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36- and 42-Membered cyclophosphazene-containing macrocycles

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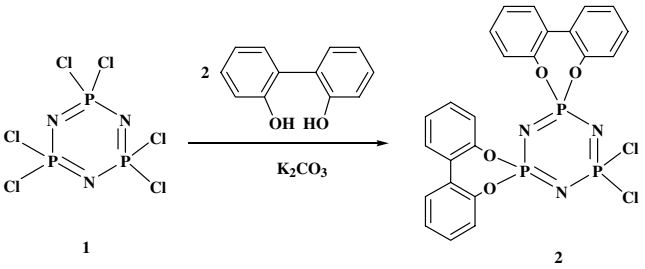
Abstract—Novel 36- **6** and 42- **7** membered cyclophosphazene-containing macrocycles were obtained by [2+2] condensation reactions of $N_3P_3(O_2C_{12}H_8)_2$[–O–C_6H_4–*p*-CHO]$_2$ **3** with PhP(O)[N(Me)NH_2]$_2$ **4** or 1,6-diaminohexane **5**.

Cyclophosphazenes are an important family of heterocyclic ring systems and have been attracting interest for a variety of reasons.[1] Nucleophilic substitution of the P–Cl bonds of chlorocyclophosphazenes such as $N_3P_3Cl_6$ or $N_4P_4Cl_8$ has been a subject of intense investigation.[1,2] The ring-opening polymerization of $N_3P_3Cl_6$ to the linear polymer $[NPCl_2]_n$ and the utility of the latter as a precursor to over 800 polyphosphazenes has also spurred interest in these compounds.[3] More recently, we and others have shown that cyclophosphazenes can be utilized as scaffolds for supporting a multi-site coordination manifold[4,5] as well as an electroactive ferrocenyl periphery.[6] In this context it is interesting to ask if cyclophosphazenes could be utilized as platforms for supporting macrocycles with potential coordination sites. Studies carried out hitherto in this area have been sporadic with limited success. Most of such work is limited to the reactions of difunctional reagents with chlorocyclophosphazenes.[7] In this letter we report a new strategy for the construction of large cyclophosphazene-containing macrocycles by a relatively simple synthetic protocol.

The parent hexachlorocyclotriphosphazene, $N_3P_3Cl_6$ **1** has six points of reactivity in the form of P–Cl bonds and is not amenable for controlled macrocyclic synthesis. Consequently **1** was converted into $N_3P_3Cl_2(O_2C_{12}H_8)_2$ **2** by adapting a known synthetic procedure (Scheme 1).[8] Compound **2** is an ideal precursor for further elaboration, containing two reactive P–Cl bonds. Reaction of



1 2

Scheme 1.

2 with the sodium salt of 4-hydroxybenzaldehyde afforded $N_3P_3(O_2C_{12}H_8)_2$[–O–C_6H_4–*p*-CHO]$_2$ **3**.[9] The design of compound **3** was made on the basis that it possesses two reactive CHO groups which could be readily elaborated under mild reaction conditions. The $^{31}P\{^1H\}$ NMR spectrum of compound **3** is of the AB_2 type. The spirocyclic phosphorus atoms ≡P($O_2C_{12}H_8$) resonate at 25.0 ppm (doublet) while ≡P(–O–C_6H_4–*p*-CHO) was seen at 8.9 ppm (triplet). These chemical shifts may be contrasted with those observed for **2**: δ PCl_2 [29.3 ppm (triplet) and δ P($O_2C_{12}H_8$); 19.6 (doublet)]. $N_3P_3(O_2C_{12}H_8)_2$[–O–C_6H_4–*p*-CHO]$_2$ was utilized in a 2+2 condensation reaction with the phosphohydrazide C_6H_5P(O)[N(Me)NH_2]$_2$ **4**.[10]

The choice of the latter was dictated by its successful use in macrocycle and cryptand synthesis by Majoral and co-workers.[11] Simultaneous slow addition of a methanolic solution of compound **4** and a tetrahydrofuran solution of **3** to a flask containing methanol at 0 °C proceeded smoothly to afford (after work-up and purification by preparative TLC) a novel 36-membered

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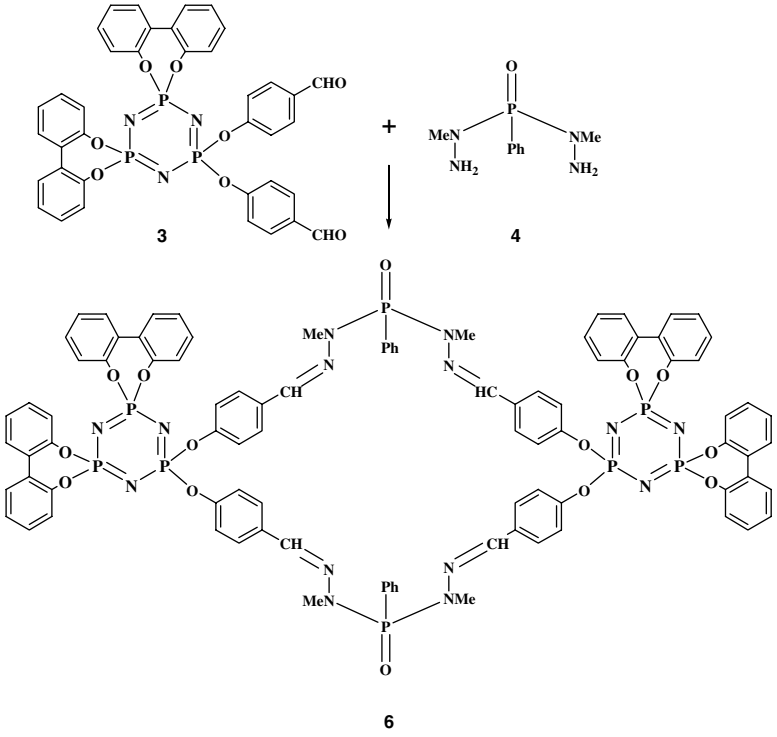
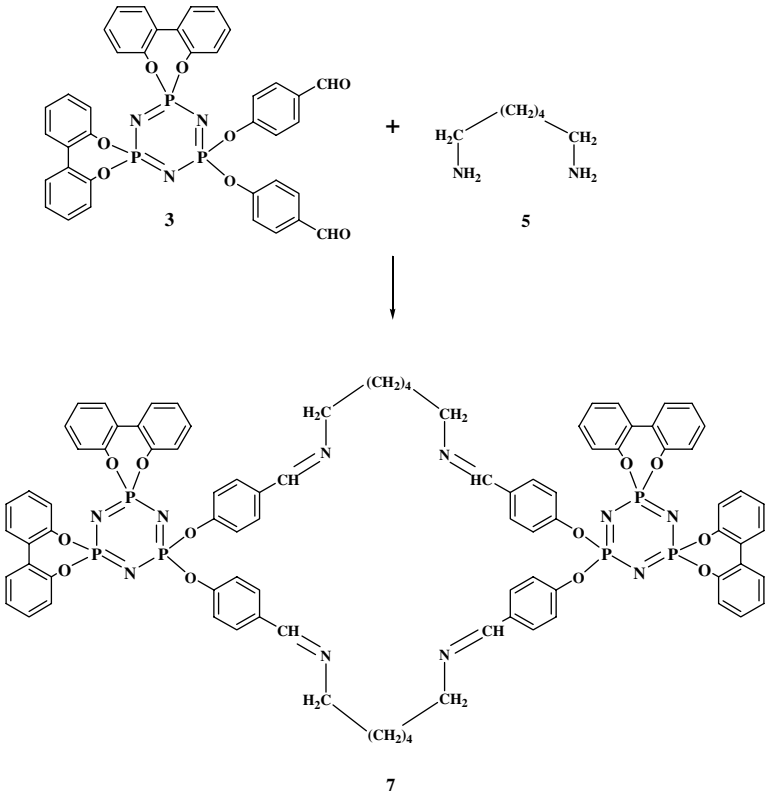
macrocycle **6** (Scheme 2).[9] Macrocycle **6** was characterized by the presence of a $[M+2]^+$ ion at 1848 in its FAB mass spectrum. The $^{31}P\{^1H\}$ NMR spectrum of **6** revealed the presence of three distinct signals. A doublet resonating at 25.4 ppm corresponds to δ P($O_2C_{12}H_8$) while a triplet at 9.6 ppm was assigned to δ P(–O–C_6H_4–*p*-CH=). The singlet at 14.1 ppm was due to δ P[(O)[N(Me)–N=]]. It is of interest to note that the



Scheme 2.



Scheme 3.

chemical shift of the latter is upfield with respect to the free hydrazide $(C_6H_5)P(O)[N(Me)NH_2]_2$.[10]

In order to verify if the macrocycle formation could also be accomplished by reaction with diamines, we reacted **3** with hexamethylenediamine **5** under identical reaction conditions. This reaction afforded a 42-membered macrocycle **7** (Scheme 3).[9] Compound **7** showed a molecular ion peak at 1651 $(M+1)^+$ in its FAB mass spectrum and its ^{31}P NMR spectrum showed two resonances, a doublet at 25.4 [δ $P(O_2C_{12}H_8)$], and a triplet at 9.3 [δ $P(O–C_6H_4–p\text{-}CH=)$].

In conclusion we have reported a facile procedure for the assembly of large macrocycles containing cyclophosphazene rings. The imino nitrogen atoms present in the macrocyclic cavity could be utilized for coordination to metal ions. This aspect is being investigated.

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9. All products were characterized on the basis of spectral data (IR, ^1H NMR, ^{13}C NMR, ^{31}P NMR and MS). Compound **3**: Sodium hydride (60% suspension in paraffin oil) (0.64 g, 16.0 mmol) was stirred with hexane (3×10 mL) and the washings were removed using a syringe before adding dry THF (30 mL). This mixture was cooled to 0 °C, and to it 4-hydroxybenzaldehyde (1.96 g, 16.0 mmol) dissolved in THF (45 mL) was added dropwise over 30 min and the reaction mixture then stirred for 3 h at 25 °C. $N_3P_3(O_2C_{12}H_8)_2Cl_2$ (4.2 g, 7.3 mmol) dissolved in THF (75 mL) was added dropwise at 25 °C over 45 min to the above suspension of the sodium salt of 4-hydroxybenzaldehyde and the mixture was stirred for 12 h and then heated under reflux for 9 h. Sodium chloride formed in the reaction mixture was filtered using a sintered frit (G-4) and the filtrate was evaporated in vacuo to yield a solid. This was recrystallized from chloroform–hexane (1:2) mixture (mp 163 °C). Yield = 4.4 g (80%); ^{31}P NMR ($CDCl_3$, 161.7 MHz) δ 25.0 (d, $–P(O_2C_{12}H_8)_2$), 8.9 (t, $–P(–OC_6H_4CHO)_2$), (^2J(P–N–P) = 95.4 Hz); ^1H NMR ($CDCl_3$, 400 MHz) δ 10.01 (s, 2H, $–CHO$), 7.95 (d, 4H, C_6H_4, $^2J = 8.8$ Hz), 7.52 (t, 8H, $C_{12}H_8$, $^2J = 8.11$ Hz), 7.29–7.39 (m, 8H, $C_{12}H_8$), 7.07 (d, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 121.59, 126.22, 128.49, 129.64, 131.45, 133.53, 147.7, 155.2, 190.77. IR (KBr): 1702 s, 1596 s, 1501 m, 1187 s, 938 s, 889 s cm^{-1}; MS (FAB): 746 $(M+1)^+$, 624 $[(M+1)^+–OC_6H_4CHO$, 504 $[(M+1)^+–2OC_6H_4CHO]$. Anal. Calcd for $C_{38}H_{26}N_3O_8P_3$: C, 61.22; H, 3.52; N, 5.64. Found: C, 61.07; H, 3.46; N, 5.49. Compound **6**: A solution of $\{(C_6H_5)P(O)[N(Me)NH_2]_2\}$ **4** (0.21 g, 1.0 mmol) in methanol (100 mL) and **3** (0.75 g, 1.0 mmol) in tetrahydrofuran (100 mL) was added simultaneously dropwise (150 min) to a RB flask containing methanol (100 mL) maintained at 0 °C under constant stirring. The reaction mixture was stirred at 25 °C for about 8 h and the solvent evaporated in vacuo to afford a solid product. This was purified by PTLC [eluent: methanol–ethyl acetate (20:80) mixture] (mp 248 °C). Yield: 0.34 g (18%); ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ 25.4 (d, $–P(–O_2C_{12}H_8)_2$), 9.6 (t, $–P(–OC_6H_4CH=)_2$, ^2J(P–N–P) = 90.6 Hz), 14.1 (s, $(O)P(N(Me)–)_2$); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.89–7.87 (m, 62H, aromatic, imino), 3.12 (d, 12H, $N(CH_3)$ $^2J = 9$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.68, 45.57, 121.34, 121.74, 118.27, 121.99, 126.1–129.6 (60 C). IR (KBr): 1675 s, 1602 s, 1507 m, 1372 s, 1250 m, 994 s cm^{-1}. MS (FAB): 1848 $(M+2)^+$. Anal. Calcd for $C_{92}H_{74}N_{14}O_{14}P_8$: C, 59.80; H, 4.01; N, 16.62. Found: C, 59.40; H, 3.87; N, 16.12. Compound **7**: A solution of 1,6-diaminohexane **5** (0.12 g, 1.0 mmol) in methanol (100 mL) and **3** (0.75 g, 1.0 mmol) in tetrahydrofuran (100 mL) was added simultaneously dropwise (150 min) to a RB flask containing methanol (100 mL) maintained at 0 °C under constant stirring. The reaction

mixture was stirred for about 8 h and the solvent was evaporated in vacuo to afford a solid product. This was purified by PTLC [eluent: methanol–ethyl acetate (30:70) mixture] (mp 276 °C). Yield: 0.30 g (18%); ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ 25.4 (d, $-P(O_2C_{12}H_8)_2$), 9.3 (t, $-P(-OC_6H_4CH{=})_2$, ^2J(P–N–P) = 90.6 Hz); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.9–8.15 (m, 52H, aromatic), 3.47–3.51 (m, 8H, $-CH_2-$), 1.16–1.61 (m, 16H, $-CH_2-$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.1, 30.78, 61.56, 121.25–159.56 (76 C). IR (KBr): 1646 m, 1502 m, 1273 m, 1230 s, 1091 m, 934 s cm^{-1}. MS (FAB): 1651 $(M+1)^+$. Anal. Calcd for $C_{88}H_{76}N_{10}O_{12}P_6$: C, 64.0; H, 4.61; N, 8.49. Found: C, 63.83; H, 4.12; N, 8.51.

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