SELECTIVE SYNTHESIS OF 2,2-DIAMINO-4,4,6,6-
TETRAKIS(ARYLOXY)CYCLOTRIPHOSPHAZENES \( \text{N}_3\text{P}_3\text{-(NH}_2\text{)}_2\text{-}
4,4,6,6\text{-}(\text{ArO})_4 \)

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Abstract – To synthesize cyclotriphosphazene derivatives having multi-functional
groups, aryloxylation of 2,2-diamino-4,4,6,6-tetrachlorocyclotriphosphazene \( \text{2} \)
was examined. A mixture of gem-disubstituted \( \text{N}_3\text{P}_3\text{(NH}_2\text{)}_2\text{(ArO)}_2\text{Cl}_2 \text{9}_{\text{gem}} \),
tri-substituted \( \text{N}_3\text{P}_3\text{(NH}_2\text{)}_2\text{(ArO)}_3\text{Cl}_1 \text{10} \), and tetra-substituted \( \text{N}_3\text{P}_3\text{(NH}_2\text{)}_2\text{(ArO)}_4 \text{11} \)
was obtained, especially \( \text{11} \) was obtained selectively when excess amount (6 equiv.)
of \( \text{ArONa} \) was used. On the other hand, mono-substituted \( \text{N}_3\text{P}_3\text{(NH}_2\text{)}_2\text{(ArO)}_2\text{Cl}_3 \text{8} \)
and non-gem-di-substituted \( \text{N}_3\text{P}_3\text{(NH}_2\text{)}_2\text{(ArO)}_2\text{Cl}_2 \text{9}_{\text{non-gem-cis}} \) and \( \text{9}_{\text{non-gem-trans}} \) were
not detected.

Hexachlorocyclotriphosphazene (HCCP, \( \text{N}_3\text{P}_3\text{Cl}_6 \)) has a flat six-membered ring in which three \( \text{N} \) atoms
and three \( \text{P} \) atoms connect alternately, and two \( \text{Cl} \) atoms on each \( \text{P} \) atom.\(^1\) The \( \text{Cl-P} \) bond of HCCP easily
reacts with several kinds of nucleophiles. To prepare multi-functionalized cyclotriphosphazene
derivatives for developing multi-functionalized materials,\(^2\) partial substitution of HCCP would be an
important method to introduce more than one kind of substituent (Figure 1).

![Figure 1. Preparation of Cyclotriphosphazene Derivatives Having Multi-types of Nucleophiles](image)

We previously reported that gaseous \( \text{NH}_3 \) was allowed to react with HCCP to afford 2,2-diamino-4,4,6,6-
tetrachlorocyclotriphosphazene \( \text{2} \) (in \( \text{Et}_2\text{O} \)) and/or 2,2,4,4-tetraamino-6,6-dichlorocyclotriphosphazene
(3) (in MeCN), respectively, and 3 was converted to 2,2,4,4-tetraamino-6,6-bis(aryloxy)cyclotriphosphazene (4) by treatment with ArOH/K$_2$CO$_3$ (Scheme 1).$^3$ HCCP was allowed to react with arylthiol (ArSH) in the presence of NEt$_3$ in MeCN to give 2,2-bis(arylthio)-4,4,6,6-tetrachlorocyclotriphosphazene (5, ArSH, NEt$_3$ = 2 equiv.) and 2,2,4,4-tetakis(arylthio)-6,6-dichlorocyclotriphosphazene (6, ArSH, NEt$_3$ = 4 equiv.) (Scheme 2).$^4$ In these reactions, nucleophiles were introduced in gem-manner, and non-gem-derivatives were not detected (Scheme 3). On the other hand, phenols were introduced in HCCP in non-gem-manner: Non-gem-cis-derivatives and non-gem-trans-derivatives were obtained as major isomers.$^5$ We also reported the second substitution of 5.$^6$

![Scheme 1. Synthesis of Aminochlorocyclotriphosphazenes 2 and 3](image1)

![Scheme 2. Synthesis of Arylthiochlorocyclotriphosphazenes 5 and 6](image2)

![Scheme 3. Synthesis of Di-substituted Tetrachlorocyclotriphosphazenes](image3)

In this paper, we described the second substitution of 2 with phenols 7 to give N$_3$P$_3$(NH$_2$)$_2$Cl$_{4-n}$(OAr)$_n$ 9-11.$^7$ In this case, there are several problems in partial aryloxylation: (1) Is number of ArOH introduced controllable? (2) How is the regio/stereochemistry of di-substituted product 9? Gem 9$_{gem}$/non-gem-cis 9$_{non-gem-cis}$/non-gem-trans 9$_{non-gem-trans}$? (Scheme 4).
Scheme 4. Synthesis of 2,2-Diaminochloroaryloxycyclotriphosphazenes 9-11

Firstly, we examined solvent effect, since solvent played an important role in the reaction of HCCP with ammonia (Table 1). Compound 2 was treated with 1 equiv. of 4-chlorophenol (7c) and K$_2$CO$_3$, revealing that acetone having highest (relative dielectric constant) value among 7 solvents gave the best result. Interestingly, only a mixture of di-substituted product 9$_{gem}^c$ and 2 was obtained even 1 equiv. of 7c was used, whereas mono-substituted 8c was not detected. On the other hand, when HCCP was treated with 1 equiv. of sodium 4-chlorophenoxide, a mixture of HCCP, mono-substituted N$_3$P$_3$Cl$_2$(OC$_6$H$_4$-Cl-4)$_2$, and non-gem-di-substituted products N$_3$P$_3$Cl$_4$(OC$_6$H$_4$-Cl-4)$_2$ (a 1:1 mixture of cis and trans-isomers) was obtained, and gem-di-substituted isomer was not detected.

Table 1. Solvent Effect in the Reaction of 2 with 4-Chlorophenol in the Presence of K$_2$CO$_3$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solv</th>
<th>dielectric constant</th>
<th>Product ratio$^a$</th>
<th>9$_{gem}^c$</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>2.3</td>
<td>7</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Et$_2$O</td>
<td>4.3</td>
<td>n.d.$^b$</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>7.7</td>
<td>4</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2-butanone</td>
<td>18.5</td>
<td>n.d.$^b$</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Relative product ratio was determined by $^{31}$P NMR of the reaction mixture. $^b$Not detected. $^c$A complex mixture not including 2 was obtained.
Next, we examined equiv. of phenols (Table 2). When 2 was treated with 6 equiv. of 4-hydroxyacetophenone (7a) with K₂CO₃, a mixture of 10a (tri-substituted) and 11a (tetra-substituted products) was obtained and 2 and 9_gem_a (di-substituted) were not detected (Entry 1). When 7a/NaH (6 equiv.) was used at 50 ºC, only 11a was obtained (Entry 2), whereas a mixture of 2 and di-substituted 9_gem_a was obtained and 10a and 11a were not detected when less than 3 equiv. of NaH was used (Entries 3, 4). Li and/or Na phenoxides (7a’, and 7a”, 6 equiv.) gave a mixture of 2, 9_gem_a, 10a, and 11a (Entries 5-8). As a result, use of phenols (6 equiv.) and NaH (6 equiv.) in acetone at 50 ºC gave tetra-substituted 11a selectively.

Table 2. Reaction Conditions and Products Distribution

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp</th>
<th>reagents</th>
<th>Product ratio&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>rt</td>
<td>7a + K₂CO₃ (6.0/6.0 equiv.)</td>
<td>n.d.&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>7a + NaH (6.0/6.0 equiv.)</td>
<td>n.d.&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>7a + NaH (4.0/2.4 equiv.)</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>7a + NaH (3.0/1.8 equiv.)</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>-20</td>
<td>7a’ (Li phenoxide, 6.0 equiv.)</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>rt</td>
<td>7a’ (Li phenoxide, 6.0 equiv.)</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>7a’ (Li phenoxide, 6.0 equiv.)</td>
<td>n.d.&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>7a” (Na phenoxide, 6.0 equiv.)</td>
<td>n.d.&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Product ratio was determined by ³¹P NMR of the reaction mixture.
<sup>b</sup>Not detected.
Finally, we examined the aryloxylation with several phenols (Table 3). Phenols having electron-withdrawing groups (EWG: Entries 1-4) and electron-donating groups (EDG: Entries 5-6) gave tetra-substituted products 11: a small amount of tri-substituted 10f was detected with phenol having a strong EDG group (p-methoxyphenol (3f): Entry 6).

Table 3. Aryloxylation of 2,2-Diamino-4,4,6,6-tetrachlorocyclotriophosphazene 2 with Phenols

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArOH (7)</th>
<th>Hammett parameter as ρ-substituent</th>
<th>ratio of 11/%</th>
<th>Isolated yield of 11/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO-C₆H₄-C(=O)Me-ρ (7a)</td>
<td>0.50</td>
<td>11a 100</td>
<td>62°C</td>
</tr>
<tr>
<td>2</td>
<td>HO-C₆H₄-C(=O)OMe-ρ (7b)</td>
<td>0.45</td>
<td>11b 100</td>
<td>58°C</td>
</tr>
<tr>
<td>3</td>
<td>HO-C₆H₄-Cl-ρ (7c)</td>
<td>0.23</td>
<td>11c 100</td>
<td>86°C</td>
</tr>
<tr>
<td>4</td>
<td>HO-C₆H₄-F-ρ (7d)</td>
<td>0.06</td>
<td>11d 100</td>
<td>84°C</td>
</tr>
<tr>
<td>5</td>
<td>HO-C₆H₄-Me-ρ (7e)</td>
<td>-0.17</td>
<td>11e 100</td>
<td>88°C</td>
</tr>
<tr>
<td>6</td>
<td>HO-C₆H₄-OMe-ρ (7f)</td>
<td>-0.27</td>
<td>11f 85b</td>
<td>68°C</td>
</tr>
</tbody>
</table>

*Product ratio was determined by ³¹P NMR. b11% 10f and 4% unidentified product. cIsolated by recrystallization. dIsolated by silica gel column chromatography.

In conclusion, aryloxylation of 2,2-diamino-4,4,6,6-tetrachlorocyclotriophosphazene 2 was examined. When 1 equiv. of ArOH/K₂CO₃ was used, a mixture of 2 and gem-di-substituted 9_gem_ was obtained, whereas mono-substituted N₃P₃(NH₂)₂(OAr)Cl 8 and non-gem-di-substituted 9_non-gem-cis_ and 9_non-gem-trans_ were not detected. On the other hand, tetra-substituted N₃P₃(NH₂)₂(OAr)₄ 11 and a small amount of tri-substituted N₃P₃(NH₂)₂(OAr)₃Cl 10 were obtained under conditions of phenols (6 equiv.), NaH (6 equiv.), acetone, 50 °C.

**EXPERIMENTAL**

**Synthesis of 2,2-Diamino-4,4,6,6-tetrachlorocyclotriophosphazene (2):**
Et₂O (200 mL) solution of HCCP (6.96 g, 20 mmol) was stirred for 20 h under NH₃ atmosphere at room temperature to give colorless precipitates. The reaction mixture was filtered, and the precipitates were washed with Et₂O (20 mL x 2). Then the precipitates were washed with hot MeCN (50 mL x 4), and the MeCN washings were concentrated under reduced pressure and dried in vacuo to give 2 (colorless solid, 5.97 g, 19.3 mmol, 96% yield).¹²

2,2-Diamino-4,4,6,6-tetrachlorocyclotriphosphazene (2): ¹³P NMR (162 MHz, CDCl₃) δ 21.63 (d, J = 50.8 Hz, 2P), 9.17 (t, J = 50.8 Hz, 1P).

Reaction of 2 with Aryloxides (Table 2)

2 was treated with ArOH and base under conditions summarized in Table 2. The reaction mixture was poured into sat. aq. K₂CO₃ and extracted with EtOAc. The combined organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was analyzed by ¹³P NMR.

2,2-Diamino-4,4-bis(4-chlorophenoxy)-6,6-dichlorocyclotriphosphazene (9<sub>gem</sub>): ¹³P NMR (162 MHz, CDCl₃) δ 24.16 (dd, J = 53.3, 68.1 Hz, 1P), 16.31 (dd, J = 59.5, 68.1 Hz, 1P), 11.86 (t, J = 58.2 Hz, 1P).

2,2-Diamino-4,4-bis(4-acetylphenoxy)-6,6-dichlorocyclotriphosphazene (9<sub>gem</sub>): ¹³P NMR (162 MHz, CDCl₃) δ 24.16 (dd, J = 53.3, 70.6 Hz, 1P), 15.93 (dd, J = 57.0, 66.9 Hz, 1P), 11.79 (t, J = 57.0 Hz, 1P).

2,2-Diamino-4,4,6-tris(4-acetylphenoxy)-6-chlorocyclotriphosphazene (10a): ¹³P NMR (162 MHz, CDCl₃) δ 21.02 (dd, J = 65.6, 83.0 Hz, 1P), 15.69 (t, J = 68.1 Hz, 1P), 6.36 (dd, J = 68.1, 83.0 Hz, 1P).

2,2-Diamino-4,4,6-tris(4-methoxyphenoxy)-6-chlorocyclotriphosphazene (10f): ¹³P NMR (162 MHz, CDCl₃) δ 22.74 (dd, J = 63.2, 76.8 Hz, 1P), 17.05 (t, J = 63.2 Hz, 1P), 9.20 (dd, J = 63.2, 76.8 Hz, 1P).
Synthesis of 2,2-Diamino-4,4,6,6-tetrakis(aryloxy)cyclotriphosphazene:

To an acetone (5 mL) solution of ArOH (7, 3 mmol) was added NaH (3 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 0.5 h. To the resultant mixture was added 2 (0.5 mmol), and the resultant was stirred at 50 °C for 20 h. The reaction mixture was poured into sat. aq. K₂CO₃ and extracted with EtOAc (20 mL x 4). The combined organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography or recrystallization to give the desired product.

2,2-Diamino-4,4,6,6-tetrakis(4-acetylphenoxy)cyclotriphosphazene (11a); ³¹P NMR (162 MHz, CDCl₃) δ 16.94 (t, J = 70.6 Hz, 1P), 8.29 (d, J = 70.6 Hz, 2P); ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, J = 8.7 Hz, 8H), 7.18 (d, J = 8.7 Hz, 8H), 2.55 (s, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 196.83, 154.36, 134.20, 121.05, 26.64; ESI-MS (neg. mode) 742.1180 (M + Cl -), Calcd for C₃₂H₃₂Cl₅N₅O₈P₃ 742.1152.

2,2-Diamino-4,4,6,6-tetrakis(4-methoxycarbonylphenoxy)cyclotriphosphazene (11b); ³¹P NMR (162 MHz, CDCl₃) δ 16.95 (t, J = 70.6 Hz, 1P), 8.27 (d, J = 68.1 Hz, 2P); ¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, J = 8.7 Hz, 8H), 7.16 (d, J = 8.7 Hz, 8H), 3.89 (s, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 166.27, 154.35, 131.38, 131.38, 127.09, 120.96, 52.32; ESI-MS (neg. mode) 770.1188 (M - H -), Calcd for C₃₂H₃₁N₅O₁₂P₃ 770.1182.

2,2-Diamino-4,4,6,6-tetrakis(4-chlorophenoxy)cyclotriphosphazene (11c); ³¹P NMR (162 MHz, CDCl₃) δ 17.72 (t, J = 69.4 Hz, 1P), 10.10 (d, J = 69.4 Hz, 2P); ¹H NMR (400 MHz, CDCl₃) δ 7.21 (d, J = 9.2 Hz, 8H), 7.02 (d, J = 9.2 Hz, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 149.27, 130.58, 129.58, 122.54; ESI-MS (neg. mode) 709.9159 (M + Cl -), Calcd for C₂₄H₂₁Cl₃N₅O₄P₃ 709.9171.

2,2-Diamino-4,4,6,6-tetrakis(4-fluorophenoxy)cyclotriphosphazene (11d); ³¹P NMR (162 MHz, CDCl₃) δ 17.62 (t, J = 66.9 Hz, 1P), 10.13 (d, J = 66.9 Hz, 2P); ¹H NMR (400 MHz, CDCl₃) δ 7.05 (dd, J = 9.2, 4.4 Hz, 8H), 6.93 (dd, J = 9.2, 8.2 Hz, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 243.45 (d, J = 243.5 Hz), 146.68, 122.58 (d, J = 7.67 Hz), 116.08 (d, J = 24.0 Hz); ¹⁹F NMR δ from -117.48 to -117.7 (m); ESI-MS (neg. mode) 646.0395 (M + Cl -), Calcd for C₂₄H₂₀ClF₃N₅O₄P₃ 646.0353.
2,2-Diamino-4,4,6,6-tetrakis(4-methylphenoxy)cyclotriphosphazene (11e); $^{31}$P NMR (162 MHz, CDCl$_3$) δ 17.94 (t, $J = 66.7$ Hz, 1P), 10.72 (d, $J = 66.7$ Hz, 2P); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.50-6.80 (m, 16H), 2.29 (s, 12H), $^{13}$C NMR (100 MHz, CDCl$_3$) δ 148.84, 134.28, 129.88, 121.16, 20.90; ESI-MS (neg. mode) 630.1329 (M + Cl$^-$), Calcd for C$_{28}$H$_{32}$ClN$_5$O$_4$P$_3$ 630.1356.

2,2-Diamino-4,4,6,6-tetrakis(4-methoxyphenoxy)cyclotriphosphazene (11f); $^{31}$P NMR (162 MHz, CDCl$_3$) δ 19.04 (t, $J = 65.6$ Hz, 1P), 11.52 (d, $J = 65.6$ Hz, 2P); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.02 (s, 8H), 6.74 (s, 8H), $^{13}$C NMR (100 MHz, CDCl$_3$) δ 156.58, 144.54, 122.23, 114.37, 55.62; ESI-MS (neg. mode) 694.1140 (M + Cl$^-$), Calcd for C$_{28}$H$_{32}$ClN$_5$O$_8$P$_3$ 694.1152.

Synthesis of Lithium 4-Acetylphenoxide (7a')

\[
\begin{array}{c}
\text{LiOH·H}_2\text{O} \\
\text{H}_2\text{O}
\end{array}
\]

A mixture of 4-hydroxyacetophenone (3a, 1.36 g, 10 mmol), LiOH·H$_2$O (0.422 g, 10.1 mmol), and H$_2$O (25 mL) was stirred at room temperature for 30 min, and poured into toluene (100 mL). The mixture was evaporated at 1 atm to remove H$_2$O by azeotrope, and the residue was dried under reduce pressure to obtain lithium 4-acetylphenoxide (7a').

Synthesis of Sodium 4-Acetylphenoxide (7a'')

\[
\begin{array}{c}
\text{NaOH} \\
\text{H}_2\text{O}
\end{array}
\]

A suspension of 4-hydroxyacetophenone (3a, 1.36 g, 10 mmol) and aq. NaOH (0.5 M, 20 mL, 10.0 mmol) was stirred at room temperature for 30 min, and poured into toluene (100 mL). The mixture was evaporated at 1 atm to remove H$_2$O by azeotrope, and the residue was dried under reduce pressure to obtain sodium 4-acetylphenoxide (7a'').

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES


8. Nucleophilicity of OAr\(^-\) would be high in polar solvent because solvation of counter cationic metal would occur efficiently. Dielectric constant was used as a measure of polarity of the solvent. Solubility of 2 (high in a polar solvent) would also have an effect on the reactivity.

9. PCl\(_2\) of HCCP and 2 appeared at 20-24 ppm, whereas P(NH\(_2\))\(_2\) and PCl(OAr) appeared at 9.2 and 12-14 ppm (unpublished result) in \(^{31}\)P NMR. Substituted product showed at 24.2 (PCl\(_2\)), 11.9 (P(NH\(_2\))\(_2\)), and 16.3 ppm. Therefore, substituted product was deduced to be a gem-di-substituted species.


11. Though the selectivity (HCCP gave *non-gem*-products, whereas 2 only gave 9\(_{gem}\)) is a very interesting problem, the authors have no evidence for this problem in this stage. When mono-substituted compound 7 will be isolated and analyzed by X-ray crystallography and IR, some evidences will be obtained (bond length, vibration wave number, etc). Now, the authors are trying to make the 2,2-diamino-4-mono-phenoxydicyclotriphosphazene derivatives.

12. Ether solution, hot MeCN washings, and remained precipitates included unreacted 1 (HCCP), 2, and NH\(_4\)Cl, respectively.