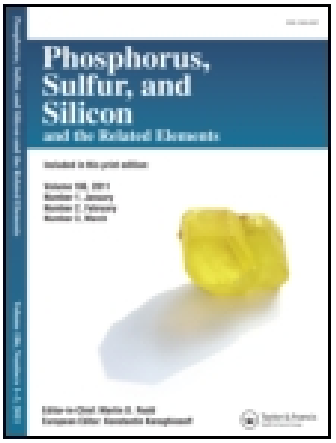


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis and Characterization of Side Group-Modified Tetradentate Cyclotriphosphazene Derivatives

X. Yang [a] , R.-Y. Zou [a] , R. Li [a] , J.-L. Yang [a] , Y. Ye [a] & Y.-F. Zhao [a b c]

[a] Department of Chemistry, Phosphorus Chemical Engineering Research Center of Henan Province , Zhengzhou University , Zhengzhou , China

[b] Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry , Tsinghua University , Beijing , China

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

Accepted author version posted online: 04 Jan 2012.Published online: 05 Apr 2012.

To cite this article: X. Yang , R.-Y. Zou , R. Li , J.-L. Yang , Y. Ye & Y.-F. Zhao (2012) Synthesis and Characterization of Side Group-Modified Tetradentate Cyclotriphosphazene Derivatives, Phosphorus, Sulfur, and Silicon and the Related Elements, 187:6, 722-727, DOI: 10.1080/10426507.2011.643434

To link to this article: http://dx.doi.org/10.1080/10426507.2011.643434

Phosphorus, Sulfur, and Silicon, 187:722–727, 2012

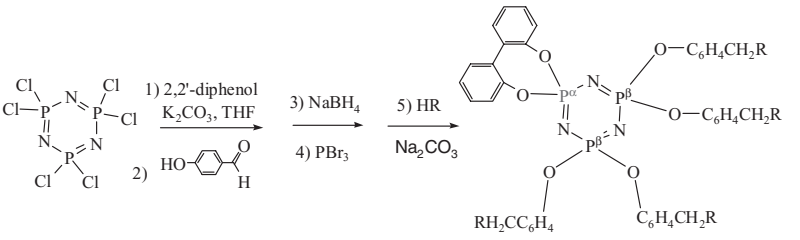
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2011.643434

SYNTHESIS AND CHARACTERIZATION OF SIDE GROUP-MODIFIED TETRADENTATE CYCLOTRIPHOSPHAZENE DERIVATIVES

X. Yang,[1] R.-Y. Zou,[1] R. Li,[1] J.-L. Yang,[1] Y. Ye,[1] and Y.-F. Zhao[1,2,3]

[1]Department of Chemistry, Phosphorus Chemical Engineering Research Center of Henan Province, Zhengzhou University, Zhengzhou, China
[2]Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing, China
[3]Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen, China

GRAPHICAL ABSTRACT



Abstract *A series of novel side group-modified cyclotriphosphazene derivatives were synthesized by the reaction of hexachlorocyclotriphosphazene [$N_3P_3Cl_6$] with 2,2′-diphenol and the potassium salt of 4-hydroxybenzaldehyde, and subsequent reduction of aldehyde groups to alcohol groups by the use of sodium borohydride. The bromination reaction was carried out with PBr_3 to give $N_3P_3(O_2C_{12}H_8)$ (p-$BrCH_2$-C_6H_4-O-)$_4$. This compound was employed in reactions with macrocyclic polyamides, imidazole, or morpholine to produce title compounds. The target compounds were characterized by ^1H NMR, ^{31}P NMR, ^{13}C NMR, and electrospray ionization mass spectrometry.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

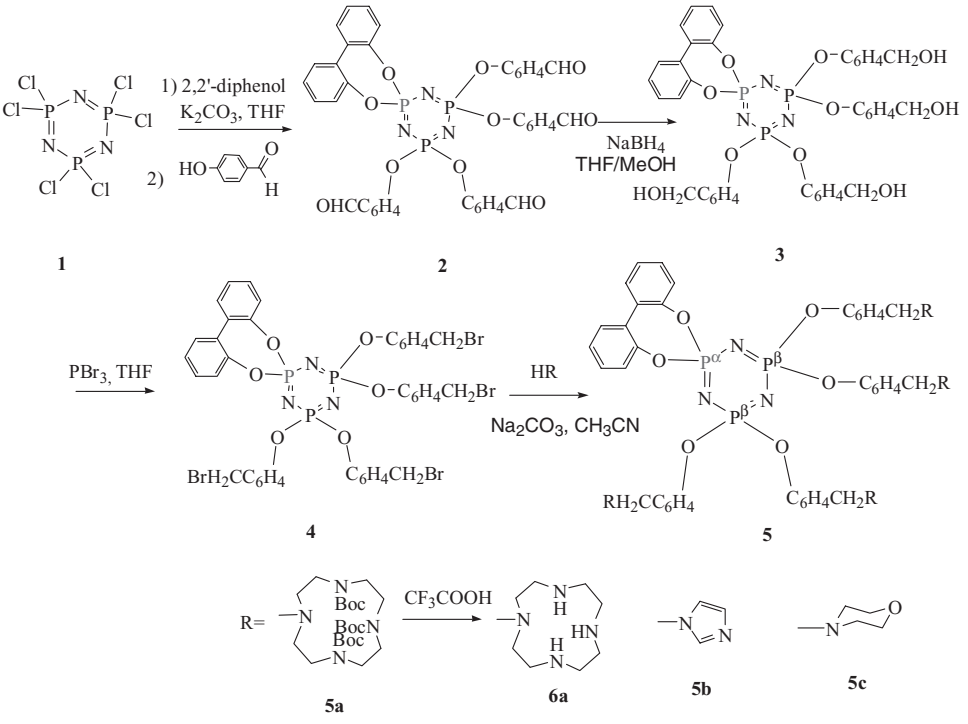
Keywords Macrocyclic polyamide; cyclotriphosphazene derivatives; imidazole; morpholine

Received 10 October 2011; accepted 18 November 2011.
We are grateful for financial support from the NSFC (Nos. 20972143, 20732004, 20972130).
Address correspondence to Yong Ye, Phosphorus Chemical Engineering Research Center of Henan Province, Department of Chemistry, Zhengzhou University, Zhengzhou 450052, China. E-mail: yeyong03@tsinghua.org.cn

INTRODUCTION

With high abilities in recognizing specific DNA sequences and catalyzing the hydrolysis of phosphate diester bonds, artificial nucleases have rapidly become an invaluable research tool in the fields of biology, bioorganic chemistry, therapy, and molecular biology.[1–3] Although many 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 due to their wide spectrum of chemical and physical properties but also due to their importance in synthetic chemistry. Different side-group structures affect the chemical and physical properties of ring systems and high polymers based on a phosphazene skeleton.[4–11] Recently, we reported some polydentate cyclotriphosphazene ligands,[12–14] which showed good nuclease activity with hydrolytic cleavage mechanism. To obtain more insight into the selective recognition and efficient cleavage of DNA by different metal complexes of cyclotriphosphazene, in this work we synthesized a series of novel tetradentate cyclotriphosphazene derivatives in good yield via convenient reactions. Their synthetic route is outlined in Scheme 1. The title compounds were characterized by means of ^{1}H NMR, ^{31}P NMR, ^{13}C NMR, and mass spectrometry. The DNA cleavage activity of the title compounds is currently being examined.



Scheme 1 Synthesis route of title compounds.

RESULTS AND DISCUSSION

In the synthesis of compound **2** (Scheme 1), hexachlorocyclotriphosphazene [$N_3P_3Cl_6$] (**1**) was first reacted with 2,2′-diphenol at room temperature to give $N_3P_3(O_2C_{12}H_8)Cl_4$. Then, the chlorine atom of $N_3P_3(O_2C_{12}H_8)Cl_4$ was substituted by 4-hydroxybenzaldehyde to afford compound **2**, which was further purified by recrystallization from ethyl acetate.

The tetrakis-aldehyde **2** was easily reduced to the corresponding tetrakis-alcohol **3** with sodium borohydride in THF/MeOH. The process was monitored by thin layer chromatography (TLC). Several reagents are 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 **3**. The bromination reaction was achieved using PBr_3. Compound **4** was characterized by ^{1}H NMR, ^{31}P NMR, and electrospray ionization mass spectrometry (ESI-MS). The ^{1}H NMR spectrum showed that all four hydroxyl groups were replaced by bromo substituents. Three doublet peaks for aromatic ring protons appeared at 7.48 ppm, 7.10 ppm, and 6.64 ppm, and a single peak for the bromomethyl group proton was observed at 4.49 ppm.

Compound **5a** was firstly synthesized from compound **4** in $CHCl_3$/Et_3N or THF/Na_2CO_3. However, as indicated by the ^{31}P NMR spectrum, compound **4** did not disappear completely. In addition, there were three or four spots in the TLC, which were very close to each other. After further optimization, the pure compound **5a** was obtained in good yield (54%) when Na_2CO_3 was selected as base in CH_3CN and the reaction time was prolonged to 48 h. The ^{1}H NMR spectrum of compound **5a** exhibits two singlets at 1.42 ppm and 1.46 ppm due to non-equivalency of the Boc groups. The trifluoroacetate of compound **6a** was obtained by deprotection of compound **5a** with trifluoroacetic acid in dichloromethane at room temperature. Subsequent basification with NaOH gave the free base **6a**. Similar to compound **5a**, compounds **5b** and **5c** were produced with 59.6% and 93.4% yield respectively.

The target compounds **5b** and **5c** were characterized by ^{1}H NMR, ^{31}P NMR, ^{13}C NMR, IR, and ESI-MS spectra. ESI-MS for all compounds showed the $[M+H]^+$ ion. Their structures were similar, and compound **5c** was chosen as a characteristic example. In its ^{1}H NMR spectrum, two doublet peaks at 7.24 ppm and 7.1 ppm were assigned to protons on the benzene ring due to their interaction with each other. A single peak at 3.46 ppm was assigned to the methylene group protons between benzene and morpholine. Two triplet peaks for the morpholine group protons were observed at 3.67 ppm and 2.41 ppm.

There are two kinds of phosphorus atoms in compounds **2**–**6**. The ^{31}P NMR spectra of compounds **2**–**6** are similar and the full spectrum consists of a doublet and a triplet. Those compounds, where the P atoms have different substituents give two different ^{31}P signals (here $\delta = 23.9$–25.3 and 8.0–9.4 for α-P and β–P, respectively), each showing the effect of ^{31}P–^{31}P coupling. For these particular compounds, $^2J_{pp}$ is 92–95 Hz.

EXPERIMENTAL

General

Melting points were measured using a WC-1 microscopic apparatus and were corrected. Infrared spectra (cm^{-1}) were recorded on a Bruker VECTOR22 spectrophotometer in KBr pellets. ^{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 references, 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 $m/z = 20{,}000$. Elemental analyses were carried out with a Flash EA 1112 instrument. Solvents were purified and dried by standard procedures. Compound **1** and Boc-cyclen were prepared by the method described previously.[15,16]

Preparation of 2

To a solution of compound **1** (1.035 g, 3 mmol) in THF (80 mL) K_2CO_3 (2 g) was added, and 2,2′-diphenol solution (0.12 g in 20mL THF) was dropped in at 0 °C under N_2. The reaction mixture was stirred for 2 h at room temperature. Then p-hydroxybenzaldehyde (1.648 g, 13.5 mmol) was added and the mixture was stirred for 48 h. After the removal of solvent under reduced pressure, the pure **2** was obtained by recrystallization from ethyl acetate. Yield 80%, m.p.: 137 °C–139 °C; ^{1}H NMR ($CDCl_3$): δ 9.97 (s, 4H, CHO), 7.82 (d, 8H, $J = 8.8$ Hz, H_{ar}), 7.54 (d, 2H, $J = 8$ Hz, H_{ar}), 7.35 (m, 4H, H_{ar}), 7.31 (d, 8H, $J = 8.8$ Hz, H_{ar}), 6.80–6.77 (m, 2H, H_{ar}); ^{13}C NMR ($CDCl_3$): δ 190.5, 154.8, 147.6, 133.7, 131.4, 129.8, 128.4, 126.5, 121.5, 121.3; ^{31}P NMR ($CDCl_3$): δ 23.9 [t, $P(O_2C_{12}H_8)$, $J = 95.5$ Hz], 8.0 [d, $P(OC_6H_4)_2$, $J = 95.5$ Hz]; ESI-MS: m/z 825.9 $[M+Na]^+$.

Preparation of 3

To a solution of compound **2** (2.230 g, 2.7 mmol) in THF/MeOH (40:10 mL) $NaBH_4$ (1.0 g) was added at 0 °C under N_2. The reaction mixture was stirred for 5 h at room temperature. After the removal of solvent under reduced pressure, pure **3** was obtained by recrystallization from ethanol. Yield 64%, m.p.: 79–82 °C. ^{1}H NMR (DMSO): δ 7.58 (d, 2H, $J = 7.2$ Hz, H_{ar}), 7.42–7.36 (m, 4H, H_{ar}), 7.32 (d, 8H, $J = 8.8$ Hz, H_{ar}), 7.02 (d, 8H, $J = 8.8$ Hz, H_{ar}), 6.59 (d, 2H, $J = 7.2$ Hz, H_{ar}), 4.49 (s, 8H, $ArCH_2$); ^{13}C NMR (DMSO): δ 149.1, 147.5, 140.1, 130.5, 130.2, 128.3, 128.2, 126.9, 121.8, 120.8, 62.6; ^{31}P NMR (DMSO): δ 25.3 [t, $P(O_2C_{12}H_8)$, $J = 94.4$ Hz], 9.2 [d, $P(OC_6H_4)_2$, $J = 94.4$ Hz]; ESI-MS: m/z 812 $[M+H]^+$. Anal. calcd. for $C_{40}H_{36}N_3O_{10}P_3$ (811.77): C 59.19, H 4.47, N 5.18. Found: C 59.22, H 4.48, N 5.20.

Preparation of 4

Into a 100-mL round-bottom flask was placed 1.444 g (1.7 mmol) of compound **3** with 30 mL of THF under Ar. Then, 1 mL of PBr_3 in 30-mL THF was added drop-wise at 0 °C and the mixture was stirred for 5 h. Aqu. K_2CO_3 (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give crude **4**, which was purified by silica gel column chromatography (petroleum ether/CH_2Cl_2) to yield pure **4** (1.192 g) as a colorless solid. Yield 63.7%, m.p.: 139 °C–142 °C; ^{1}H NMR ($CDCl_3$): δ 7.48 (d, 2H, $J = 7.6$ Hz, H_{ar}), 7.34–7.28 (m, 12H, H_{ar}), 7.10 (d, 8H, $J = 8$ Hz, H_{ar}), 6.64 (d, 2H, $J = 7.6$ Hz, H_{ar}), 4.49 (s, 8H, $ArCH_2$); ^{13}C NMR ($CDCl_3$): δ 150.4, 147.8, 134.7, 130.3, 129.7, 129.5, 128.6, 126.1, 121.7, 121.4, 32.7; ^{31}P NMR ($CDCl_3$): δ 24.8 [t, $P(O_2C_{12}H_8)$, $J = 92.0$ Hz], 9.2 [d, $P(OC_6H_4)_2$, $J = 92.0$ Hz]; IR: 3027, 2374, 1601, 1502, 1435, 1272, 1178, 1091, 946, 888, 846; ESI-MS: m/z 1085.5

$[M+Na]^+$. Anal. calcd. for $C_{40}H_{32}Br_4N_3O_6P_3$ (1063.39): C 45.19, H 3.03, N 3.95. Found: C 45.17, H 3.06, N 3.92.

Preparation of 5

Imidazole (10 mmol), Boc-cyclen or morpholine, and compound **4** were placed in a 50-mL round-bottom flask with 30 mL of CH_3CN and 0.5 g of Na_2CO_3. The reaction mixture was heated to reflux and stirred for 72 h under Ar. The solvent was removed by rotatory evaporation and the residue was chromatographed on a silica gel column with PE/EA = 2:1 to give pure title compounds **5a–c**.

Compound **5a**: Yield 54%; ^{1}H NMR ($CDCl_3$): δ 7.49 (d, 2H, J = 8.0 Hz, H_{ar}), 7.35–7.29 (m, 4H, H_{ar}), 7.19 (d, 8H, J = 8 Hz, H_{ar}), 7.10 (s, 8H, H_{ar}), 6.72 (s, 2H, H_{ar}), 3.54 (m, 8H, $ArCH_2$), 3.57 (s, 17H, CH_2), 3.49–3.39 (m, 32H, CH_2), 2.65 (s, 15H, CH_2), 1.42 [s, 54H, 6 $C(CH_3)_3$], 1.46 [s, 54H, 6 $C(CH_3)_3$]; ^{13}C NMR ($CDCl_3$): δ 155.6, 149.9, 147.9, 133.3, 131.3, 129.6, 129.4, 128.6, 125.9, 121.7, 120.6, 97.3, 61.7, 55.6, 54.6, 49.9, 48.0, 47.5, 47.2, 28.6; ^{31}P NMR ($CDCl_3$): δ 25.1 [t, $P(O_2C_{12}H_8)$, J = 92.5 Hz], 8.7 [d, $P(OC_6H_4)_2$, J = 92.5 Hz]; ESI-MS: *m/z* 2628.4 $[M+H]^+$. Anal. calcd. for $C_{132}H_{204}N_{19}O_{30}P_3$ (2630.1): C 60.28, H 7.82, N 10.12. Found: C 60.22, H 7.78, N 10.20.

Compound **5b**: Yield 59.6%; ^{1}H NMR ($CDCl_3$): δ 7.39 (s, 4H, H_{ar}), 7.61 (d, 2H, J = 7.6 Hz, H_{ar}), 7.45–7.24 (m, 16H, H_{ar}), 7.04–6.98 (m, 12H, H_{ar}), 6.48 (d, 2H, J = 7.6 Hz, H_{ar}), 5.22 (s, 8H, $ArCH_2$); ^{31}P NMR ($CDCl_3$): δ 24.8 [t, $P(O_2C_{12}H_8)$, J = 92.4 Hz], 9.4 [d, $P(OC_6H_4)_2$, J = 92.4 Hz]; IR: 3368, 3105, 1606, 1506, 1438, 1272, 1164, 1094, 952, 885; ESI-MS: *m/z* 1012 $[M+H]^+$. Anal. calcd. for $C_{52}H_{44}N_{11}O_6P_3$ (1011.91): C 61.72, H 4.38, N 15.23. Found: C 61.75, H 4.36, N 15.20.

Compound **5c**: Yield 93.4%; ^{1}H NMR ($CDCl_3$): δ 7.49 (dd, 2H, J = 6.0 Hz, H_{ar}),7.30–7.26 (m, 4H, H_{ar}), 7.24 (d, 8H, J = 8.4 Hz, H_{ar}), 7.10 (d, 8H, J = 8.4 Hz, H_{ar}), 6.71 (m, 2H, H_{ar}), 3.67 (t, 16H, J = 4.8 Hz, OCH_2), 3.46 (s, 8H, $ArCH_2$), 2.41 (t, 16H, J = 4.8 Hz, NCH_2); ^{13}C NMR ($CDCl_3$): δ 149.8, 147.9, 134.5, 130.1, 129.5, 129.4, 128.6, 125.9, 121.6, 120.9, 66.9, 62.7, 53.5; ^{31}P NMR ($CDCl_3$) δ 25.2 [t, $P(O_2C_{12}H_8)$, J = 92.3 Hz], 9.1 [d, $P(OC_6H_4)_2$, J = 92.3 Hz]; IR: 2853, 1605, 1504, 1439, 1270, 1177, 1116, 952, 884; ESI-MS: *m/z* 1088.1 $[M+H]^+$. Anal. calcd. for $C_{56}H_{64}N_7O_{10}P_3$ (1088.07): C 61.82, H 5.93, N 9.01. Found: C 61.85, H 5.90, N 9.04.

Preparation of 6a

To a solution of **5a** (0.399 g, 0.15 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C, CF_3COOH (2 mL) was added drop-wise under N_2. The mixture was stirred for 7 h at room temperature. After removal of the solvent, the residue was adjusted to pH 12 with aqu. NaOH 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, **6a** was obtained as a colorless solid (95.4% yield). ^{1}H NMR ($CDCl_3$): δ 7.47 (d, 2H, J = 7.2 Hz, H_{ar}), 7.31–7.28 (m, 3H, H_{ar}), 7.25–7.22 (m, 1H, H_{ar}), 7.21 (d, 8H, J = 8.4 Hz, H_{ar}), 7.11 (d, 8H, J = 8.4 Hz, H_{ar}), 6.74 (d, 2H, J = 7.6 Hz, H_{ar}), 3.63 (s, 8H, $ArCH_2$), 2.78 (t, 16H, J = 4.8 Hz, CH_2), 2.65 (d, 16H, J = 4.4 Hz, CH_2), 2.56 (t, 32H, J = 4.8 Hz, CH_2); ^{13}C NMR ($CDCl_3$): δ 149.9, 148.0, 135.2, 130.0, 129.5, 129.4, 128.7, 125.8, 121.9, 120.9, 58.6, 51.1, 47.3, 46.3, 45.0; ^{31}P NMR ($CDCl_3$): δ 25.3 [t, $P(O_2C_{12}H_8)$, J = 92.3 Hz], 8.7 [d, $P(OC_6H_4)_2$, J = 92.3 Hz]; IR: 3405, 2925, 2819, 1605, 1503, 1459, 1271, 1177, 1095, 950, 886; ESI-MS: *m/z* 1427.7 $[M+H]^+$. Anal.

calcd. for $C_{72}H_{108}N_{19}O_6P_3$ (1428.69): C 60.53, H 7.62, N 18.63. Found: C 60.52, H 7.65, N 18.60.

CONCLUSION

We designed and synthesized three novel tetradentate cyclotriphosphazene derivatives from hexachlorocyclotriphosphazene. The reactions were convenient and efficient. The target compounds were characterized by 1H NMR, 31P NMR, 13C NMR, and ESI-MS. The DNA cleavage activity of the title compounds is currently being examined.

REFERENCES

1. Westheimer, F. H. *Science* **1987,** 235, 1173-1178.
2. Williams, N. H.; Wyman, P. *Chem. Commun.* **2001,** 14, 1268-1269.
3. Eigner, J.; Boedtker, H.; Michaels, G. *Biochim. Biophys. Acta* **1961,** 51, 165-168.
4. Kumaraswamy, S.; Muthiah, C.; Swamy, K. C. K. *J. Am. Chem. Soc.* **2000,** 122, 964-965.
5. Kumara Swamy, K. C.; Satish Kumar, N. *Acc. Chem. Res.* **2006,** 39, 324-333.
6. Uslu, A.; Kilic, A.; Guvenaltin, S. *Polyhedron* **2010,** 29, 2516-2521.
7. Fushimi, T.; Allcock, H. R. *Dalton Trans.* **2009,** 14, 2477-2481.
8. Allcock, H. R.; Hartle, T. J.; Taylor, J. P.; Sunderland, N. J. *Macromolecules* **2001,** 34, 3896-3904.
9. Krogman, N. R.; Hindenlang, M. D.; Nair, L. S.; Laurencin, C. T.; Allcock, H. R. *Macromolecules* **2008,** 41, 8467-8472.
10. Allcock, H. R.; Tollefson, N. M.; Arcus, R. A.; Whittle, R. R. *J. Am. Chem. Soc.* **1985,** 107, 5166-5177.
11. Fei, S. T.; Wood, R. M.; Lee, D. K. K.; Stone, D. A.; Chang, H. L.; Allcock, H. R. *Memb. Sci.* **2008,** 320, 206-214.
12. Wang, L.; Ye, Y.; Zhong, S.; Zhao, Y. F. *Chin. Chem. Lett.* **2009,** 20, 58-61.
13. Wang, L.; Ye, Y.; Zhong, S.; Zhang, D.; Zhao, Y. F. *Chem. J. Chin. Univ.* **2009,** 30, 493-496.
14. Wang, L.; Ye, Y.; Lykourinou, V.; Angerhofer, A.; Ming, L.; Zhao, Y. *Eur. J. Inorg. Chem.* **2011**, 674-682.
15. Ju, Z. Y.; Ye, Y.; Wang, L.; Liao, X. C.; Zhao, Y. F. *Phosphorus Sulfur Silicon Relat. Elem.* **2009,** 184, 2103-2108.
16. Huang, Y.; Zhang, Y.; Zhang, D. W.; Lu, Q. S.; Liu, J. L.; Chen, S. Y.; Lin, H. H.; Yu, X. Q. *Org. Biomol. Chem.* **2009,** 7, 2278-2285.