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SELECTIVE SYNTHESIS OF 2,2-DIAMINO-4,4,6,6-TETRAKIS(ARYLOXY)CYCLOTRIPHOSPHAZENES N_3P_3-2,2-$(NH_2)_2$-4,4,6,6-$(ArO)_4$

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Abstract – To synthesize cyclotriphosphazene derivatives having multi-functional groups, aryloxylation of 2,2-diamimo-4,4,6,6-tetrachlorocyclotriphosphazene **2** was examined. A mixture of *gem*-disubstituted $N_3P_3(NH_2)_2(ArO)_2Cl_2$ **9*gem***, tri-substituted $N_3P_3(NH_2)_2(ArO)_3Cl$ **10**, and tetra-substituted $N_3P_3(NH_2)_2(ArO)_4$ **11** was obtained, especially **11** was obtained selectively when excess amount (6 equiv.) of ArONa was used. On the other hand, mono-substituted $N_3P_3(NH_2)_2(ArO)Cl_3$ **8** and *non-gem*-di-substituted $N_3P_3(NH_2)_2(ArO)_2Cl_2$ **9*non-gem-cis*** and **9*non-gem-trans*** were not detected.

Hexachlorocyclotriphosphazene (HCCP, $N_3P_3Cl_6$) has a flat six-membered ring in which three N atoms and three P atoms connect alternately, and two Cl atoms on each P atom.[1] The 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).

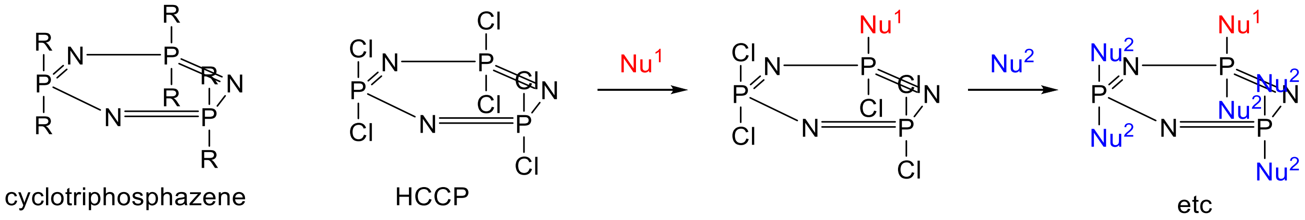
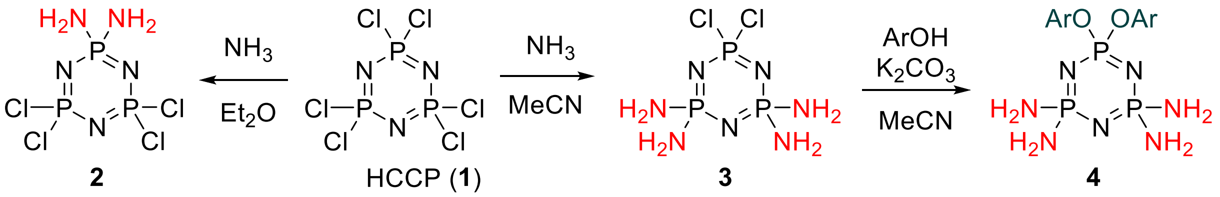


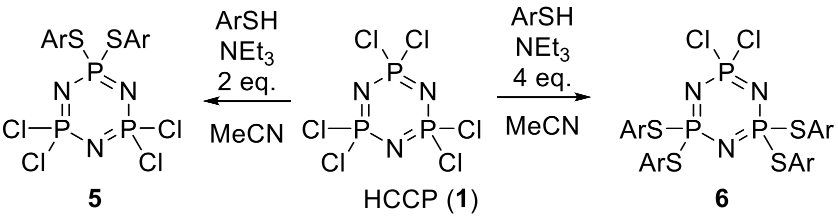
Figure 1. Preparation of Cyclotriphosphazene Derivatives Having Multi-types of Nucleophiles

We previously reported that gaseous NH_3 was allowed to react with HCCP to afford 2,2-diamino-4,4,6,6-tetrachlorocyclotriphosphazene (**2**) (in Et_2O) and/or 2,2,4,4-tetraamino-6,6-dichlorocyclotriphospohazene

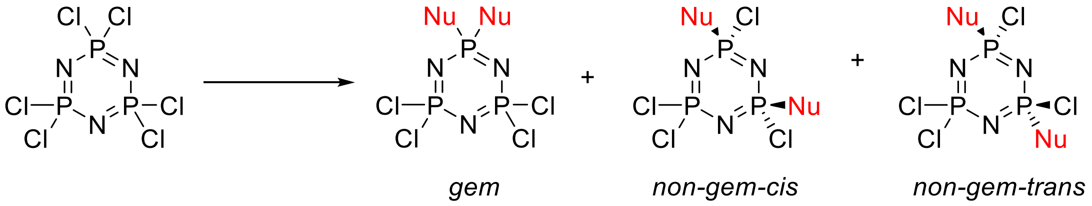
(**3**) (in MeCN), respectively, and **3** was converted to 2,2,4,4-tetraamino-6,6-bis(aryloxy)cyclotriphosphazene (**4**) by treatment with ArOH/K_2CO_3 (Scheme 1).[3] HCCP was allowed to react with arylthiol (ArSH) in the presence of NEt_3 in MeCN to give 2,2-bis(arylthio)-4,4,6,6-tetrachlorocyclotriphosphazene (**5**, ArSH, NEt_3 = 2 equiv.) and 2,2,4,4-tetrakis(arylthio)-6,6-dichlorocyclotriphospohazene (**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**

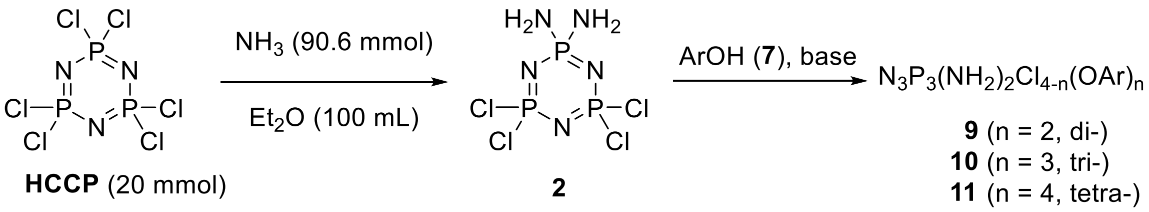


Scheme 2. Synthesis of Arylthiochlorocyclotriphosphazenes **5** and **6**



Scheme 3. Synthesis of Di-substituted Tetrachlorocyclotriphosphazenes

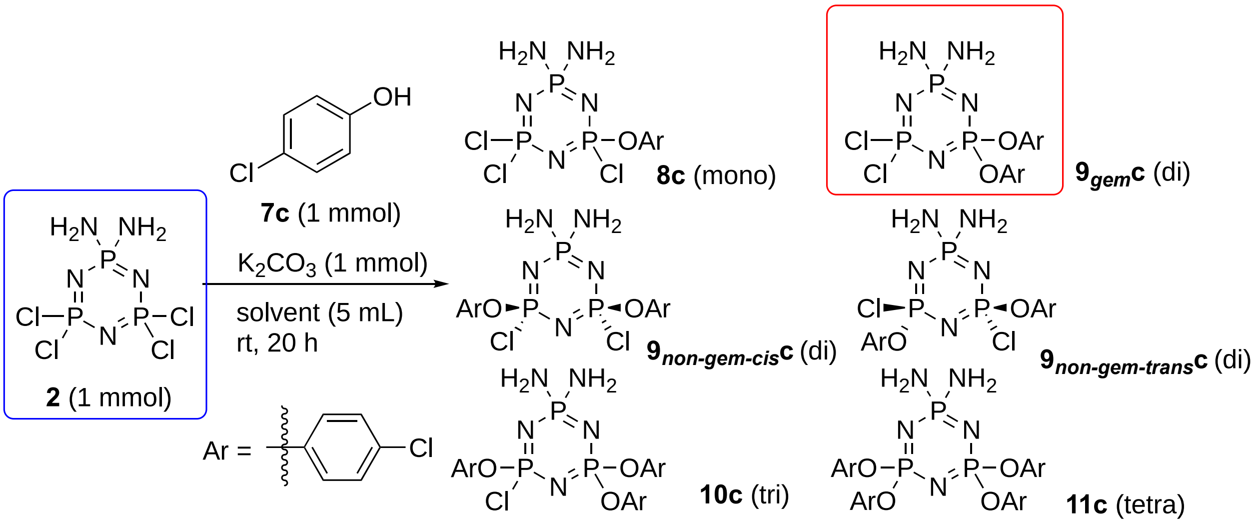
In this paper, we described the second substitution of **2** with phenols **7** to give $N_3P_3(NH_2)_2Cl_{4-n}(OAr)_n$ **9**-**11**.[7] In this case, there are several problems in partial aryloxylation: (1) Is number of ArOH introduced controllable? (2) How is the regio/stereochemistry of di-substituted product **9**? *Gem* $\mathbf{9}_{gem}$/*non-gem-cis* $\mathbf{9}_{non\text{-}gem\text{-}cis}$/*non-gem-trans* $\mathbf{9}_{non\text{-}gem\text{-}trans}$? (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).[3] Compound **2** was treated with 1 equiv. of 4-chlorophenol (**7c**) and K_2CO_3, revealing that acetone having highest (relative dielectric constant) value among 7 solvents gave the best result.[8] Interestingly, only a mixture of di-substituted product **9*gem*c**[9] 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 $N_3P_3Cl_5(OC_6H_4\text{-}Cl\text{-}4)$,[10] and *non-gem*-di-substituted products $N_3P_3Cl_4(OC_6H_4\text{-}Cl\text{-}4)_2$ (a 1 : 1 mixture of *cis* and *trans*-isomers) was obtained, and *gem*-di-substituted isomer was not detected.[11]

Table 1. Solvent Effect in the Reaction of **2** with 4-Chloropheol in the Presence of K_2CO_3

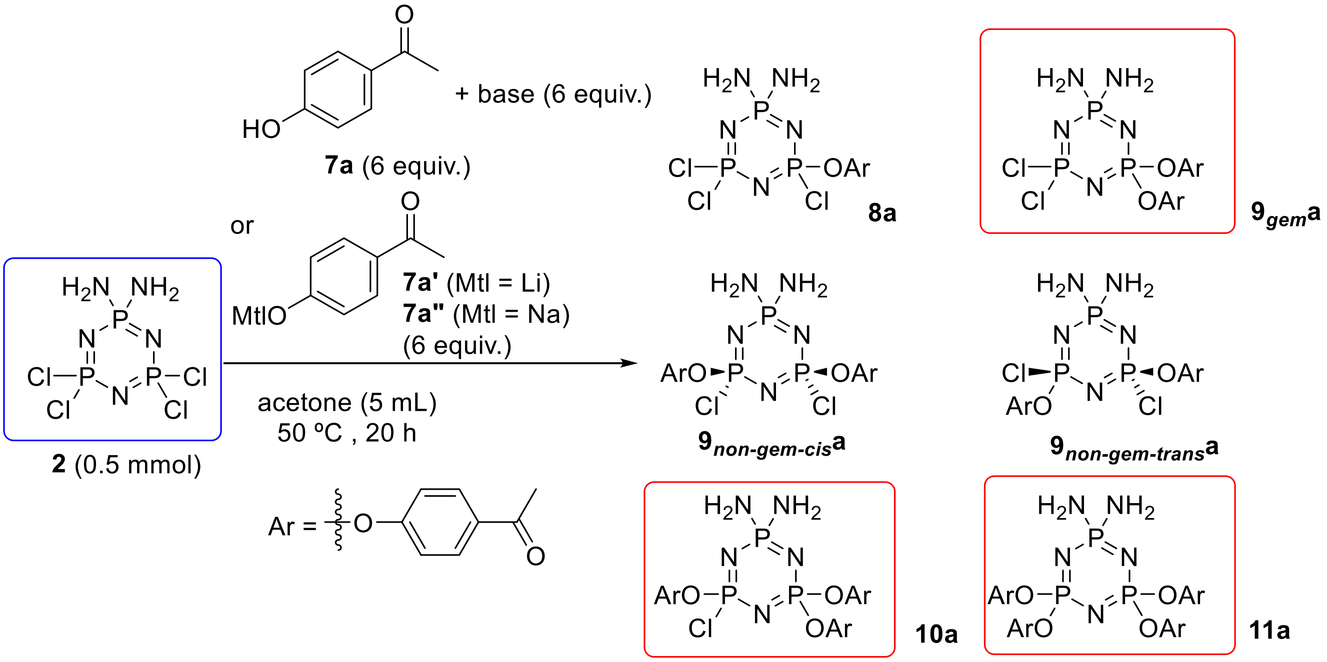


Entry	Solv	dielectric constant	Product ratio[a] 9*gem*c	2
1	Toluene	2.3	7	93
2	Et_2O	4.3	n.d.[b]	100
3	THF	7.7	4	96
4	2-butanone	18.5	n.d.[b]	100
5	acetone	20.5	22	78
6	PrCN	28.9	n.d.[b]	100
7[c]	MeCN	35.9	complex	n.d.[b]

[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 K_2CO_3, 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

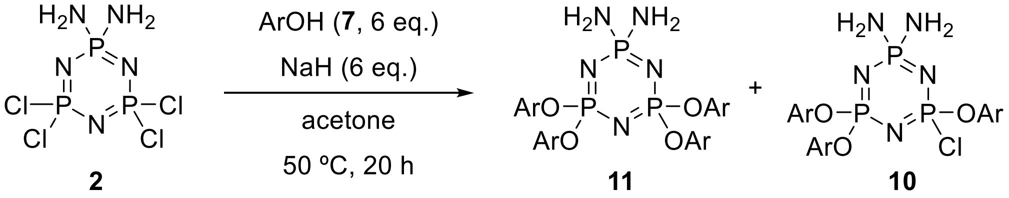


Entry	Temp	reagents	Product ratio[a]			
			2	**9*gem*a**	**10a**	**11a**
1	rt	**7a** + K_2CO_3 (6.0/6.0 equiv.)	n.d.[b]	n.d.[b]	60	40
2	50	**7a** + NaH (6.0/6.0 equiv.)	n.d.[b]	n.d.[b]	n.d.[b]	100
3	50	**7a** + NaH (4.0/2.4 equiv.)	57	43	n.d.[b]	n.d.[b]
4	50	**7a** + NaH (3.0/1.8 equiv.)	71	29	n.d.[b]	n.d.[b]
5	-20	**7a'** (Li phenoxide, 6.0 equiv.)	100	n.d.[b]	n.d.[b]	n.d.[b]
6	rt	**7a'** (Li phenoxide, 6.0 equiv.)	24	68	n.d.[b]	n.d.[b]
7	50	**7a'** (Li phenoxide, 6.0 equiv.)	n.d.[b]	n.d.[b]	76	24
8	50	**7a"** (Na phenoxide, 6.0 equiv.)	n.d.[b]	n.d.[b]	74	26

[a] Product ratio was determined by ^{31}P NMR of the reaction mixture.
[b] 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-Diamimo-4,4,6,6-tetrachlorocyclotriphosphazene **2** with Phenols



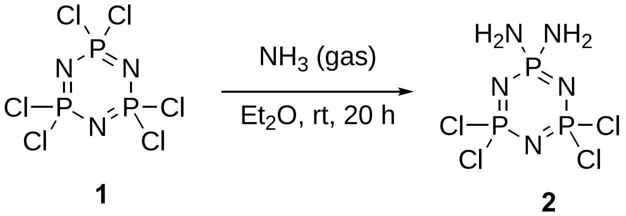
Entry	ArOH (**7**)	Hammett parameter as *p*-substituent		ratio of **11**/%[a]	Isolated yield of **11**/%
1	HO-C_6H_4-C(=O)Me-*p* (**7a**)	0.50	**11a**	100	62[c]
2	HO-C_6H_4-C(=O)OMe-*p* (**7b**)	0.45	**11b**	100	58[c]
3	HO-C_6H_4-Cl-*p* (**7c**)	0.23	**11c**	100	86[d]
4	HO-C_6H_4-F-*p* (**7d**)	0.06	**11d**	100	84[d]
5	HO-C_6H_4-Me-*p* (**7e**)	-0.17	**11e**	100	88[d]
6	HO-C_6H_4-OMe-*p* (**7f**)	-0.27	**11f**	85[b]	68[d]

[a] Product ratio was determined by ^{31}P NMR. [b] 11% **10f** and 4% unidentifird product.
[c] Isolated by recrystallization. [d] Isolated by silica gel column chromatography.

In conclusion, aryloxylation of 2,2-diamimo-4,4,6,6-tetrachlorocyclotriphosphazene **2** was examined. When 1 equiv. of ArOH/K_2CO_3 was used, a mixture of **2** and *gem*-di-substituted **9***gem* was obtained, whereas mono-substituted $N_3P_3(NH_2)_2(OAr)Cl_3$ **8** and *non-gem*-di-substituted **9***non-gem-cis* and **9***non-gem-trans* were not detected. On the other hand, tetra-substituted $N_3P_3(NH_2)_2(OAr)_4$ **11** and a small amount of tri-substituted $N_3P_3(NH_2)_2(OAr)_3Cl$ **10** were obtained under conditions of phenols (6 equiv.), NaH (6 equiv.), acetone, 50 °C.

EXPERIMENTAL

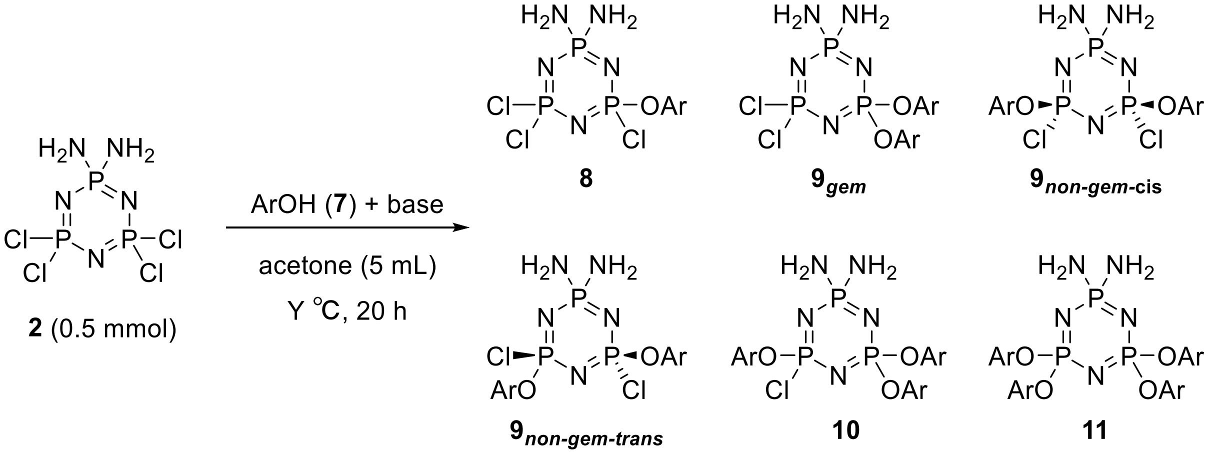
Synthesis of 2,2-Diamino-4,4,6,6-tetrachlorocyclotriphosphazene (2):



Et_2O (200 mL) solution of HCCP (6.96 g, 20 mmol) was stirred for 20 h under NH_3 atmosphere at room temperature to give colorless precipitates. The reaction mixture was filtered, and the precipitates were washed with Et_2O (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**); **^{31}P NMR** (162 MHz, $CDCl_3$) 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. K_2CO_3 and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was analyzed by ^{31}P NMR.

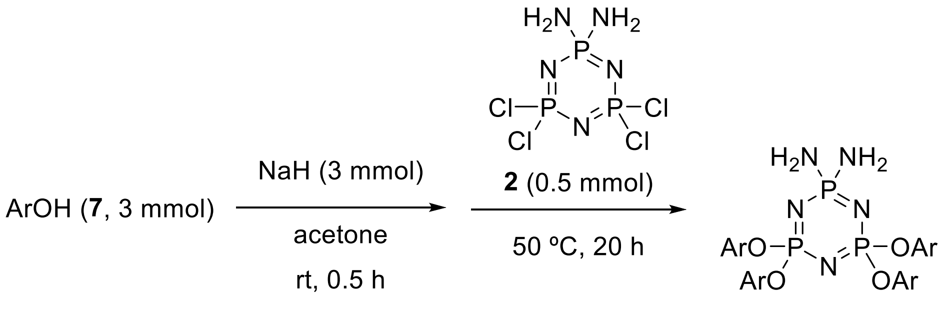
2,2-Diamino-4,4-bis(4-chlorophenoxy)-6,6-dichlorocyclotriphosphazene (**9**$_{gem}$**c**); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 24.16 (dd, *J* = 53.3, 68.1 Hz 1P), 16.31 (dd, *J* = 59.5, 68.1 Hz, 1P), 11.86 (t, *J* = 58.2 Hz, 1P).

2,2-Diamino-4,4-bis(4-acetylphenoxy)-6,6-dichlorocyclotriphosphazene (**9**$_{gem}$**a**); **^{31}P NMR** (162 MHz, $CDCl_3$) 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**); **^{31}P NMR** (162 MHz, $CDCl_3$) 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**); **^{31}P NMR** (162 MHz, $CDCl_3$) 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:



11

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 ºC for 20 h. The reaction mixture was poured into sat. aq. K_2CO_3 and extracted with EtOAc (20 mL x 4). The combined organic layer was dried over Na_2SO_4, 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**); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.94 (t, *J* = 70.6 Hz, 1P), 8.29 (d, *J* = 70.6 Hz, 2P); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.7 Hz, 8H), 7.18 (d, *J* = 8.7 Hz, 8H), 2.55 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.83, 154.36, 134.20, 121.05, 26.64; ESI-MS (neg. mode) 742.1180 (M + Cl$^-$), Calcd for $C_{32}H_{32}Cl_5N_5O_8P_3$ 742.1152 .

2,2-Diamino-4,4,6,6-tetrakis(4-methoxycarbonylphenoxy)cyclotriphosphazene (**11b**); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.95 (t, *J* = 70.6 Hz, 1P), 8.27 (d, *J* = 68.1 Hz, 2P); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.7 Hz, 8H), 7.16 (d, *J* = 8.7 Hz, 8H), 3.89 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{32}H_{31}N_5O_{12}P_3$ 770.1182.

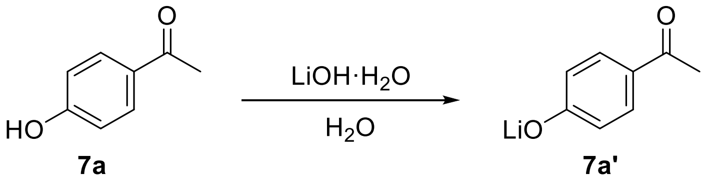
2,2-Diamino-4,4,6,6-tetrakis(4-chlorophenoxy)cyclotriphosphazene (**11c**); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 17.72 (t, *J* = 69.4 Hz, 1P), 10.10 (d, *J* = 69.4 Hz, 2P); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 9.2 Hz, 8H), 7.02 (d, *J* = 9.2 Hz, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.27, 130.58, 129.58, 122.54; ESI-MS (neg. mode) 709.9159 (M + Cl$^-$), Calcd for $C_{24}H_{20}Cl_5N_5O_4P_3$ 709.9171.

2,2-Diamino-4,4,6,6-tetrakis(4-fluorophenoxy)cyclotriphosphazene (**11d); ^{31}P NMR** (162 MHz, $CDCl_3$) δ 17.62 (t, *J* = 66.9 Hz, 1P), 10.13 (d, *J* = 66.9 Hz, 2P); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 9.2, 4.4 Hz, 8H), 6.93 (dd, *J* = 9.2, 8.2 Hz, 8H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 243.45 (d, *J* = 243.5 Hz), 146.68, 122.58 (d, *J* = 7.67 Hz), 116.08 (d, *J* = 24.0 Hz); ^{19}F NMR δ from -117.48 to -117.7 (m); ESI-MS (neg. mode) 646.0395 (M + Cl$^-$), Calcd for $C_{24}H_{20}ClF_4N_5O_4P_3$ 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 $C_{28}H_{32}ClN_5O_4P_3$ 630.1356.

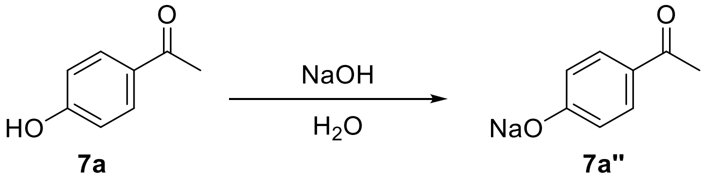
2,2-Diamino-4,4,6,6-tetrakis(4-methoxyphenoxy)cyclotriphosphazene (**11f**); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 19.04 (t, *J* = 65.6 Hz, 1P), 11.52 (d, *J* = 65.6 Hz, 2P); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 8H), 6.74 (s, 8H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.58, 144.54, 122.23, 114.37, 55.62; ESI-MS (neg. mode) 694.1140 (M + Cl^-), Calcd for $C_{28}H_{32}ClN_5O_8P_3$ 694.1152.

Synthesis of Lithium 4-Acetylphenoxide (**7a'**)



A mixture of 4-hydroxyacetophenone (**3a**, 1.36 g, 10 mmol), $LiOH \cdot H_2O$ (0.422 g, 10.1 mmol), and H_2O (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_2O by azeotrope, and the residue was dried under reduce pressure to obtain lithium 4-acetylphenoxide (**7a'**).

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



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_2O by azeotrope, and the residue was dried under reduce pressure to obtain sodium 4-acetylphenoxide (**7a''**).

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. L. W. Daasch and D. C. Smith, *Anal. Chem.*, 1951, **23**, 853; A. Wilson and D. F. Carroll, *Chem. Ind*. 1958, 1558; A. Wilson and D. F. Carroll, *J. Chem. Soc.*, 1960, 2548.
2. M. Kuroboshi and H. Tanaka, *Heterocycles*, 2020, **100**, 1513, and references cited herein.
3. M. Kuroboshi, M. Morita, Y. Masumoto, M. Mikasa, R. Toza, and H. Tanaka, *Heterocycles*, 2019, **98**, 931.
4. M. Kuroboshi, M. Misaki, and H. Tanaka, *Heterocycles*, 2019, **98**, 940.
5. Y. W. Chen-Yang and B. D. Tsai, *Polyhedron*, 1993, **12**, 59.
6. M. Kuroboshi, A. Ueno, A. Kawano, and H. Tanaka, *Heterocycles*, 2022, **104**, 69.
7. G. E. Peters, R. J. Radel, and R. Medina, *J. Agric. Food Chem.*, 1988, **36**, 384.
8. Nucleophilicity of OAr^- would 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.
10. D. Dell, E. W. Fitzsimmons, and R. A. Shaw, *J. Chem. Soc.*, 1965, 4070.
11. Though the selectivity (HCCP gave *non-gem*-products, whereas **2** only gave $\mathbf{9_{gem}}$) 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-phenoxycyclotriphosphazene derivatives.
12. Ether solution, hot MeCN washings, and remained precipitates included unreacted **1** (HCCP), **2**, and NH_4Cl, respectively.