Synthesis and Characterization of Cyclotriphosphazenes Bearing Six Bile Acid Arms

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Four novel cyclotriphosphazene bile acid derivatives (**1** – **4**) were prepared starting from hexakis[4-(chloromethyl)phenoxy]cyclotriphosphazene (**8**) as the scaffold. The structures of the compounds were defined by elemental analysis, IR and ^{1}H, ^{13}C and ^{31}P NMR spectroscopy.

Key words: Cyclotriphosphazene, Bile Acid, Synthesis, Podant

Introduction

Bile acids are a most valuable group of compounds due to their large, rigid and curved steroidal skeletons, chemically different hydroxyl groups, enantiomeric purity, unique amphiphilicity, availability, and low cost [1]. For these reasons bile acids are versatile building blocks for the design and synthesis of macrocyclic and open chain supramolecular hosts [2]. There are many kinds of acyclic structures based on bile acids, among which the most interesting are: cleft-type structures [3], molecular tweezers [4], ionophores [5], molecular umbrellas [6], dendrons [7], gelling agents [8], and inclusion compounds (clathrates) [9]. On the other hand, the core ring of cyclotriphosphazenes has proven to be a versatile and valuable building block for new applications in molecular recognition, and a component of functional materials [10]. Despite the versatility of phosphazene chemisty, there is no report, to our knowledge, on the preparation of hexakis-bile acid-substituted cyclotriphosphazene derivatives.

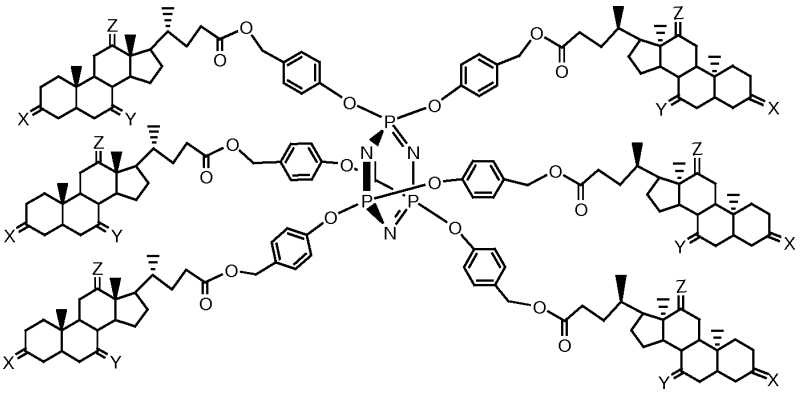
In this paper we report the synthesis of four new cyclotriphosphazene derivatives **1** – **4** containing six bile acid arms using the phenoxymethylene fragment as linker (Fig. 1).

Results and Discussion

Our idea was to build a cyclotriphosphazene bearing six bile acid units, having in principle supramolecular properties. However, the attempts to link directly six steroidal subunits *via* carboxyl or hydroxyl groups to the cyclotriphosphazene core using the hexachloro derivative **5** failed, probably for steric hindrance, as previously reported [11]. In the hope to overcome the steric crowding, we used chloromethylphenoxy groups as connecting units between the phosphazene ring and the bile acid moieties.

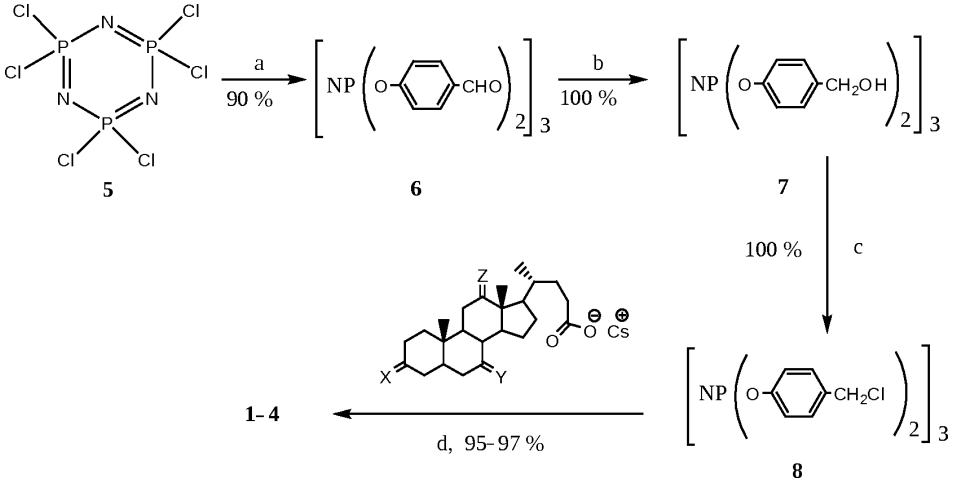
Preparation of phosphazenes containing bile acids was achieved from the scaffold of hexakis[4-(chloromethyl)phenoxy]cyclotriphosphazene **8** according to Scheme 1. The structures of the compounds obtained were confirmed by ^{1}H, ^{13}C, ^{31}P NMR and IR spectroscopy and elemental analysis.

Our synthesis involved quantitative conversion of the hexaaldehyde **6**, readily prepared from hexachlorocyclotriphosphazene **5**, and of 4-hydroxybenzaldehyde [10a] into the hexakis-[4-(hydroxymethyl)phenoxy]cyclotriphosphazene **7** *via* complete reduction of the six formyl groups with an excess of $NaBH_4$ in methanol at 0 °C. The hexaalcohol **7** was subsequently treated with thionyl chloride for two days to produce the hexachloromethyl derivative **8** in quantitative yield. The last step consisted of the grafting of 6 equiv. of the appropriate bile acid cesium salt onto hexakis-[4-(chloromethyl)phenoxy]cyclotriphosphazene. The reaction was carried out with an excess of bile acid salt (10 equiv.) in DMF at 40 °C and needed 3 days to complete, as shown by ^{31}P NMR monitoring. After simple workup (see Experimental Section) the hexa(bile acid) cyclotriphosphazene derivatives **1** – **4** were obtained in almost quantitative yield without tedious purification.



Compound	X	Y	Z
1	α-OH, H	H, H	α-OH, H
2	α-OH, H	α-OH, H	α-OH, H
3	O	H, H	O
4	O	O	O

Fig. 1. The newly synthetized cyclotriphosphazene-bile acid derivatives **1** – **4**.



Scheme 1. Synthetic pathway for the preparation of compounds **1** – **4**. Reagents and conditions: a: 4-HOC_6H_4CHO, NEt_3, THF; see ref. [10a]; b: $NaBH_4$, MeOH, 0 °C; c: $SOCl_2$; d: DMF, 40 °C.

Conclusion

Four new bis-tripodant claw-shaped molecules **1** – **4** based on bile acid and cyclotriphosphazene were easily obtained in good yields in typical procedures shown in Scheme 1. All these compounds are potential supramolecular systems capable to complex guest molecules or ions. This kind of physicochemical studies is under way.

Experimental Section

General methods. Melting points are uncorrected and were determined on a 510 Büchi melting point instrument. TLC was performed on precoated silica gel plates (thickness 0.25 mm, Merck), and silica gel (Fluka, Kieselgel 60, 70 – 230 mesh) was used for preparative column chromatography. The ^1H, ^{13}C and ^{31}P NMR spectra were recorded in $CDCl_3$ and/or CD_3OD solution in 5 mm tubes at r. t., with a Varian Gemini 300 spectrometer with TMS as internal standard for ^1H and ^{13}C spectra and with phosphoric acid as external standard for ^{31}P spectra. IR spectra were recorded on a Perkin-Elmer 1310 infrared spectrometer using the Nujol suspension technique. Elemental analyses were performed on a 1106 Microanalyzer (Carlo Erba). Hexachlorocyclotriphosphazene **5** was purchased from Aldrich and purified by vacuum sublimation until a constant melting point (113 °C) was obtained.

*Hexakis(4-formylphenoxy)cyclotriphosphazene (**6**)*

Compound **6** was prepared according to a described procedure [10a]. To a solution of hexachlorocyclotriphosphazene **5** (0.521 g, 1.5 mmol) in 10 mL of THF was added a solution of triethylamine (2.5 mL, 18 mmol) and 4-hydroxybenzaldehyde (2.20 g, 18 mmol) in 30 mL of anhydrous THF. The resulting mixture was refluxed for 16 h and then filtered, and the solvent evaporated. The resulting oil was washed with methanol (2 × 50 mL) to give **6** as a white powder; m. p. 140 – 142 °C; (141 – 142 °C [10a]); 90 % yield. – IR: ν = 1704 (C=O), 1200 – 1150, 950 cm^{-1}. – $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$): δ = 7.08 (s). – ^1H NMR (300.1 MHz, $CDCl_3$): δ = 7.12 (d, J = 8 Hz, 12H, Ar-H), 7.72 (d, J = 8 Hz, 12H, Ar-H), 9.91 (s, 6H, CHO). – $^{13}C\{^1H\}$ NMR (78.5 MHz, $CDCl_3$): δ = 120.8, 130.7, 133.4, 154.0 (C_{arom}) 189.6 (C=O). – $C_{42}H_{30}N_3O_{12}P_3$ (861.62): calcd. C 58.54, H 3.51, N 4.87; found C 58.90, H 3.78, N 4.80.

*Hexakis[4-(hydroxymethyl)phenoxy]cyclotriphosphazene (**7**)*

To a stirred suspension of hexakis(4-formylphenoxy)-cyclotriphosphazene (**6**) (1 g, 1.16 mmol) in methanol (50 mL) $NaBH_4$ (0.14 g, 3.7 mmol) was added portionwise at 0 °C. After 30 min acetone (1 mL) was added, and the reaction mixture was treated with 5 % aqueous HCl up to pH = 5 and then diluted with water (25 mL). The precipitated alcohol **7** was filtered off and used without further purification. Yield 100 %. – M. p. 210 – 212 °C. – IR: ν = 3345 (O-H), 1200 – 1150, 950 cm^{-1}. – $^{31}P\{^1H\}$ NMR (121.5 MHz, CD_3OD): δ = 10.03 (s). – ^1H NMR (300.1 MHz, CD_3OD): δ = 4.59 (s, 12H, CH_2O), 6.88 (d, J = 9 Hz, 12H, Ar-H), 7.20 (d, J = 9 Hz, 12H, Ar-H). – $^{13}C\{^1H\}$ NMR (78.5 MHz, $CD_3OD/CDCl_3$): δ = 64.3 (CH_2O), 121.5, 128.8, 139.2, 150.5 (C_{arom}). – $C_{42}H_{42}N_3O_{12}P_3$ (873.72): calcd. C 57.74, H 4.85, N 4.81; found C 57.90, H 4.78, N 4.90.

*Hexakis[4-(chloromethyl)phenoxy]cyclotriphosphazene (**8**)*

1 g (1 mmol) of the hydroxymethylene derivative **7** was dissolved, at 0 °C, in $SOCl_2$ (2 mL, 0.027 mol). The reaction mixture was left at r. t. for 24 h and, after removing excess thionyl chloride, the residue was treated with H_2O (20 mL). The precipitate was filtered and washed up to pH = 7 with distilled water. Yield almost quantitative. – M. p. 140 – 142 °C. – IR: ν = 1200 – 1150, 950 cm^{-1}. – $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$): δ = 9.73 (s). – ^1H NMR (300.1 MHz, $CDCl_3$): δ = 4.58 (s, 12H, CH_2Cl), 6.93 (d, J = 9 Hz, 12H, Ar-H), 7.24 (d, J = 9 Hz, 12H, Ar-H). – $^{13}C\{^1H\}$ NMR (78.5 MHz, $CDCl_3$): δ = 45.5 (CH_2Cl), 121.1, 129.9, 134.2, 150.5 (C_{arom}). – $C_{42}H_{36}Cl_6N_3O_6P_3$ (984.39): calcd. C 51.24, H 3.68, N 4.27; found C 51.00, H 3.78, N 4.40.

General procedure for the preparation of bile acid cesium salts

The bile acid cesium salts were obtained following [12]. Solid Cs_2CO_3 (1.23 mmol) was added to a solution of the appropriate bile acid (2.45 mmol) in $MeOH/H_2O$ (24 mL, 5 : 1 v/v). The reaction mixture was stirred at r. t. for 15 min, then concentrated under vacuum and azeotropically dried with toluene. The obtained cesium salt was used without further purification.

*General procedure for the synthesis of the hexapodant N_3P_3-(O-$C_6H_4CH_2$-bile acid)$_6$ (**1** – **4**)*

0.108 g (0.11 mmol) of hexakis[4-(chloromethyl)phenoxy]cyclotriphosphazene (**8**) and 1.1 mmol of the appropriate bile acid cesium salt are added to 3 mL of dimethylformamide. The suspension, kept at 40 °C, was shaken for 72 h. An aqueous solution of $NaHCO_3$ (15 mL) was added and the resulting solid collected by filtration and washed with distilled water.

*Hexakis[4-(3α,12α-dihydroxy-5β-colanoyloxymethyl)phenoxy]cyclotriphosphazene (**1**)*

Yield 95 %; obtained as white crystals. M. p. 240 – 242 °C. – IR: ν = 3400 (O-H), 1735 (C=O), 1595, 1200 – 1150, 950 cm^{-1}. – $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$): δ = 9.78 (s). – ^1H NMR (300.1 MHz, $CDCl_3$): significant sorting δ = 0.68 (s, 18H, 18-CH_3), 0.92 (s, 18H, 19-CH_3), 0.98 (d, J = 6.8 Hz, 18H, 21-CH_3), 3.62 (m, 6H, 3β-CH), 3.98 (br s, 6H, 12β-CH), 5.05 (A part of AB system, J = 12.6 Hz, 6H, Ar-CH-O), 5.10 (B part of AB system d, J = 12.6 Hz, 6H, Ar-CH-O), 6.90 (d, J = 9 Hz, 12H, Ar-H), 7.20 (d, J = 9 Hz, 12H, Ar-H). – $^{13}C\{^1H\}$ NMR (78.5 MHz, $CD_3OD/CDCl_3$): significant sorting δ = 65.2 (Ar-CH_2-O), 71.2 (3-CH), 72.7 (12-CH), 120.8 (ArCH), 129.3 (ArCH), 132.8 (ArC), 150.8 (ArC), 174.2 (COO). – $C_{186}H_{270}N_3O_{30}P_3$ (3121.06): calcd. C 71.58, H 8.72, N 1.35; found C 71.90, H 8.78, N 1.50.

*Hexakis[4-(3α,7α,12α-trihydroxy-5β-colanoyloxymethyl)phenoxy]cyclotriphosphazene (**2**)*

Yield 96 %; obtained as white crystals. M. p. 252 – 255 °C. – IR: ν = 3400 (O-H), 1720 (C=O), 1495, 1150, 945 cm^{-1}. – $^{31}P\{^1H\}$ NMR (121.5 MHz, CD_3OD): δ = 10.12 (s). – ^1H NMR (300.1 MHz, $CD_3OD/CDCl_3$): significant sorting δ = 0.68 (s, 18H, 18-CH_3), 0.90 (s, 18H, 19-CH_3), 1.00 (d, J = 6.8Hz, 18H, 21-CH_3), 3.38 (m, 6H, 3β-CH), 3.80 (br s, 6H, 7β-CH), 3.94 (br s, 6H, 12β-CH), 5.13 (br s, 12H, Ar-CH_2-O), 6.86 (d, J = 9 Hz, 12H, Ar-H), 7.24 (d, J = 9 Hz, 12H, Ar-H). – $^{13}C\{^1H\}$ NMR (78.5 MHz, $CD_3OD/CDCl_3$): significant

sorting δ = 66.2 (Ar-CH_2-O), 68.9 (7-CH), 72.6 (3-CH), 73.8 (12-CH), 121.9 (ArCH), 130.5 (ArCH), 134.5 (ArC), 151.2 (ArC), 175.3 (COO). – $C_{186}H_{270}N_3O_{36}P_3$ (3217.05): calcd. C 69.44, H 8.46, N 1.31; found C 69.51, H 8.70, N 1.42.

*Hexakis[4-(3,12-dioxo-5β-colanoyloxymethyl)phenoxy] cyclotriphosphazene (**3**)*

Yield 95 %; obtained as white crystals. M. p. 170 – 175 °C. – IR: ν = 1695 (C=O), 1150, 945 cm^{-1}. – $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$): δ = 9.49 (s). – ^1H NMR ($CDCl_3$): significant sorting δ = 0.86 (d, J = 6.8Hz, 18H, 21-CH_3), 1.05 (s, 18H, 18-CH_3), 1.13 (s, 18H, 19-CH_3), 5.08 (br s, 12H, Ar-CH_2-O), 6.92 (d, J = 9 Hz, 12H, Ar-H), 7.20 (d, J = 9 Hz, 12H, Ar-H). – $^{13}C\{^1H\}$ NMR (78.5 MHz, $CDCl_3$): significant sorting δ = 65.3 (Ar-CH_2-O), 120.9 (ArCH), 129.4 (ArCH), 133.0 (ArC), 150.3 (ArC), 173.8 (COO), 212.2 (3C=O), 214.1 (12C=O). – $C_{186}H_{246}N_3O_{30}P_3$ (3096.87): calcd. C 72.14, H 8.01, N 1.35; found C 71.27, H 8.08, N 1.30.

*Hexakis[4-(3,7,12-trioxo-5β-colanoyloxymethyl)phenoxy] cyclotriphosphazene (**4**)*

Yield 95 %; obtained as white crystals. M. p. 180 – 185 °C (dec.). – IR: ν = 1695 (C=O), 1145, 945 cm^{-1}. – $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$): δ = 9.52 (s). – ^1H NMR (300.1 MHz, $CDCl_3$): significant sorting δ = 0.84 (d, J = 6.8Hz, 18H, 21-CH_3), 1.06 (s, 18H, 18-CH_3), 1.20 (s, 18H, 19-CH_3), 5.05 (A part of AB system, J = 12 Hz, 6H, Ar-CH-O), 5.12 (B part of AB system d, J = 12 Hz, 6H, Ar-CH-O), 6.92 (d, J = 9 Hz, 12H, Ar-H), 7.21 (d, J = 9 Hz, 12H, Ar-H). – $^{13}C\{^1H\}$ NMR (78.5 MHz, $CDCl_3$): significant sorting δ = 65.3 (Ar-CH_2-O), 121.0 (ArCH), 129.5 (ArCH), 133.0 (ArC), 150.2 (ArC), 173.7 (COO), 208.7 (7C=O), 209.2 (3C=O), 211.9 (12C=O). – $C_{186}H_{234}N_3O_{36}P_3$ (3180.77): calcd. C 70.23, H 7.42, N 1.32; found C 70.67, H 7.88, N 1.30.

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