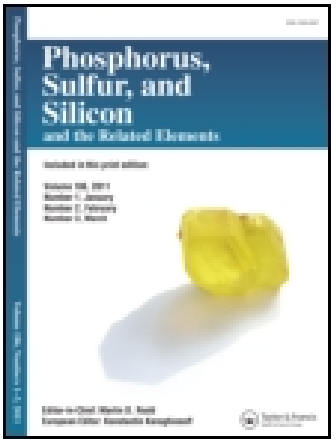


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# Synthesis and Characterization of Bidentate Cyclotriphosphazene Derivatives

Rui Han [a], Xue-lin Ren [b], Di Zhang [a], Min Wang [a], Jun-liang Yang [a], Yong Ye [a] & Yufen Zhao [a c]

[a] Phosphorus Chemical Engineering Research Center of Henan Province, Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, Department of Chemistry, Zhengzhou University, Zhengzhou, China

[b] School of Pharmaceutical Science, Zhengzhou University, Ke Xue Da Dao 100, Zhengzhou, P. R. China

[c] Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen, China

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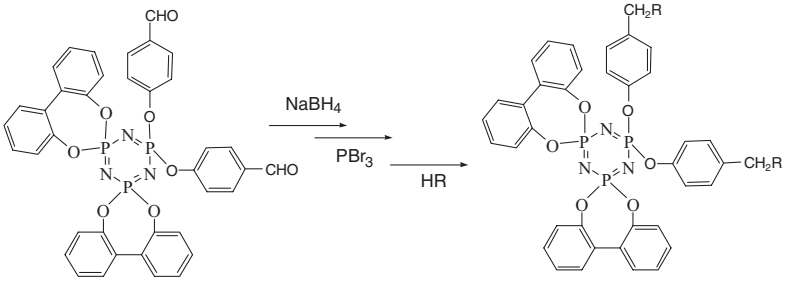
# SYNTHESIS AND CHARACTERIZATION OF BIDENTATE CYCLOTRIPHOSPHAZENE DERIVATIVES

**Rui Han,[1] Xue-lin Ren,[2] Di Zhang,[1] Min Wang,[1] Jun-liang Yang,[1] Yong Ye,[1] and Yufen Zhao[1,3]**

*[1]Phosphorus Chemical Engineering Research Center of Henan Province, Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, Department of Chemistry, Zhengzhou University, Zhengzhou, China*
*[2]School of Pharmaceutical Science, Zhengzhou University, Ke Xue Da Dao 100, Zhengzhou, P. R. China*
*[3]Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen, China*

## GRAPHICAL ABSTRACT




**1** **4a-c**: R=cyclen, imdazolyl, morpholino

**Abstract** *Three novel cyclotriphosphazene derivatives were designed. Title compounds were synthesized by the reaction of the dichlorocyclotriphosphazene derivative* $[N_3P_3Cl_2(O_2C_{12}H_8)_2]$ *with the potassium salt of 4-hydroxybenzaldehyde, and subsequent reduction of aldehyde groups to alcohol groups using sodium borohydride. The bromination reaction was carried out using* $PBr_3$ *to give* $N_3P_3(O_2C_{12}H_8)_2$ $(OC_6H_4\text{-}p\text{-}CH_2Br)_2$. *This compound was employed in reactions with macrocyclic polyamide, imidazole, or morpholine to produce title compounds. The target compounds were characterized using* $^1H$ *NMR,* $^{31}P$ *NMR,* $^{13}C$ *NMR, IR, and electrospray ionization mass spectra (ESI-MS).*

*[Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental resource*: *Figures S1–S6.]*

**Keywords** Macrocyclic polyamide; cyclotriphosphazene derivatives; imidazole; morpholine

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Address correspondence to Yong Ye, Phosphorus Chemical Engineering Research Center of Henan Province, Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, Department of Chemistry, Zhengzhou University, Zhengzhou 450052, China. E-mail: yeyong03@mail.nankai.edu.cn

## INTRODUCTION

The phosphodiester bonds of DNA are remarkably resistant to hydrolysis under physiological conditions.[1–3] Although many types of enzymes have been harnessed for use in the laboratory, there is a great deal of interest in the design of artificial nucleases, small molecular scissors that can cleave DNA hydrolytically. Therefore, designing new ligands suitable for cleaving DNA under hydrolytic conditions is of considerable importance.

Cyclotriphosphazenes have received considerable interest, not only because of their wide spectra of chemical and physical properties but also for their importance in synthetic chemistry. Different side-group structures affect the chemical and physical properties of the ring systems.[4–11] Recently, we reported some polydentate cyclotriphosphazene ligands,[12–14] which showed good nuclease activity with a hydrolytic cleavage mechanism. In this work, we synthesized three bidentate cyclotriphosphazene derivatives in order to obtain more insight into the selective recognization and efficient cleavage of DNA by different metal complexes of the cyclotriphosphazene. Their synthetic route is outlined in Scheme 1.

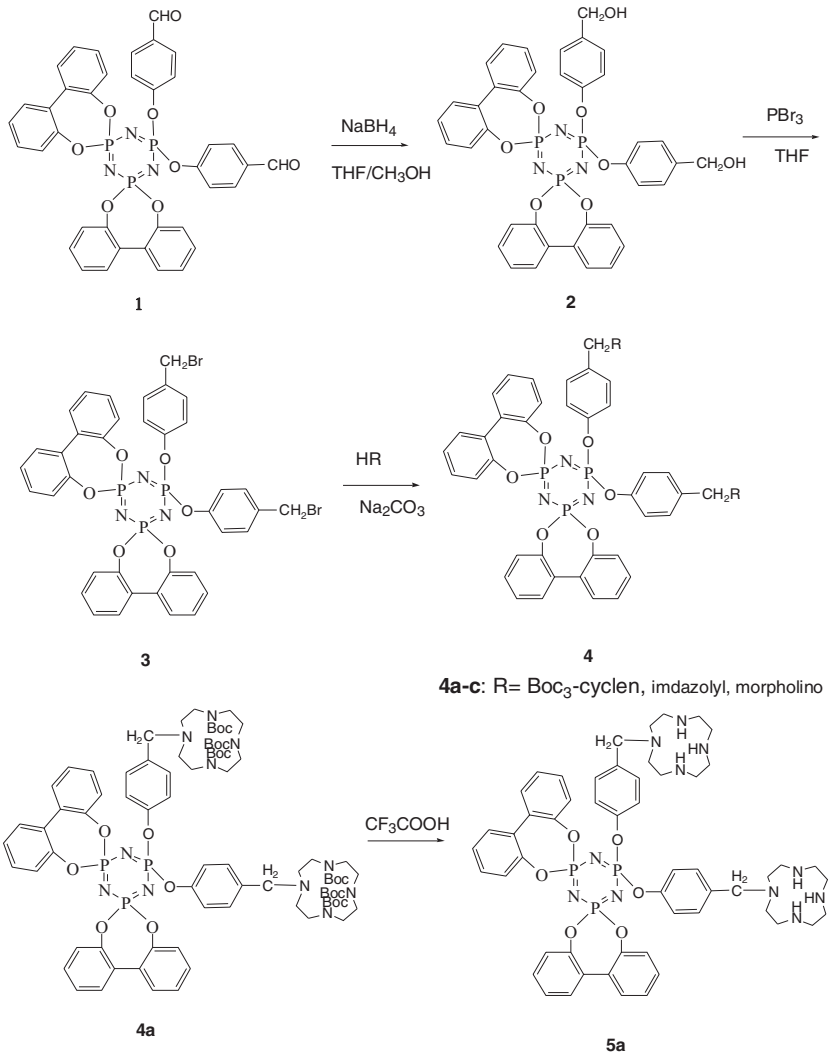
## RESULTS AND DISCUSSION

Compound **1** was synthesized according to a modified procedure reported by Carriedo et al.[15] The reaction of $[N_3P_3Cl_6]$ with 2 equiv. of $HOC_6H_4C_6H_4OH$ and $K_2CO_3$ in acetone gave the known spiro derivatives $[N_3P_3Cl_2(O_2C_{12}H_8)_2]$, and the dichloro derivative reacted directly with parasubstituted phenol $HOC_6H_4CHO$ and NaH in tetrahydrofuran (THF) to give the compound **1**. We found that the reactant ratio had an important effect on the yield of compound **1** by following the reaction using $^{31}P$ NMR tracking. Consequently, a satisfactory yield of the expected compounds can be obtained when an optimum 2.1:1 NaOPhCHO: $N_3P_3Cl_2(O_2C_{12}H_8)_2$ ratio was used.

The aldehyde group of compound **1** was easily reduced to an alcohol by sodium borohydride in THF/MeOH. The process was monitored by TLC. Several reagents were available for converting alcohols to alkyl bromides. Bromination reagents based on hydrobromic acid–sulfuric acid were found unemployable, as the reaction was hard to control and formed insoluble intermediates through reaction with the hydroxyl groups of compound **2**. The bromination reaction was achieved using $PBr_3$. Compound **3** was characterized by $^1H$ NMR, $^{31}P$ NMR, and electrospray ionization mass spectra (ESI-MS). $^1H$ NMR spectra showed that both the hydroxyl groups were replaced by bromo groups. Two doublet peaks for aromatic ring protons appeared at 7.03 and 7.43 ppm, and a single peak for bromomethyl group protons was observed at 4.51 ppm.

Compound **4a** was first synthesized from compound **3** in $CHCl_3/Et_3N$ or $THF/Na_2CO_3$. However, as indicated by the $^{31}P$ NMR spectra, compound **3** did not completely disappear. In addition, there were four spots in the TLC, which were very close. After further optimization, pure compound **4a** was obtained in good yield (77%) when $Na_2CO_3$ was selected as the base in $CH_3CN$ and the reaction time prolonged to 48 h. The trifluoroacetic acid (TFA) salts of **5a** were obtained by deprotection of 4a with a solution of TFA in dichloromethane at room temperature. Subsequent basification with NaOH gave the free compound **5a** which was characterized by $^1H$ NMR, $^{31}P$ NMR, $^{13}C$ NMR, and ESI-MS.

Similar to **4a**, compounds **4b** and **4c** were produced in 59.6% and 62.0% yield, respectively. The target compounds **4b** and **4c** were characterized by $^1H$ NMR, $^{31}P$ NMR, $^{13}C$ NMR, HRMS, and ESI-MS spectra. ESI mass spectra for all compounds showed




**Scheme 1**

$[M+H]^+$ ion. Their structures were similar and **4b** was chosen as a sample to explain. In $^1H$ NMR spectra, two doublet peaks at 7.03 and 7.51 ppm were assigned to the protons on the benzene ring due to their interaction with each other. A single peak at 5.13 ppm was assigned to methylene group protons between benzene and imidazole. Three singlet peaks for imidazole group protons were observed at 6.91, 7.1, and 7.58 ppm, respectively.

The $^{31}P$ NMR spectra of compounds **1–5** are similar. It shows that the two phosphorus nuclei are chemically equivalent, and their chemical shifts are recorded as doublets ($^2J_{PP}$ = 93 Hz) at low magnetic fields around 25 ppm. The only explanation for the coupling split is that the two phosphorus nuclei are substituted by diphenol groups. A triplet peak at high magnetic fields, observed around 9 ppm, was assigned to the phosphorus nuclei which were substituted by two phenol groups.

## CONCLUSION

Three novel bidentate cyclotriphosphazene derivatives were synthesized from spiro derivatives [$N_3P_3Cl_2(O_2C_{12}H_8)_2$]. The title compounds were obtained through subsequent reduction of aldehyde groups, bromination reaction of alcohol groups, and substitution reactions with macrocyclic polyamide, imidazole, or morpholine. The target compounds were characterized using IR, $^1$H NMR, $^{31}$P NMR, $^{13}$C NMR, and mass spectrometry. The DNA cleavage activity of the title compounds is currently being examined.

## EXPERIMENTAL

### General

$^1$H NMR and $^{31}$P NMR spectra were measured by using a Bruker AC-P400 spectrometer with TMS and 85% $H_3PO_4$ as the internal and external reference, respectively, and with $CDCl_3$ or DMSO as the solvent. Mass spectra were acquired in positive ion mode using a Bruker ESQUIRE-LCTM ion trap spectrometer equipped with a gas nebulizer probe, capable of analyzing ions up to *m/z* 20,000. The high-resolution mass spectral data for **4b** was recorded on a Bruker APEXII Fourier transform ion cyclotron resonance (FTICR) MS instrument with an external ion source and analyzed using liquid secondary ion (LSI) MS with a Cs ion gun in the positive ion mode. Solvents were purified and dried by standard procedures.

### Preparation of 1,1,3,3-Tetraphenylyloxy-5,5,-Bikis(4-Hydroxylmethyl phenoxy)Cyclotri- Phosphazene (2)

To a solution of **1** (0.75 g, 1 mmoL) in THF/MeOH (20:10 mL) was added sodium borohydride (0.12 g) at 0 °C under $N_2$. The reaction mixture was stirred for 5 h at room temperature. After removal of the solvent under reduced pressure, the pure solid was obtained by recrystallized from ethanol. Yield 85%, mp: 112–114 °C; $^{31}$P NMR ($CDCl_3$): $\delta$ 24.7 (d,-P($O_2C_{12}H_8$)$_2$, $J$ = 93.9 Hz), 8.8 (t, P(-O-$C_6H_4$-)$_2$, $J$ = 92.3 Hz); ESI-MS: *m/z* 750 $[M+H]^+$, *m/z* 772 $[M+Na]^+$, *m/z* 788 $[M+K]^+$.

### Preparation of 1,1,3,3-Tetraphenylyloxy-5,5,-Bikis(4-Bromomethyl phenoxy)Cyclotri- Phosphazene (3)

Compound **2** (1.49 g, 2 mmol) was placed into a 100 mL round-bottom flask with THF (30 mL) under an argon atmosphere. Then, phosphorus tribromide (1.1 mL) in THF (10 mL) was added dropwise at 0 °C and the mixture was stirred 5 h. The organic solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The residue washed with aq. $K_2CO_3$, extracted with $CHCl_3$ (3 × 10 mL). The organic layer was dried over $Na_2SO_4$ and the evaporated under reduced pressure. The remaining residue was purified by silica gel column chromatography ($CH_2Cl_2$/petroleum ether) to provide **3** as a colorless solid. Yield 72.4%, mp 219 °C–221 °C; $^1$H NMR ($CDCl_3$): $\delta$ 7.49 (d, 4*H*, $J$ = 7.6 Hz), 7.43 (d, 4H, $J$ = 8.2 Hz), 7.39–7.25 (m, 12H), 7.03 (d, 4*H*, $J$ = 8.2 Hz), 4.51 (s, 4H, -$CH_2$-Ph-); $^{13}$C NMR ($CDCl_3$): $\delta$ 150.6, 148.0, 134.8, 130.4, 129.7, 129.5, 128.6, 126.0, 121.8, 121.5, 32.8; $^{31}$P NMR ($CDCl_3$): $\delta$ 25.3 (d, -P($O_2C_{12}H_8$)$_2$, $J$ = 92.7 Hz), 9.8 (t, P(-O-$C_6H_4$-)$_2$, $J$ = 93.6 Hz); ESI-MS: *m/z* 876 $[M+H]^+$.

## Preparation of 4

Imidazole, Boc-cyclen, or morpholine (10 mmoL) and compound **3** (10 mmol) were placed into a 50 mL round-bottom flask with $CH_3CN$ (30 mL) and $Na_2CO_3$ (0.5 g). The reaction mixture was allowed to warm to reflux and stirred 48 h under Ar. The solvent was removed by rotary evaporation and the residue was chromatographed on a silica gel column (petroleum ether:AcOEt = 1:1.5) to give pure title compound **4**.

**1,1,3,3-tetraphenylyloxy-5,5,-bikis[4-(1,4,7,10-(1,4,7-tricarboxylic acid tri-*tert*-butyl)- tetraazacyclododecanyl)methylphenoxy]cyclotriphosphazene (4a):** yield 77%; $^1$H NMR ($CDCl_3$): $\delta$ 7.49 (dd, 4H, -$C_6H_4$, $J$ = 7.6 Hz), 7.39 (t, 4H, -$C_{12}H_8$, $J$ = 6.8 Hz), 7.33–7.28 (m, 12H, -$C_{12}H_8$), 7.08 (d, 4H, -$C_6H_4$, $J$ = 8.0 Hz), 3.77 (s, 4H, -$CH_2$-Ph), 3.57 (s, 8H, -$CH_2$-cyclen), 3.39–3.17 (m, 16H, -$CH_2$-cyclen) 2.69 (s, 8H, -$CH_2$-cyclen), 1.43 (t, 54H, -$CH_3$, $J$ = 11.6 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ 156.1, 155.6, 155.2, 150.0, 148.0, 133.8, 131.3, 129.7, 129.5, 128.7, 126.0, 121.7, 120.9, 120.8, 79.5, 79.4, 79.2, 56.3, 55.9, 55.3, 50.0, 48.7, 48.0, 47.5, 47.2, 28.6, 28.4; $^{31}$P NMR ($CDCl_3$): $\delta$ 25.6 (d, -P($O_2C_{12}H_8$)$_2$, $J$ = 92.7 Hz), 9.2 (t, P(-O-$C_6H_4$-)$_2$, $J$ = 92 Hz); ESI-MS: *m/z* 1681 $[M+Na]^+$.

**1,1,3,3-tetraphenylyloxy-5,5,-bikis(4-imdazolylmethylphenoxy)cyclotriphosphazene (4b)**: yield 59.6%; $^1$H NMR ($CDCl_3$): $\delta$ 7.58 (s, 2H, -N-CH=N-), 7.51 (dd, 4*H*, -$C_6H_4$, $J$ = 7.4 Hz), 7.38–7.29 (m, 12H, -$C_{12}H_8$), 7.18 (d, 4H, -$C_{12}H_8$, $J$ = 8.4Hz), 7.10 (s, 2H, =CH-N=), 7.03 (d, 4*H*, -$C_6H_4$, $J$ = 8.0 Hz), 6.91 (s, 2H, -N-$CH_2$ = C-), 5.13 (s, 4H, -$CH_2$-Ph); $^{13}$C NMR ($CDCl_3$): $\delta$ 150.5, 147.9, 137.3, 133.2, 129.9, 129.7, 129.6, 128.6, 128.5, 126.1, 121.7, 121.6, 119.1; $^{31}$P NMR ($CDCl_3$): $\delta$ 25.3 (d, P($O_2C_{12}H_8$)$_2$, $J$ = 93.2 Hz); 9.5 (t, P(-O-$C_6H_4$-)$_2$, $J$ = 92.3 Hz); ESI-MS: *m/z* 850 $[M+H]^+$; HR-MS: *m/z* found 850.1866 (calcd. 850.1862) $[M+H]^+$.

**1,1,3,3-tetraphenylyloxy-5,5-bikis(4-morpholinomethylphenoxy)cyclotriphosphazene (4c)**: yield 62.0%; $^1$H NMR ($CDCl_3$): $\delta$7.51 (dd, 4H, -$C_6H_4$, $J$ = 7.6 Hz), 7.40–7.29 (m, 16H, -$C_{12}H_8$), 7.07 (d, 4H, -$C_6H_4$, $J$ = 7.6 Hz), 3.69 (t, 8H, $CH_2$-O-, $J$ = 4.4 Hz), 3.51 (s, 4H, -$CH_2$-Ph), 2.54 (t, 8H, N-$CH_2$-C-, $J$ = 4.4 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$149.9, 148.0, 134.7, 130.2, 129.5, 128.7, 126.0, 121.0, 121.0, 120.9, 66.9, 62.8, 53.5; $^{31}$P NMR ($CDCl_3$): $\delta$ 25.6 (d, -P($O_2C_{12}H_8$)$_2$, $J$ = 92.3 Hz), 9.7 (t, P(-O-$C_6H_4$-)$_2$, $J$ = 92.3 Hz); ESI-MS: *m/z* 888 $[M+H]^+$, *m/z* 910 $[M+Na]^+$.

## Preparation of 5a

To a solution of **4a** (1.68 g, 1 mmol) in dry $CH_2Cl_2$ (50 mL) at 0 °C, $CF_3COOH$ (15 mL) was added dropwise under $N_2$. The mixture was stirred for 7 h at room temperature. After removal of the solvent, the residue was adjusted to pH 14 by NaOH aqueous solution, and extracted with $CHCl_3$ (5 × 15 mL). The organic phase was collected and dried over $Na_2SO_4$. After removal of the solvent, the desired colorless solid was obtained in 95.4% yield.

**1,1,3,3-tetraphenylyloxy-5,5,-bikis[4-(1,4,7,10-tetraazacyclododecanyl)methylphenoxy]cyclotriphosphazene (5a):** $^1$H NMR ($CDCl_3$): $\delta$ 7.45 (dd, 4H, -$C_6H_4$, $J$ = 7.6 Hz), 7.38 (m, 4H, -$C_{12}H_8$), 7.29 (m, 12H, -$C_{12}H_8$), 7.10 (d, 4H, -$C_6H_4$, $J$ = 7.6 Hz), 3.67 (s, 4H, -$CH_2$-Ph), 2.78 (t, 8H, -$CH_2$-cyclen, $J$ = 4.4 Hz), 2.66 (d, 8H, -$CH_2$-cyclen, $J$ = 5.6 Hz), 2.62 (d, 8H, -$CH_2$-cyclen, $J$ = 5.6 Hz), 2.56 (t, 8H, -$CH_2$-cyclen, $J$ = 5.2 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ 149.9, 148.3, 135.7, 130.1, 129.6, 129.5, 128.7, 126.0, 121.8, 121.0, 58.9, 51.4, 47.6, 46.3, 45.7; $^{31}$P NMR ($CDCl_3$): $\delta$ 25.6 (d, -P($O_2C_{12}H_8$)$_2$, $J$ = 91.5 Hz), 9.2 (t, P(-O-$C_6H_4$-)$_2$, $J$ = 89.3 Hz); ESI-MS: *m/z* 1058 $[M+H]^+$.

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