HETEROCYCLES, Vol. 98, No. 7, 2019, pp. 931 - 939. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 17th May, 2019, Accepted, 17th June, 2019, Published online, 1st July, 2019
DOI: 10.3987/COM-19-14099

SYNTHESIS OF AMINATED CYCLOTRIPHOSPHAZENES. SOLVENT EFFECTS ON THE PRODUCT-SELECTIVITY OF THE AMINATION

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Abstract – We investigated the reaction between hexachlorocyclotriphosphazene ($(NPCl_2)_3$) and gaseous ammonia in several solvents to find that $(NPCl_2)_2(NP(NH_2)_2)$ was obtained in solvents having low dielectric constant such as toluene and ether, whereas novel compound, $(NPCl_2)(NP(NH_2)_2)_2$, was selectively obtained in solvents having high dielectric constant such as acetonitrile.

INTRODUCTION

Cyclotriphosphazene has a six-membered flat ring containing three nitrogen and three phosphorus atoms which are alternately connected, and also has six substituents on the phosphorus atoms in upper/lower directions. Hexachlorocyclotriphosphazene ($(NPCl_2)_3$, HCCP, **1**) was firstly synthesized in 1834.[1] The chlorine atoms can be easily substituted with nucleophiles such as amines, alkoxides, phenoxides, and thiols, and various derivatives have been developed which have been used as flame retardant compounds,[2] fertilizers,[3] hard coat agents,[4] lubricants for hard disk drives,[5] dental resin cements,[6] non-flammable additives for electrolyte of Li secondary batteries,[7] and so on. Recently, cyclotriphosphazenes have been focused as a core material of dendrimers,[8] and HCCP is expected as a starting material of highly accumulated functional molecules. In substitution of HCCP, selectivity (number of introduced nucleophiles, and regio-/stereo-chemistry) depends on nucleophiles and reaction conditions. Thus, when 2 equivalents of nucleophiles are introduced, geminal disubstituted isomer, non-geminal *trans* disubstituted isomer, and non-geminal *cis* disubstituted isomer would be obtained (Figure 1).[9]

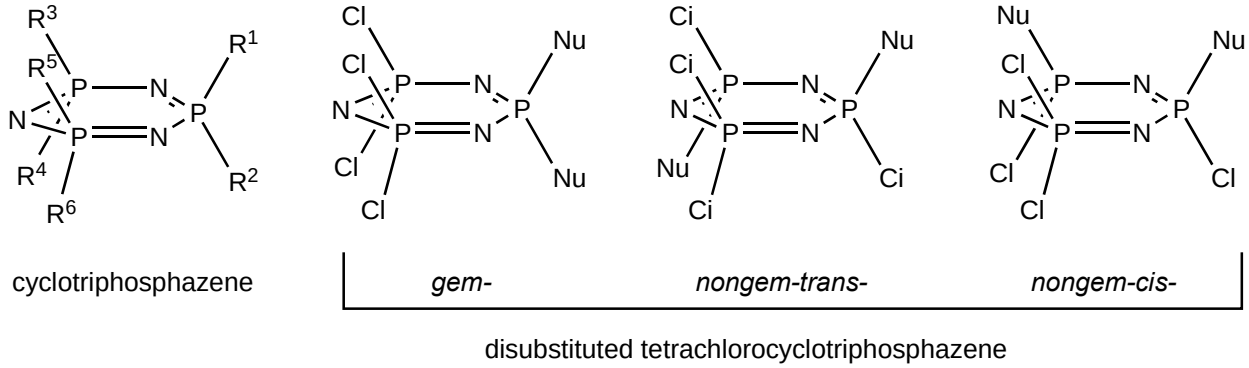
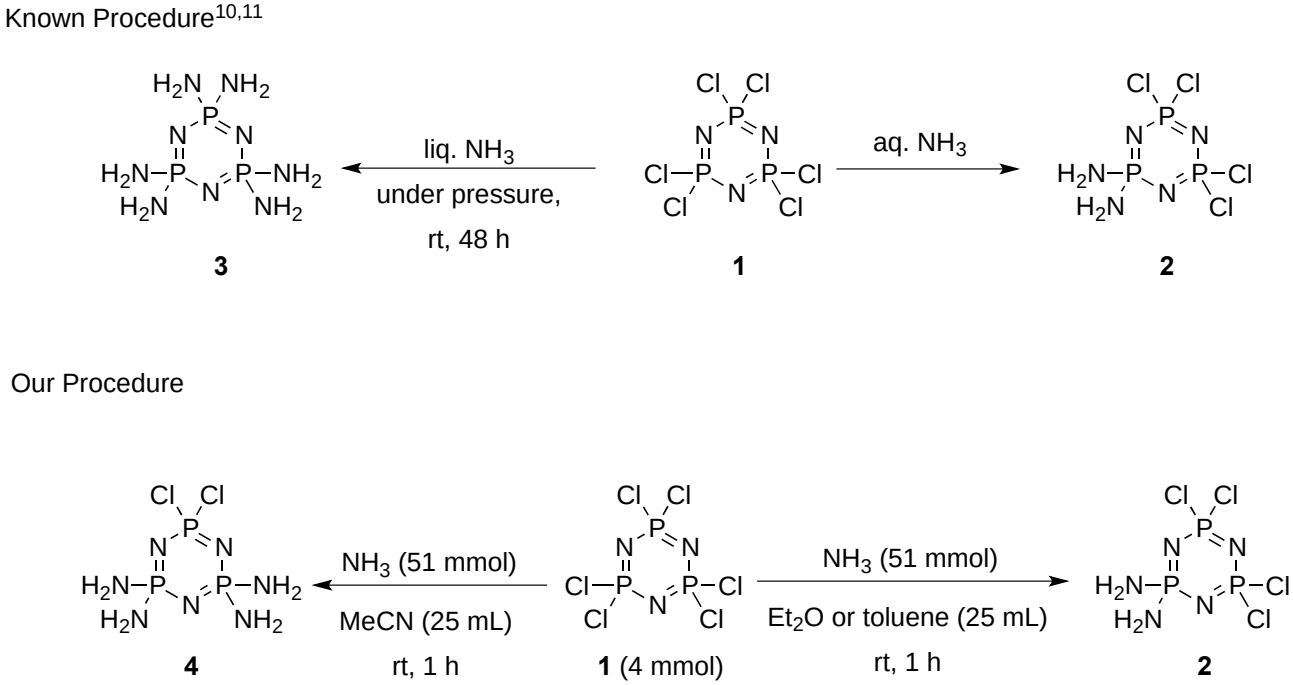


Figure 1. Cyclotriphosphazene and disubstituted tetrachlorocyclotriphosphazenes

Ammonia easily reacts with **1** to give 2,2-diamino-4,4,6,6-tetrachlorocyclotriphosphazene ($(NPCl_2)_2(NP(NH_2)_2)$, **2**[10]) and hexaaminocyclotriphosphazene ($(NP(NH_2)_2)_3$, **3**[11]), and they can be used as curative agents for epoxy resins. Though **2** was prepared from **1** and gaseous and/or aqueous ammonia and **3** was prepared from reaction with liquid ammonia, tetraamino derivatives, $(NPCl_2)(NP(NH_2)_2)_2$ (**4**), could not be obtained even though excess ammonia was used. We investigated the reaction between **1** and gaseous ammonia in several solvents to find that diamino derivative **2** was obtained in solvents having low dielectric constant such as toluene and diethyl ether, whereas tetraamino derivative **4**, novel compound, was selectively obtained in solvents having high dielectric constant such as acetonitrile (Scheme 1). We also confirmed the structure of **4** by X-ray crystal analysis.



Scheme 1. Synthesis of aminated cyclotriphosphazenes

RESULTS AND DISCUSSION

Into an Et_2O solution of **1** was introduced gaseous NH_3 (13 mmol/mmol-**1**) by using syringe and syringe pump at room temperature for 30 min. The mixture was stirred for 1 h to form colorless precipitates. Di-aminated **2** easily dissolves in MeCN at room temperature, whereas tetra-aminated **4** does not dissolve in MeCN at room temperature and dissolves in hot MeCN. Therefore, **2** (80% yield) and **4** (3% yield) could be separated easily by filtration (Table 1, Entry 10). When the reaction was carried out at 0 ºC, **4** was not detected in the crude product (^{31}P NMR) and **2** was obtained in 95% yield (Entry 11). The amination was carried out in several solvents. The results are summarized in Table 1 and Figure 2.

Table 1. Solvent effects on the product-selectivity of reaction between HCCP (**1**) and gaseous NH_3

Entry	Solvent	ε[a]	Product (%)	
			2	**4**
1	MeCN	36.6	1	91
2	EtCN	29.7	6	92
3	PrCN	24.8	6	92
4	^{i}PrCN	24.4	11	88
5	acetone	21.0	1	91
6	2-butanone	18.6	5	89
7	1,2-dichloroethane	10.4	20	52
8	THF[b]	7.5	15	75
9	PhCl	5.7	65	6
10	Et_2O	4.3	80	3
11	Et_2O[b]	4.3	95	n.d.[c]
12	toluene	2.4	85	7

[a]Dielectric constant. [b]0 ºC. [c]Not detected.

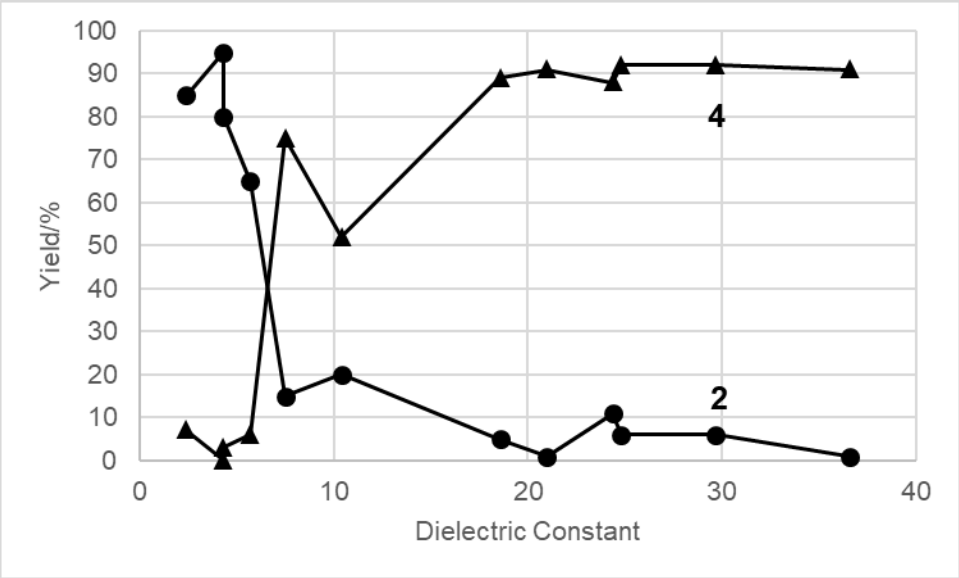


Figure 2. Product yields of **2** and **4** in reaction between **1** and gaseous NH_3

We confirmed the structure of tetraamino derivative **4** by single-crystal X-ray diffraction analysis. The structure is shown in Figure 3.

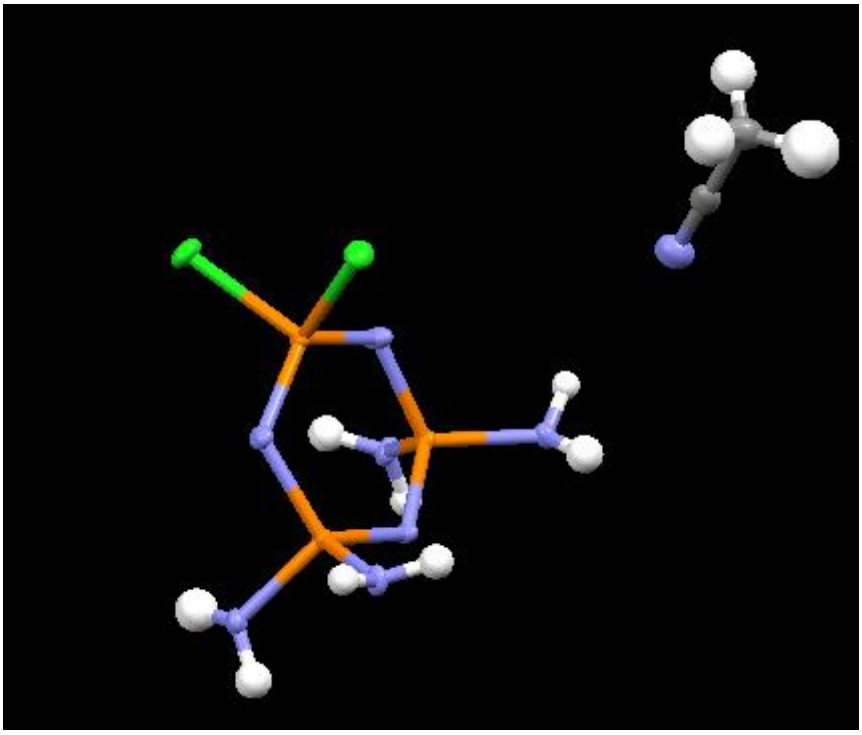


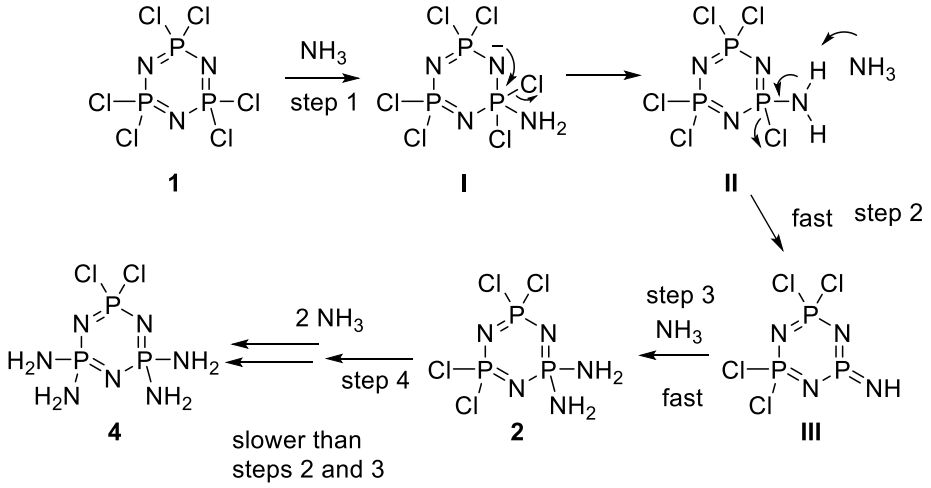
Figure 3. Single-crystal X-ray diffraction analysis of Compound **4**/MeCN complex

The feature of the reaction is as follows:

1) Though a large excess of ammonia was used, only **2** and **4** were obtained and other aminated cyclotriphosphazenes such as $(NP(NH_2)_2)_3$ (**3**), penta-substituted $(NP(NH_2)_2)_2(NPCl(NH_2))$, tri-substituted $N_3P_3(NH_2)_3Cl_3$, and mono-substituted $N_3P_3(NH_2)Cl_5$ were not detected.
2) When solvents having high dielectric constant, such as MeCN, EtCN, PrCN, and acetone, were used, tetra-aminated product **4** was obtained as a major product (Entries 1,2,3,5). On the other hand, when solvents having low dielectric constant, such as PhCl, Et_2O, and toluene were used, di-aminated product **2** was predominantly obtained (Entries 9-12).
3) Only substitution of Cl with ammonia occurred, and side reactions such as ring opening did not occur.
4) Ammonia was introduced at geminal position: Non-geminal isomers were not detected.

A plausible mechanism is as follows (Scheme 2): Addition of NH_3 to HCCP gives intermediate **I**. Two-step dechlorination gives intermediates **II** and **III**, followed by addition of NH_3 gives di-aminated product **2**. Further addition of NH_3 and dechlorination finally gives tetra-aminated product **4**.

Solubility of ammonia and **2**/**4** would also affect the product yields. Since THF can coordinate and stabilize cationic intermediates, product ratio of **4** is still high in spite of low dielectric constant.

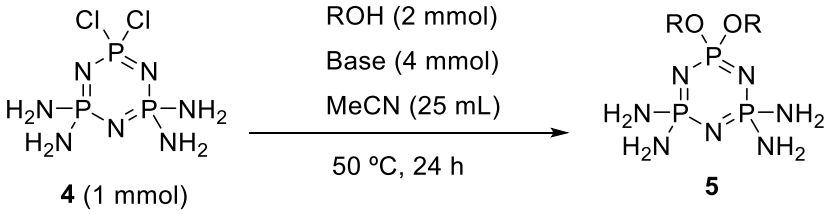


Scheme 2. A plausible mechanism of amination of HCCP

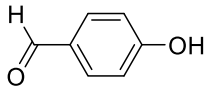
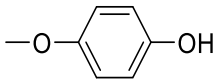
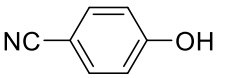
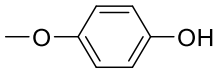
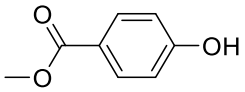
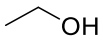
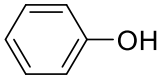
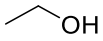
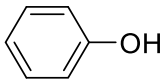
When the tetra-aminated cyclotriphosphazene **4** was treated with phenols under basic conditions, 2 moles of phenol were introduced to afford the corresponding 2,2,4,4-tetraamino-6,6-diaryloxycyclotriphosphazenes **5** in good yield. Thus, to the MeCN solution of **4** were added 2 equivalents of phenol and 4 equivalents of K_2CO_3, and the whole mixture was heated to 50 ºC for 24 h. Usual workup and purification by silica gel column chromatography gave the desired product, 2,2,4,4-tetraamino-6,6-dipheoxycyclotriphosphazene **5d** in 73% yield (Table 2, Entry 4). KOH could be used as the base to give **5d** in 58% yield (Entry 5). Only substitution of Cl atom with phenol occurred and no other side reactions such as ring opening and isomerization were detected.

Both phenols having electron-withdrawing (Entries 1-3) and electron-donating (Entry 6) groups reacted with **4** to give the corresponding **5** in moderate to good yields. Bases should be properly chosen depending on the acidity of the phenols: For the reaction with phenols having electron-withdrawing groups, K_2CO_3 worked efficiently, whereas for the reaction with phenols having electron-donating group, 4-methoxypheol, K_2CO_3 gave only a complex mixture (Entry 7), and KOH gave **5e** in 70% yield (Entry 6). On the other hand, alcohols such as ethanol gave only a complex mixture, and no desired product, 2,2,4,4-tetraamino-6,6-diethoxycyclotriphosphazene, was detected in the crude mixture (^{31}P NMR, Entries 8, 9).

Table 2. Reaction of tetraaminocyclophosphazene **4** and phenols/alchohols



4 (1 mmol) **5**

Entry	ROH	Base	Yield (%)	Entry	ROH	Base	Yield (%)
1		K_2CO_3	**5a**, 84	6		KOH	**5e**, 70
2		K_2CO_3	**5b**, 68	7		K_2CO_3	complex
3		K_2CO_3	**5c**, 52	8		NaH	complex
4[a]		K_2CO_3	**5d**, 73	9		NaH	complex
5[b]		KOH	**5d**, 58				

[a]48 h. [b]8 h.

In conclusion, the reaction between **1** and gaseous ammonia gave diamino derivatives **2** in solvents having low dielectric constant such as toluene and diethyl ether, whereas tetraamino derivatives **4**, novel compound, was selectively obtained in solvents having high dielectric constant such as acetonitrile. The tetraamino derivative **4** reacted with phenoxides to give tetraamino-diaryloxycyclotriphosphazenes **5**.

EXPERIMENTAL

Reaction of HCCP (1) and gaseous ammonia: A typical procedure is as follows. Into a 100 mL two-necked flask were placed HCCP (**1**, 1392.4 mg, 4.0 mmol), MeCN (25 mL), and a stirrer bar. The reaction vessel was purged with He, and NH_3 (1283 mL, 51 mmol) was introduced by using a syringe and a syringe pump for 30 min. The reaction mixture was stirred for 1 h to form colorless precipitates. The reaction mixture was filtered, and the precipitates were washed with hot MeCN. The filtrate was concentrated under reduced pressure to give colorless solids. The solids were dispersed in Et_2O, filtered, and washed with Et_2O to give 2,2-diamino-4,4,6,6-tetrachlorocyclotriphosphazene (**2**, filtrate, 14.4 mg, 0.05 mmol, 1%) and 2,2,4,4-tetraamino-6,6-dichlorocyclotriphosphazene (**4**, precipitates, 978.8 mg, 3.63 mmol, 91%). The filtrate only contained **2** and the precipitates only contained **4**. **2**: **^{1}H NMR** (399.3

MHz, $CDCl_3$) δ 2.00 (s, 4H), **^{31}P NMR** (161.6 MHz, MeCN (D_2O))[12] δ 20.0 (d, *J* = 49.4 Hz, 2P), 10.8 (t, *J* = 49.5 Hz, 1P). **4**: **^{1}H NMR** (399.3 MHz, CD_3CN) δ 1.92 (s, 8H), **^{31}P NMR** (161.6 MHz, MeCN (D_2O))[12] δ 22.6 (t, *J* = 53.2 Hz, 1P), 13.8 (d, *J* = 53.2 Hz, 2P).

X-Ray crystallographic data of 4/MeCN complex: 4 was recrystallized from hot MeCN solution to form **4**/MeCN 1:1 complex. $C_2H_{11}Cl_2N_8P_3$, M = 310.99, monoclinic, *a* = 10.7348(13), *b* = 5.9438(7), *c* = 19.747(3) Å, β = 96.321(7)º, V = 1252.3(3) Å^3, calculated density is 1.649 g/cm^3, T = 100 K, space group $P2_1/c$ (no. 14), Z = 4, μ(Mo-Kα) = 12.843 cm^{-1}, 18209 reflections measured, 2842 unique (Rim = 0.0407), which were used in all calculations. The final R1 = 0.0268 (I > 2σ(I), 2631 reflections) and R*w* = 0.0666 (all data).

X-Ray data for **4**/MeCN complex have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1921356. Copies of the data may be obtained free of charge from CCDC, 12 Union road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033. E-mail: deposit@ccdc.cam.ac.uk).

Reaction of 4 and phenoxide: A typical procedure is as follows. Into a 100 mL eggplant flask equipped with a stirrer bar were placed 2,2,4,4-tetraamino-6,6-dichlorophosphazene (**4**, 272.1 mg, 1.0 mmol), 4-hydroxybenzaldehyde (252.0 mg, 2.1 mmol), K_2CO_3 (564.7 mg, 4.1 mmol), and MeCN (25 mL). The suspension was stirred at 50 ºC for 24 h under Ar atmosphere. An aliquot of the supernatant was analyzed by ^{31}P NMR to find no **4** was detected. The reaction mixture was filtered, and the solids were washed with AcOEt and dispersed in Et_2O and aqueous K_2CO_3. The suspension was filtered to afford 2,2,4,4-tetraamino-6,6-bis(4-formylphenoxy)cyclophosphazene (**5a**, 374.6 mg, 0.85 mmol, 84%). **^{1}H NMR** (399.3 MHz, DMSO-*d*$_6$) δ 9.90 (s, 2H), 7.86 (d, *J* = 8.6 Hz, 4H), 7.40 (d, *J* = 8.6 Hz, 4H), 3.42 (s, 8H); **^{31}P NMR** (161.6 MHz, DMSO-*d*$_6$) δ 17.1 (d, *J* = 65.4 Hz, 2P), 9.2 (t, *J* = 65.4 Hz, 1P).

2,2,4,4-Tetraamino-6,6-bis(4-cyanophenoxy)cyclotriphosphazene (**5b**): **^{1}H NMR** (399.3 MHz, DMSO-*d*$_6$) δ 7.77 (d, *J* = 8.8 Hz, 4H), 7.36 (d, *J* = 8.7 Hz, 4H), 3.43 (s, 8H); **^{31}P NMR** (161.6 MHz, DMSO-*d*$_6$) δ 17.0 (d, *J* = 66.0 Hz, 2P), 9.4 (t, *J* = 66.0 Hz, 1P).

2,2,4,4-Tetraamino-6,6-bis(4-methoxycarbonylphenoxy)cyclotriphosphazene (**5c**): **^{1}H NMR** (399.3 MHz, DMSO-*d*$_6$) δ 7.90 (d, *J* = 8.78 Hz, 4H), 7.31 (d, *J* = 8.39 Hz, 4H), 3.79 (s, 6H), 3.44 (s, 8H); **^{31}P NMR** δ (161.6 MHz, DMSO-*d*$_6$) 17.1 (d, *J* = 66.9 Hz, 2P), 9.3 (t, *J* = 66.9 Hz, 1P).

2,2,4,4-Tetraamino-6,6-diphenoxycyclotriphosphazene (**5d**): **^{1}H NMR** (399.3 MHz, DMSO-*d*$_6$) δ 7.28-7.26 (m, 4H), 7.18-7.17 (m, 4H), 7.10-7.00 (m, 2H), 3.22 (s, 8H); **^{31}P NMR** (161.6 MHz, DMSO-*d*$_6$) δ 17.5 (d, *J* = 64.5 Hz, 2P), 9.8 (t, *J* = 64.5 Hz, 1P).

2,2,4,4-Tetraamino-6,6-bis(4-methoxyphenoxy)cyclotriphosphazene (**5e**): **^{1}H NMR** (399.3 MHz, DMSO-d_6) δ 7.10 (d, J = 8.0 Hz, 4H), 6.82 (d, J = 8.0 Hz, 4H), 3.67 (s, 6H), 3.17 (s, 8H); **^{31}P NMR** (161.6 MHz, DMSO-d_6) δ 18.64 (d, J = 63.5 Hz, 2P), 12.60 (t, J = 63.5 Hz, 1P).

ACKNOWLEDGEMENTS

The authors express their sincere thanks to Prof. Koichi Mitsudo, Graduate School of Natural Science and Technology, Okayama University, and Prof. Hiromi Ota, Okayama University Advanced Science Research Center, for X-ray crystal analysis.

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12. MeCN was used as a solvent, and D_2O, filled in a capillary and put into the NMR sample tube, was used as an external lock solvent of NMR.