CH_3) (Supporting Information Figure S16).

3.1.7. Synthesis of compound 8 (propyl 4-((2,4,4,6,6-pentakis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)−1,3,5,2λ^5, 4λ^5,6λ^5-triazatriphosphinin-2-yl)oxy)benzoate)

Triethylene glycol monomethyl ether (541 mg, 3.3 mmol) was dissolved in dry THF (50 mL) in a 250 mL round-bottomed three-necked flask in an argon atmosphere. NaH (40 mg, 2.75 mmol (60%)) solid was added to the reaction medium and heated at reflux temperature of THF under reflux for 2 h. After cooling the reaction mixture to room temperature, the outdoor was cooled to about −10 °C in an ice-salt bath. Compound **3** (100 mg, 0.55 mmol) was slowly added to the reaction mixture by dissolving in dry THF (100 mL). The reaction was allowed to warm to room temperature and stirred at room temperature for 2 days by control with TLC. The reaction mixture was filtered through a sintered filter to remove the sodium chloride salt. The solvent of the filtrate was removed in vacuo using a rotary

evaporator. Compound **8** (105 mg, 45%, white oil) was isolated from the reaction mixture in silica gel (70-230 mesh) column, using the *n*-hexane-DCM (2: 3) system as the driving phase. Spectral data of compound **8:** MS (MALDI-TOF) (DHB) *m/z* (%): Calcd. for ($C_{45}H_{86}N_3O_{23}P_3$): 1130.10; found 1086.95 $[M\text{-}C_3H_7]^+$. ^{31}P NMR decoupled to (202 MHz, $CDCl_3$, 298 K), $P(R_2)_2$ $\delta = 17.29$ ppm (2P, $^2J_{P\text{-}P} = 85.28$ Hz); $P(R_1)(R_2)$ $\delta = 14.07$ ppm (1P, $^2J_{P\text{-}P} = 85.28$ Hz) Spin system: A_2B (Supporting Information Figures S17 and S18). ^1H-NMR (500 MHz, $CDCl_3$, 298 K) δ ppm, 8.00, d, 2H, H_a ($^3J_{HH} = 6.72$ Hz); 7.14, d, 2H, H_b ($^3J_{HH} = 6.72$ Hz); 3.70–3.40, m, 62H ($-OCH_2$); 3.30, s, 15H, ($-OCH_3$); 1.73–1.67, m, 2H, ($-CH_2$); 1.01–0.91, m, 3H, ($-CH_3$) (Supporting Information Figure S19).

3.1.8. Synthesis of compound 9 (buthyl 4-((2,4,4,6,6-pentakis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)−1,3,5,2λ^5,4λ^5,6λ^5-triazatriphosphinin-2-yl)oxy)benzoate)

Triethylene glycol monomethyl ether (420 mg, 2.5 mmol) was dissolved in dry THF (50 mL) in a 250 mL round-bottomed three-necked flask in an argon atmosphere. NaH (35 mg, 2.5 mmol (60%)) solid was added to the reaction medium and heated at reflux temperature of THF under reflux for 2 h. After cooling the reaction mixture to room temperature, the outdoor was cooled to about −10 °C in an ice-salt bath. Compound **4** (100 mg, 0.51 mmol) was slowly added to the reaction mixture by dissolving in dry THF (100 mL). The reaction was allowed to warm to room temperature and stirred at room temperature for 2 days by control with TLC. The reaction mixture was filtered through a sintered filter to remove the sodium chloride salt. The solvent of the filtrate was removed in vacuo using a rotary evaporator. Compound **9** (90 mg, 40%, white oil) was isolated from the reaction mixture in silica gel (70-230 mesh) column, using the *n*-hexane-DCM (2: 3) system as the driving phase. Spectral data of compound **9:** MS (MALDI-TOF) (DHB) *m/z* (%): Calcd. for ($C_{46}H_{88}N_3O_{23}P_3$): 1144.13; found 1144.37 $[M]^+$. ^{31}P NMR decoupled to (202 MHz, $CDCl_3$, 298 K), $P(R_2)_2$ $\delta = 17.25$ ppm (2P, $^2J_{P\text{-}P} = 85.41$ Hz); $P(R_1)(R_2)$ $\delta = 14.37$ ppm (1P, $^2J_{P\text{-}P} = 85.41$ Hz) Spin system: A_2B (Supporting Information Figures S20 and S21). ^1H-NMR (500 MHz, $CDCl_3$, 298 K) δ ppm, 8.05, d, 2H, H_a ($^3J_{HH} = 7.17$ Hz); 7.30, d, 2H, H_b ($^3J_{HH} = 7.17$ Hz); 3.80–3.50, m, 62H ($-OCH_2$); 3.38, s, 15H, ($-OCH_3$); 2.10–2.02, m, 2H, ($-CH_2$); 1.66–1.59, m, 2H, ($-CH_2$); 0.93–0.81, m, 3H, ($-CH_3$) (Supporting Information Figure S22).

3.1.9. Synthesis of compound 10 (benzyl 4-((2,4,4,6,6-pentakis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)−1,3,5,2λ^5,4λ^5,6λ^5-triazatriphosphinin-2-yl)oxy)benzoate)

Triethylene glycol monomethyl ether (360 mg, 2.2 mmol) was dissolved in dry THF (50 mL) in a 250 mL round-bottomed three-necked flask in an argon atmosphere. NaH (30 mg, 2.2 mmol (60%)) solid was added to the reaction medium and heated at reflux temperature of THF under reflux for 2 h. After cooling the reaction mixture to room temperature, the outdoor was cooled to about −10 °C in an ice-salt bath. Compound **5** (100 mg, 0.43 mmol) was slowly added to the reaction mixture by dissolving in dry THF (100 mL). The reaction was allowed to warm to room temperature and stirred at room temperature for 2 days by control with TLC. The reaction mixture was filtered through a sintered filter to remove the sodium chloride salt. The solvent of the filtrate was removed in vacuo using a rotary evaporator. Compound **10** (95 mg, 43%, white oil) was isolated from the reaction mixture in silica gel (70-230 mesh) column, using the hexane-DCM (2: 3) system as the driving phase. Spectral data of compound **10:** MS (MALDI-TOF) (DHB) *m/z* (%): Calcd. for ($C_{48}H_{84}N_3O_{23}P_3$): 1164.12; found 1085.58 $[M\text{-}C_7H_9]^+$. ^{31}P NMR decoupled to (202 MHz, $CDCl_3$, 298 K), $P(R_2)_2$ $\delta = 17.24$ ppm (2P, $^2J_{P\text{-}P} = 85.21$ Hz); $P(R_1)(R_2)$ $\delta = 14.16$ ppm (1P, $^2J_{P\text{-}P} = 85.21$ Hz) Spin system: A_2B (Supporting Information Figures S23 and S24). ^1H-NMR (500 MHz, $CDCl_3$, 298 K) δ ppm, 8.03, d, 2H, H_a ($^3J_{HH} = 7.21$ Hz); 7.24, d, 2H, H_b ($^3J_{HH} = 7.21$ Hz); 7.43–7.30, m, 5H, $H_c/H_d/H_e$; 3.76–3.49, m, 62 H ($-OCH_2$); 3.36, s, 15 H, ($-OCH_3$) (Supporting Information Figure S25).

4. Conclusion

In summary, in this study, five parabens substituted cyclotriphosphazene compounds **1-5** and five new paraben-derivative cyclotriphosphazenes containing hydrophilic side groups **6-10** were successfully synthesized. The structural properties of all synthesized compounds were examined by MALDI-TOF spectrometer, ^1H, ^{31}P NMR spectroscopy. The proton decoupled ^{31}P NMR spectrum of the compounds were observed as A_2X spin system for compounds **1-5**, and as A_2B spin system for compounds **6-10**. Additionally, the photophysical properties (absorption and emission) of these compounds **1-10** in different solvents were investigated using UV-Vis and fluorescence spectroscopies. In general, the absorbance bands of the compounds **1-10** were observed at approximately 230–300 nm in all solvents studied. The highest fluorescence emission intensity of compounds **1-10** was observed in tetrahydrofuran at about 312 nm, while the lowest emission intensity was observed in chloroform. Due to the potential biological activity properties of parabens, it is thought that the synthesized new compounds may be biologically active compounds. In the future application of this study, the DNA binding properties of the synthesized paraben-cyclotriphosphazene derivatives carrying hydrophilic groups will be investigated with automatic biosensor device in our laboratories.

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