

**SYNTHESIS OF 2-ANILINO-2,4,4,6,6-PENTACHLOROCYCLOTRIPHOSHAZENES ( $N_3P_3Cl_5(NAr(R))$ )**

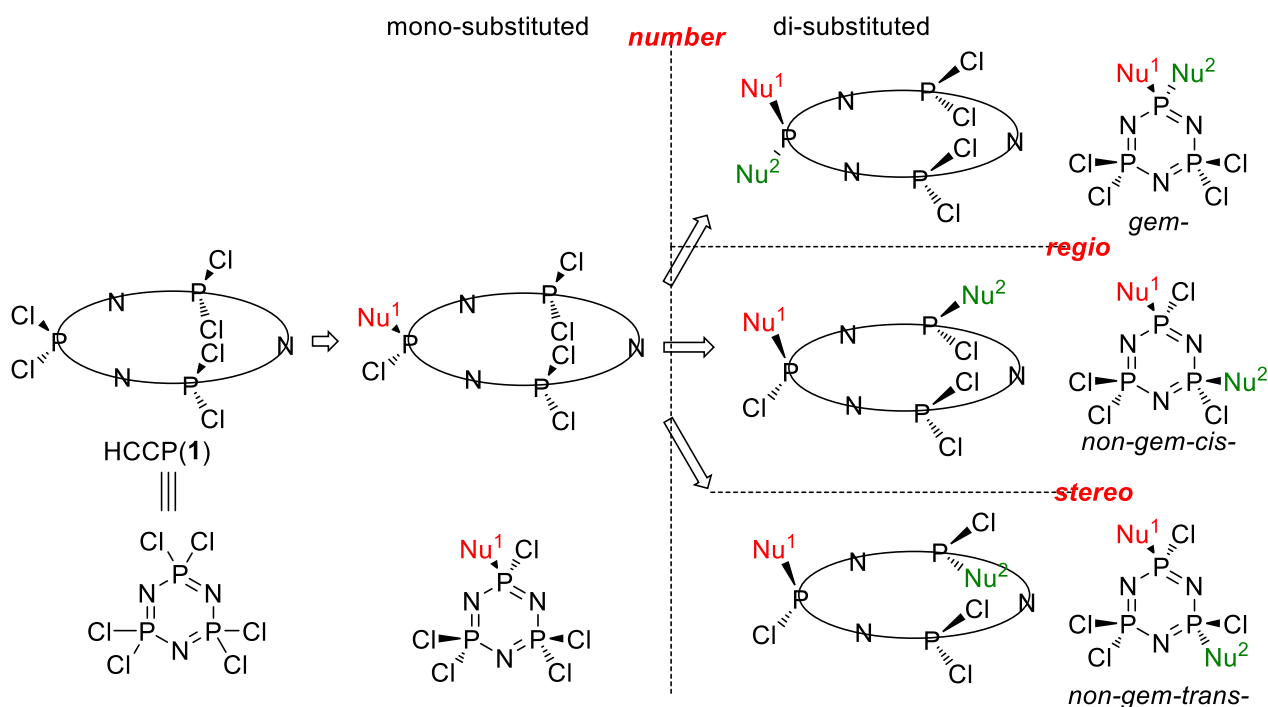
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**Abstract** – Hexachlorocyclotriphosphazene (HCCP,  $N_3P_3Cl_6$ , **1**) was treated with anilines in THF at 0 °C to give a corresponding mono-substituted 2-anilino-2,4,4,6,6-pentachlorocyclotriphosphazenes ( $N_3P_3Cl_5(NAr(R))$ , **2**) in good to moderate yield. Multi-substituted products  $N_3P_3Cl_{6-n}(NAr(R))_n$  ( $n \geq 2$ ) were not detected in  $^{31}P$  NMR spectra of the reaction mixture.

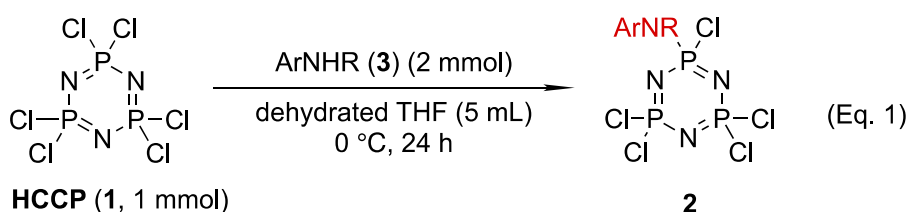
Hexachlorocyclotriphosphazene (HCCP),  $N_3P_3Cl_6$  (**1**), has a six-membered ring containing three N atoms and three P atoms connecting alternately, and each P atom has two Cl atoms upper-side and lower-side of the ring.<sup>1</sup> Though HCCP is a stable compound, its Cl-P bond is easily substituted with several nucleophiles to give a variety of cyclotriphosphazene derivatives.<sup>2</sup> Multi-functionalized materials based on HCCP can be easily prepared when multi-types of nucleophiles are introduced into HCCP. However, to synthesize functionalized cyclotriphosphazenes as designed, number of the nucleophiles, regio- (*gem/non-gem*) and stereo-chemistry (*cis/trans*) should be controlled (Scheme 1).

The number, regio-, and stereo-chemistry of the introduced substituents vary and depend on the substituent and the reaction conditions. We reported that HCCP reacts with  $NH_3$  (excess) to give 2,2-diamino-4,4,6,6-tetrachlorocyclotriphosphazene (*gem*- $N_3P_3Cl_4(NH_2)_2$ ) in  $Et_2O$  and 2,2,4,4-tetraamino-6,6-dichlorocyclotriphosphazene (*gem*- $N_3P_3Cl_2(NH_2)_4$ ) in MeCN, respectively.<sup>3</sup> We also reported 2,2-bis(arylthio)-4,4,6,6-tetrachlorocyclotriphosphazene (*gem*- $N_3P_3Cl_4(SAr)_2$ ) and 2,2,4,4-tetrakis(arylthio)-6,6-dichlorocyclotriphosphazene (*gem*- $N_3P_3Cl_2(SAr)_4$ ) were prepared with 2 and 4 equiv. of  $ArSH/NEt_3$  in MeCN.<sup>4</sup> In these cases, neither mono-, tri-, and penta-substituted derivatives nor *non-gem*-di-substituted products were detected. Recently, we found 2-phenoxy-2,4,4,6,6-pentachlorocyclotriphosphazene  $N_3P_3Cl_5(OAr)$  can be prepared in the reaction with  $ArOLi$  (excess) in THF at -40 °C.<sup>5</sup>



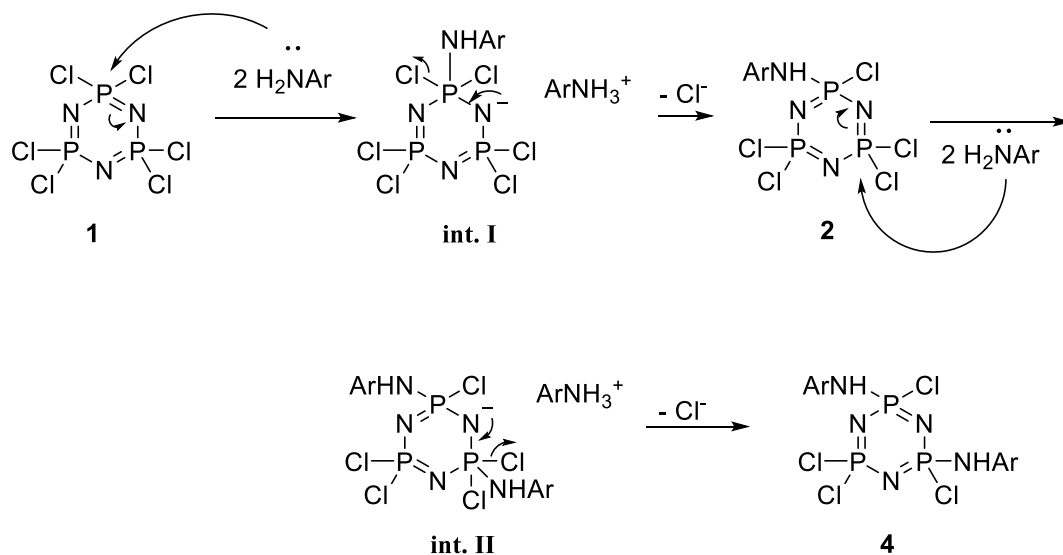
**Scheme 1**

In this paper, we report mono-substituted 2-anilino-2,4,4,6,6-pentachlorocyclotriphosphazenes ( $N_3P_3Cl_5(NAr(R))$ , **2**) was synthesized from **1** and anilines **3** (Eq. 1). Though several reports about reaction between HCCP and aniline have been published,<sup>6-9</sup> they mainly dealt with a distribution of the reaction mixture and/or kinetic study to reveal reaction mechanism, and optimization of the reaction conditions to obtain **2** was not reported.



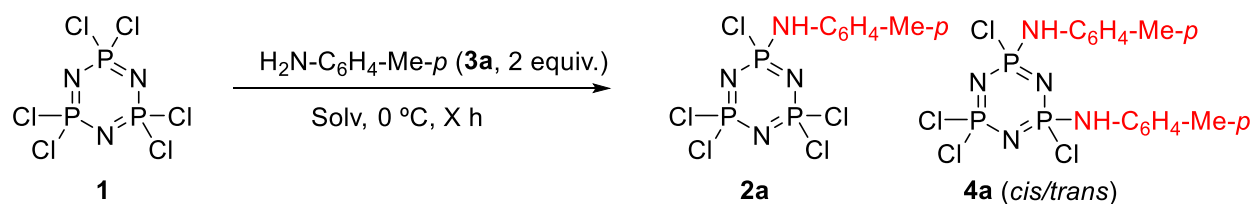
Firstly, the solvent was optimized (Table 1). A typical procedure is as follows. To a THF (5 mL) solution of *p*-toluidine (**3a**, 2 mmol) was added HCCP (**1**, 1 mmol) at 0 °C, and the mixture was stirred for 6 h at the same temperature. An aliquot of the reaction mixture was analyzed by <sup>31</sup>P NMR<sup>10</sup> to determine the products and their ratio to find that **2a** was obtained as a sole product (Entry 1). After 24 h, only **2a** and no di-substituted products were detected. When acetone (Entry 4), EtOAc (Entry 5), Et<sub>2</sub>O (Entry 6), CH<sub>2</sub>Cl<sub>2</sub> (Entry 7), and toluene (Entry 8) (medium and/or non polar solvents) were used as a solvent, the amination proceeded slowly and a mixture of **1** and **2a** was obtained. On the other hand, a mixture of **2a**

and *non-gem*-di-substituted **4a** was obtained in MeCN (Entry 3, *cis/trans* mixture), and a complex mixture of unidentified products was obtained in DMF (Entry 2) (highly polar solvents).<sup>11</sup> This reaction might proceed an addition/elimination mechanism, and polar solvents would stabilize an ionic intermediate **I** and **II** (Scheme 2).



**Scheme 2**

Next, the reaction temperature was examined in THF (Table 2). When the reaction was carried out at 0 °C, mono-substituted product **2a** was obtained quantitatively after 6 h, and no di-substituted and/or other multi-substituted products were detected even after 96 h (Entry 3). When the reaction was carried out at lower temperature such as -40 and -20 °C, a mixture of **1** and **2a** (52/48 after 72 h and 88/12 after 48 h, respectively) was obtained (Entries 1, 2), whereas *non-gem*-disubstituted products (*cis/trans* mixture) were detected (**2a/4a** = 85/15) at 25 °C after 24 h (Entry 4). Therefore, reaction should be carried out at 0 °C to obtain mono-substituted product **2a** selectively and efficiently.

**Table 1.** Solvent effect

Entry	Solv	time (h)	Ratio of phosphazenes <sup>a</sup>		
			2a (%)	4a (%)	1 (%)
1	THF	6	100	0	0
		24	100	0	0
2	DMF <sup>b</sup>	6	0	0	0
		24	0	0	0
3	MeCN	6	82	18	0
		24	83	17	0
4	Me <sub>2</sub> C(=O)	6	86	0	14
		24	93	0	7
5	EtOAc	6	60	0	40
		24	79	0	21
6	Et <sub>2</sub> O	6	8	0	92
		24	36	0	68
7	CH <sub>2</sub> Cl <sub>2</sub>	6	9	0	91
		24	17	0	83
8	toluene	6	6	0	94
		24	11	0	89

<sup>a</sup>Determined by <sup>31</sup>P NMR of the reaction mixture. <sup>b</sup>Complex mixture of unidentified products was obtained.

**Table 2.** Effect of reaction temperature<sup>a</sup>

Entry	temp (°C)	time (h)	Ratio of phosphazenes <sup>b</sup>			Entry	temp (°C)	time (h)	Ratio of phosphazenes <sup>b</sup>		
			2a (%)	4a (%)	1 (%)				2a (%)	4a (%)	1 (%)
1	-40	1	28	0	72	3	0	1	68	0	32
		72	52	0	48			6	100	0	0
2	-20	1	21	0	79	4	25	24	85	15	0
		48	88	0	12			24	85	15	0

<sup>a</sup>THF was used as a solvent. <sup>b</sup>Determined by <sup>31</sup>P NMR of the reaction mixture.

The amount of aniline was also optimized (Table 3). When 1.2 equiv. of **3a** was used in THF, a mixture of mono-substituted **2a** and HCCP (**1**) (63/37) was obtained (Entry 1), whereas **2a** was a sole product when

2 equiv. of **3a** was used (Entry 4). A similar mixture of **2a** and **1** (58/42) was obtained with 1 equiv. of **3a** together with 1 equiv. of pyridine (Entry 2). These phenomena suggested that **3a** plays both as a nucleophile and as a base. On the other hand, *non-gem*-di-substituted products **4a** were also obtained as a side product with 4 and/or 6 equiv. of **3a** (Entries 4,5). It is noteworthy that *gem*-di-substituted product **5a** was obtained in 12% as a ratio with **3a** (1 equiv.)/NEt<sub>3</sub> (1 equiv.), whereas **4a** was not detected (Entry 3).<sup>6</sup> In nucleophilic substitution of mono-substituted HCCP, the small second nucleophiles are introduced at *gem*-position of the first nucleophile, whereas sterically hindered nucleophiles are introduced at *non-gem*-position (Scheme 3).<sup>12</sup> In the absence of NEt<sub>3</sub>, the second ArNH<sub>2</sub> would be introduced directly to mono-substituted HCCP at *non-gem*-position of the first ArNH. Meanwhile, elimination of HCl would occur with NEt<sub>3</sub> to give intermediate **III** which would give *gem*-disubstituted product **5a** (Scheme 4). Pyridine would not strong enough to eliminate HCl, and the second ArNH<sub>2</sub> would be introduced via five-coordinate intermediate.<sup>7</sup>

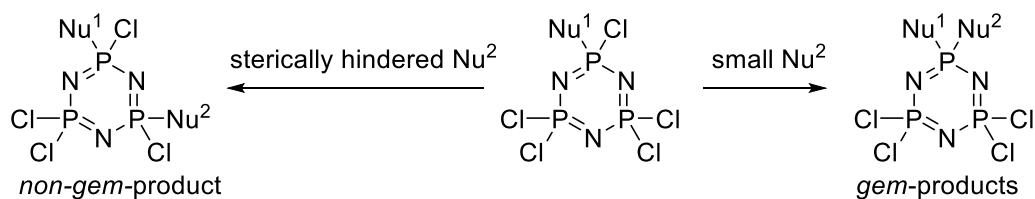
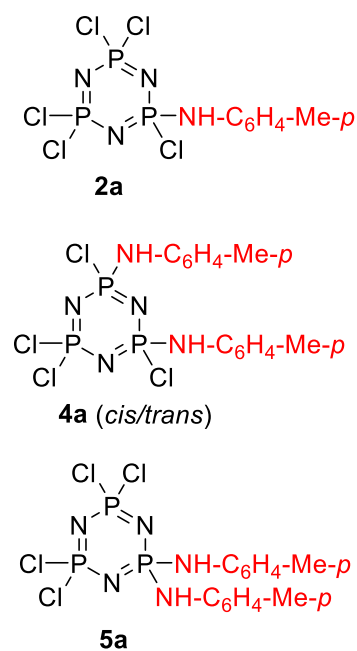
**Table 3.** Amount of aniline **3a**

Entry	<b>3a</b> (equiv.)	time (h)	Ratio of phosphazenes <sup>a</sup>			
			<b>2a</b>	<b>4a</b>	<b>5a</b>	<b>1</b>
1	1.2	24	63	0	0	37
2	1 <sup>b</sup>	24	58	0	0	42
3	1 <sup>c</sup>	24	59	0 <sup>d</sup>	12	29
4	2	1	68	0	0	32
		6	100	0	0	0
		96	100	0	0	0
5	4	6	91	9	0	0
		24	75	25	0	0
		24	57	43	0	0

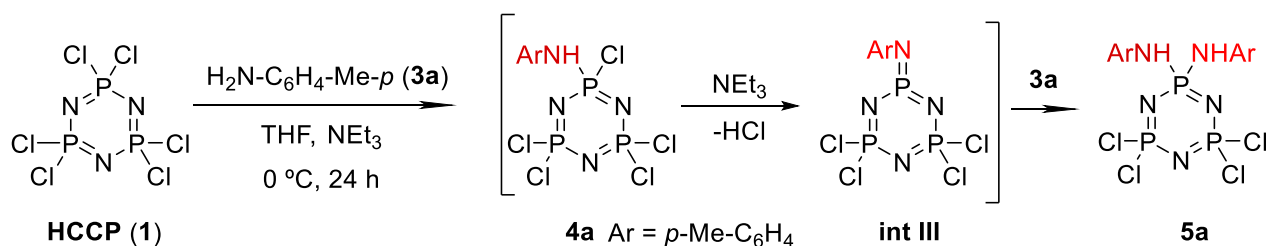
<sup>a</sup>Determined by <sup>31</sup>P NMR of the reaction mixture.

<sup>b</sup>In the presence of py (1 equiv.).

<sup>c</sup>In the presence of NEt<sub>3</sub> (1 equiv.).



**Scheme 3**<sup>7</sup>



Scope and limitation of the reaction was examined (Table 4). The desired mono-substituted products **2** were obtained in good yield with anilines having an electron-donating group such as 4-MeO, 4-Me, and 3-MeO (Entries 1-3), whereas the reaction did not proceed with anilines having an electron-withdrawing group such as 4-EtOC(=O) and 4-NO<sub>2</sub> (Entries 5, 6). The substitution with *p*-chloroaniline (**3d**) proceeded slowly to give a mixture of **2d** and **1**. The substitution also did not proceed with secondary anilines (Entries 7, 8), probably due to their steric hindrance. Reaction of **1** under the same conditions with a primary aliphatic amine (PrNH<sub>2</sub>) gave a complex mixture of unidentified products, whereas no reaction occurred with a secondary aliphatic amine (BuNHMe).

**Table 4.** Scope and limitation of the substitution reaction of **1** with anilines

Entry	aniline	pK <sub>a</sub> of ArN <sup>+</sup> H <sub>2</sub> R	Ratio of phosphazenes/% <sup>a</sup>		Isolated yield of <b>2</b> /%	
			<b>2</b>	<b>1</b>		
1	4-MeO	<b>3b</b>	5.21	100	trace	84
2	4-Me	<b>3a</b>	5.04	100	trace	85
3	3-MeO	<b>3c</b>	4.17	100	n.d. <sup>b</sup>	82
4	4-Cl <sup>c,d</sup>	<b>3d</b>	3.97	43	57	38
5	4-EtOC(=O)	<b>3e</b>	2.51	n.d. <sup>b,e</sup>	100	0
6	4-NO <sub>2</sub>	<b>3f</b>	1.01	n.d. <sup>b</sup>	100	0
7	<i>N</i> -Me	<b>3g</b>	4.70	n.d. <sup>b</sup>	100	0
8	<i>N</i> -Me-4-Cl	<b>3h</b>	4.08	n.d. <sup>b,f</sup>	100	0

<sup>a</sup>Determined by <sup>31</sup>P NMR of the reaction mixture. <sup>b</sup>Not detected. <sup>c</sup>After 48, 72, and 96 h, **2e**:**1**=52/48, 58/42, and 65/35, respectively. <sup>d</sup>After 24 h at 24 °C, a mixture of **2e** and **1** (63/37) was obtained with a small amount of unidentified by-products. <sup>e</sup>After the reaction was carried out at 24 °C for 24 h, most of **1** was remained unchanged, and trace amount of **2e** was detected in <sup>31</sup>P NMR. <sup>f</sup>**1** was remained unchanged at 25 °C for 24 h.

In conclusion, anilines were allowed to react with HCCP in THF at 0 °C to give mono-substituted 2-anilino-2,4,4,6,6-pentachlorocyclotriphosphazene **2**. Electron-rich primary anilines gave the corresponding **2** in good to moderate yield, whereas electron-poor anilines and secondary anilines did not afford **2**. Primary aliphatic amine gave a complex mixture, and the substitution did not proceed with a secondary aliphatic amine. An addition-elimination mechanism was proposed.

## EXPRIMENTAL

NMR was measured on JEOL ECS 400 (<sup>1</sup>H, 400 MHz, <sup>13</sup>C: 100 MHz, and <sup>31</sup>P: 166 MHz) in CDCl<sub>3</sub>.

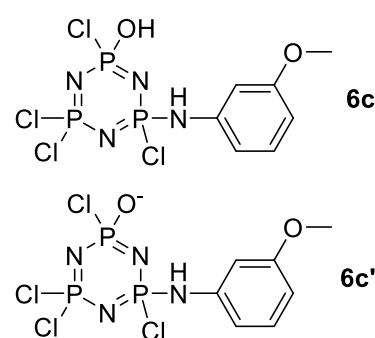
To a THF (5 mL) solution of *p*-toluidine (220 mg, 2.05 mmol) was added HCCP (344 mg, 1.00 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 24 h. The mixture was poured into aq. sat. K<sub>2</sub>CO<sub>3</sub>, and extracted with AcOEt (10 mL x 3). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, Hexane:AcOEt = 10:1) to afford 2-(4-methylanilino)-2,4,4,6,6-pentachlorocyclotriphosphazene (**2a**, 355 mg, 0.85 mmol, 85%).

**2-(4-Methylanilino)-2,4,4,6,6-pentachlorocyclotriphosphazene (2a)**<sup>6</sup> <sup>1</sup>H NMR δ 2.32 (s, 3H), 5.98 (d, *J* = 10.8 Hz, 1H), 7.15-7.06 (m, 4H); <sup>13</sup>C NMR δ 20.93, 121.26 (d, *J* = 7.7 Hz), 130.21, 133.94, 134.64; <sup>31</sup>P NMR δ 12.50 (t, *J* = 48.3 Hz, 1P), 21.36 (d, *J* = 48.3 Hz, 2P).

**2-(4-Methoxyanilino)-2,4,4,6,6-pentachlorocyclotriphosphazene (2b)**<sup>6,8</sup> <sup>1</sup>H NMR δ 3.79 (s, 3H), 5.87 (d, *J* = 10.8 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H); <sup>13</sup>C NMR δ 55.60, 114.85, 124.40 (d, *J* = 6.7 Hz), 128.86, 157.50; <sup>31</sup>P NMR δ 13.26 (t, *J* = 47.1 Hz, 1P), 21.39 (d, *J* = 47.1 Hz, 2P).

**2-(3-Methoxyanilino)-2,4,4,6,6-pentachlorocyclotriphosphazene (2c)**

<sup>1</sup>H NMR δ 3.80 (s, 3H), 5.87 (d, *J* = 10.8 Hz, 1H), 6.67-6.76 (m, 3H), 7.23 (t, *J* = 7.3 Hz, 1H); <sup>13</sup>C NMR δ 55.46, 106.66 (d, *J* = 7.7 Hz), 109.87, 112.84 (d, *J* = 8.6 Hz), 130.45, 138.05, 160.54; <sup>31</sup>P NMR δ 12.10 (dd, *J* = 49.5, 49.5 Hz, 1P), 21.87 (d, *J* = 49.5 Hz, 2P), ESI-MS During the analysis, **2c** was partially hydrolyzed to give **6c**, which ionized by deprotonation to give **6c'**. This partial hydrolysis/deprotonation is usually observed in ESI-MS of chlorophosphazenes:<sup>5</sup> Calcd for C<sub>7</sub>H<sub>8</sub>Cl<sub>4</sub>N<sub>4</sub>O<sub>2</sub>P<sub>3</sub>- 412.8620, Found . 412.8584.



**2-(4-Chloroanilino)-2,4,4,6,6-pentachlorocyclotriphosphazene (2d)**<sup>9</sup> <sup>1</sup>H NMR δ 5.77 (d, *J* = 9.6 Hz, 1H), 7.08-7.16 (m, 2H), 7.26-7.32 (m, 2H); <sup>13</sup>C NMR δ 122.07 (d, *J* = 7.7 Hz), 129.74, 130.18, 135.37; <sup>31</sup>P NMR δ 12.26 (t, *J* = 49.5 Hz, 1P), 21.92 (d, *J* = 49.5 Hz, 2P).

**2,2-Bis(4-methylanilino)-4,4,6,6-tetrachlorocyclotriphosphazene (5a)**<sup>6</sup> <sup>31</sup>P NMR δ -1.6 (t, *J* = 48.5 Hz, 1P), 21.8 (d, *J* = 48.5 Hz, 2P).

*cis*-2,4-Bis(4-methylanilino)-2,4,6,6-tetrachlorocyclotriphosphazene (**4a-cis**)<sup>6</sup> <sup>31</sup>P NMR δ 14.0 (d, *J* = 49.6 Hz, 2P), 22.5 (t, *J* = 49.6 Hz, 1P).

*trans*-2,4-Bis(4-methylanilino)-2,4,6,6-tetrachlorocyclotriphosphazene (**4a-trans**)<sup>6</sup> <sup>31</sup>P NMR δ 13.9 (d, *J* = 49.6 Hz, 2P), 22.3 (t, *J* = 49.6 Hz, 1P).

## ACKNOWLEDGEMENT

This work was supported by JSPS KAKENHI Grant Number JP20K05665. HCCP was a gift from Otsuka Chemical Co Ltd. Mass spectra were measured by Mrs. Tsugumi SHIOKAWA, Department of Instrumental Analysis & Cryogenics, Advanced Science Research Center, Okayama University.

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10. <sup>31</sup>P NMR analysis of the reaction mixture was one as follows. An aliquat (*ca.* 0.5 mL) of the reaction mixture was put into an NMR tube together with a capillary containing D<sub>2</sub>O as an internal lock solvent. NMR spectra was measured at room temperature (*ca.* 24 °C).
11. HCCP was decomposed in DMF swiftly even during <sup>31</sup>P NMR analysis (*ca.* 20 min) and only spectrum of a complex mixture of unidentified products was obtained.
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