Effect of the metal ion on the regiochemical outcome of substitution reactions promoted by crown-bearing cyclophosphazenes

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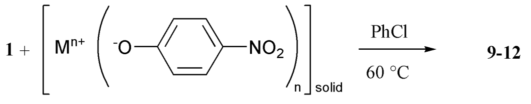
The regiochemical outcome of nucleophilic substitution reactions of PNP16C6 (**1**) by a series of alkaline-earth metal *p*-nitrophenoxides (**6–8**) in chlorobenzene–solid salt two-phase systems strongly depends on the identity of the metal ion M^{2+} (Ca^{2+}, Sr^{2+}, Ba^{2+}). The regiochemistry observed on changing the salt (*i.e.*, geminal mono- and/or disubstitution in the 'P-crown' position), in apparent contrast with the rules of classical phosphazene chemistry, has been rationalised on the basis of a transition state in which the metal cation M^{2+} interacts with the oxygens of the polyether **1** ('host-guest' complex) while the ion-paired anion simultaneously attacks the adjacent phosphorus atoms, following a concerted mechanism. According to the proposed mechanism the effect is not observed when the metal ion charge is shielded by a complexing agent, such as perhydrodibenzo-18-crown-6 (**14**), or when the bulky non-complexable tetrahexylammonium cation is used.

Functional crown ethers are gaining much interest as enzyme models because their reactivity is remarkably affected by the cation complexed inside the cavity of the macrocycle and the catalytic activity depends on the size fit of the host-guest complex with the substrate, both typical properties of enzyme chemistry.[1,2] Functional crowns like diphosphaza[16]crown-6 (PNP16C6; **1**) (Scheme 1), synthesized by the incorporation of chlorocyclophosphazene subunits into the polyether backbone,[3] have been revealed to be particularly promising ligands that combine the versatile reactivity of chlorocyclophosphazenes[4,5] with the complexing ability of crown ethers.[6–9] They can be regarded as potential anion activators and hence promoters of nucleophilic substitution reactions in homogeneous and heterogeneous systems.[10]

In complexes of **1**, the metal cation was found to play a leading role in determining not only the nucleophilic reactivity of the counteranion, but even the regiocontrol of the substitution of the chlorine atoms in the phosphazene ring.[11,12]

In a previous study on the nucleophilic substitution of PNP16C6 (**1**) with a series of alkali metal *p*-nitrophenoxides [$M^+ = Li^+$ (**2**), Na^+ (**3**), K^+ (**4**), Cs^+(**5**)] in low polarity solvents (reaction 1), we reported on the major effect of the metal ion M^+ on the regiochemical outcome of the reaction.[13] While lithium (**2**) and sodium (**3**) salts exclusively give the substitution product in the position geminal to the macrocycle ('P-crown'; **9**) the preferential formation of mono- (**10**) and di-'P-non crown' (**11**) derivatives was observed with the corresponding potassium (**4**) and cesium (**5**) salts.[13] In order to ascertain whether the effect observed is only specific for alkali metal ions or is a more general feature, we extended the study to alkaline-earth cations (Ca^{2+}, Sr^{2+}, Ba^{2+}) in consideration of the fundamental role that the latter play in biological systems (reaction 1).

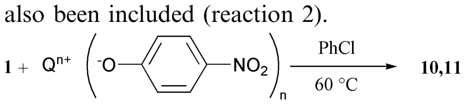


2-8

M^{n+} = (n = 1), Li^+ (**2**), Na^+ (**3**), K^+ (**4**), Cs^+ (**5**); (n = 2), Ca^{2+} (**6**), Sr^{2+} (**7**), Ba^{2+} (**8**)

(1)

In addition, a comparative study with the non-complexable tetrahexylammonium *p*-nitrophenoxide cation (**13**) and with complexes **14a–c** of perhydrodibenzo-18-crown-6 (PHDB18C6; **14**), has also been included (reaction 2).



13, 14a-c

(2)

$Q^{n+} = (C_6H_{13})_4N^+$ (**13**), n = 1; ($M^{2+} \subset$ PHDB18C6),
$M^{2+} = Ca^{2+}$ (**14a**), Sr^{2+} (**14b**), Ba^{2+} (**14c**), n = 2

Results

Reactions were carried out under solid–liquid heterogeneous conditions by stirring at 800 ± 50 rpm a 0.01 mol l^{-1} chlorobenzene solution of diphosphaza[16]crown-6 (**1**) with the solid alkaline-earth *p*-nitrophenoxides **6–8** [molar ratio (**6–8**)/**1** = 0.9] at 60 °C (reaction 1). The crude reaction mixtures were analyzed by ^{31}P NMR spectroscopy (Fig. 1 and Table 1) and the products identified by comparison with the spectra of the pure compounds.[13]

As previously found in the series of alkali metal salts **2–5**, with the alkaline-earth *p*-nitrophenoxides **6–8** the distribution of the reaction products also changes remarkably, depending on the metal ion. Whereas calcium *p*-nitrophenoxide (**6**) gives exclusively the product **9** derived from mono-substitution at

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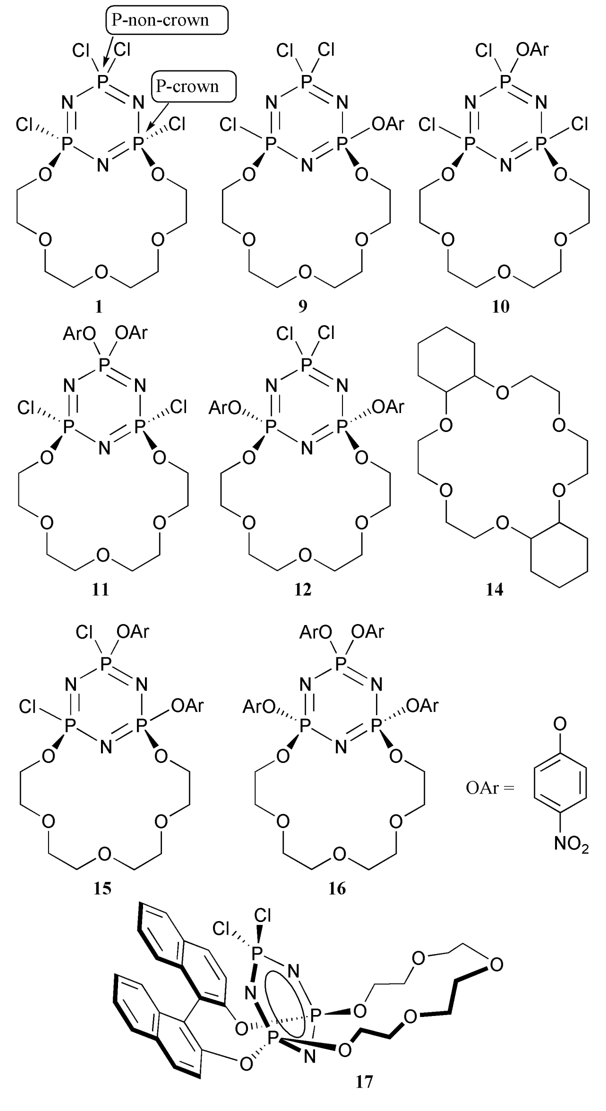


Scheme 1

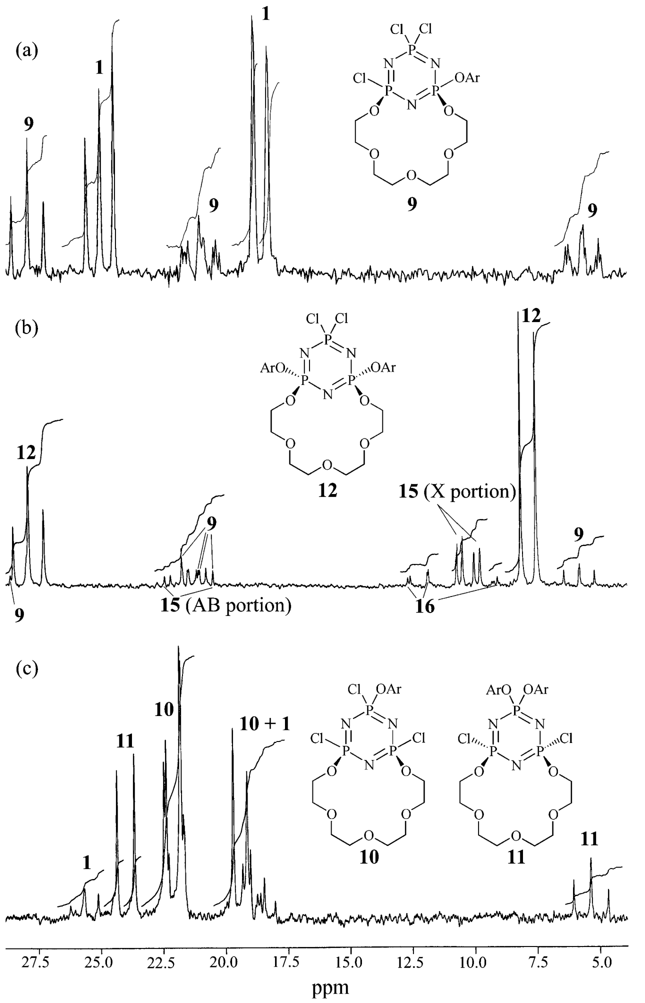


Fig. 1 $^{31}P\{^1H\}$ NMR spectra ($CDCl_3$) of the crude reaction mixtures in PhCl of: (a) diphosphaza[16]crown-6 (**1**) and calcium *p*-nitrophenoxide (**6**); (b) **1** and barium *p*-nitrophenoxide (**8**); (c) **1** and the complex ($Ba^{2+} \subset$ PHDB18C6)$(4\text{-}NO_2C_6H_4O^-)_2$ (**14c**).

the position geminal to the macrocycle (’P-crown’) (Fig. 1(a)), the corresponding strontium salt (**7**) affords a mixture of mono- (**9**) and di-substituted (**12**) derivatives in the ’P-crown’ position. Finally, with the barium *p*-nitrophenoxide (**8**) the symmetric ’P-crown’ di-substituted compound **12** is obtained as the main product together with minor quantities of the tetra-substituted derivative **16** and of the non-symmetric ’P-crown’-’P-non-crown’ di-substituted phosphazene **15** (Fig. 1(b)).

In contrast, when the same displacement reactions were performed under homogeneous conditions by reacting (reaction 2) chlorobenzene solutions of **1** (0.01–0.02 mol l^{-1}) with the preformed complexes **14a–c** (0.9 mol equiv.; obtained by reacting salts **6–8** with the crown ether **14**), all afforded a mixture of mono- (**10**) and di-substituted (**11**) ’P-non-crown’ derivatives, as indicated by their ^{31}P NMR spectra [see, for example, **14c** in Fig. 1(c)]. The same mixture of ’P-non-crown’ derivatives **10** and **11** was obtained when **1** was treated with the non-complexable lipophilic tetrahexylammonium salt **13** under homogeneous conditions (reaction 2).

The affinity of the functional crown **1** toward the alkaline-earth cations (Ca^{2+}, Sr^{2+}, Ba^{2+}) was measured by liquid secondary ion mass spectrometry (LSIMS) analysis of solutions of **1** in a *m*-nitrobenzyl alcohol (NBA) matrix in the presence of an equimolar mixture of the corresponding alkaline-earth metal perchlorates (Fig. 2) in analogy with the previous determinations for the alkali metal cations.[13] From the relative peak heights of the complexes [$M^{2+} \subset$ **1**] the following complexation percentages were obtained: Ca^{2+} (47%); Sr^{2+} (39%); Ba^{2+} (14%).

The complexing ability of crown **1** was also checked by UV-vis spectroscopy by stirring at 800 rpm chlorobenzene solutions of **1** with the appropriate solid salt **6–8** (0.0001–0.001 mol l^{-1}) at 25 °C. Complex formation was qualitatively monitored by the appearance of an absorbance maximum in the 380–400 nm region where the free ligand **1** is found to be transparent. The spectroscopic measurements showed an increase of the absorption maximum wavelength on going from the calcium to the barium salt (λ_{max} Ca^{2+} = 389 nm; λ_{max} Sr^{2+} = 390 nm; λ_{max} Ba^{2+} = 398 nm). A similar trend was obtained for the same salts complexed by PHDB18C6 (**14**) in chlorobenzene (λ_{max} Ca^{2+} = 393 nm; λ_{max} Sr^{2+} = 400 nm; $\lambda_{max}Ba^{2+}$ = 404 nm).

Discussion

The results as a whole highlight the fundamental role that the metal ion plays in determining the product distribution in reaction 1.

The regiochemistry observed (*i.e.*, geminal mono- and di-substitution in the ’P-crown’ position) seems to be in apparent contrast with the classic rules of phosphazene chemistry.[4] According to these rules the second substituent should

Table 1 $^{31}P\{^{1}H\}$ NMR spectral data of diphosphaza[16]crown-6 (**1**) and its derivatives **9–12,15,16**[a b c]

	δ_{PCl_2}	$\delta_{PCl(OCH_2)}$	$\delta_{PCl(OAr)}$	$\delta_{P(OAr)(OCH_2)}$	$\delta_{P(OAr)_2}$
1	25.1 t, 1P, $J = 69.2$	18.9 d, 2P, $J = 69.2$			
9	27.8 dd, 1P, $J = 79.5, 78.7$	21.0 dd, 1P, $J = 79.5, 71.4$		5.8 dd, 1P, $J = 78.7, 78.7$	
10	**AB₂ system:**	$\nu_B = 22.1$ $J_{AB} = -75.8$	$\nu_A = 19.1$		
11		23.4 d, 2P, $J = 85.0$			4.7 t, 1P, $J = 85.0$
12	27.9 t, 1P, $J = 74.2$			8.0 d, 2P, $J = 74.2$	
15	**ABX system:**	$\nu_A = 21.8$ $\lvert J_{AB}\rvert = 82.1$	$\nu_B = 21.1$	$\nu_X = 10.3$ $J_{AX} = 28.6, J_{BX} = 33.9$	
16	**AB₂ system:**			$\nu_B = 12.0$ $J_{AB} = -94.7$	$\nu_A = 8.6$

[a] Recorded in $CDCl_3$ solution using phosphoric acid as external reference. [b] Chemical shifts (δ) are in ppm; coupling constants (J) are in Hz. [c] ν_i are the calculated P_i chemical shifts (in ppm) in the ABX and AB_2 systems.

preferably link to the unsubstituted 'P- non-crown' atom, which is sterically and electronically more available, rather than to substitute the chloride functions proximal to the bulky electron-donating, if uncomplexed, crown substituent (non-geminal substitution pathway).[4]

These findings can be rationalized on the basis of a mechanism (Scheme 2) in which the alkaline-earth cation M^{2+} interacts with the oxygen atoms of the crown ether **1** to give host-guest complexes. In the activation process the metal ion, brought in proximity to the reaction center by the polyether, stabilizes the developing negative charge on the chlorine atom close to the macrocycle while the ion-paired nucleophile simultaneously attacks the adjacent phosphorus atom following a concerted mechanism.The latter is essentially similar to that previously proposed for the lithium **2** and sodium **3** salts[13] by assuming in the present case the possible involvement of both P atoms of the phosphazenic ring linked to the crown. Interestingly, these results confirm previous findings concerning the reaction of **1** with the disodium salt of 2,2′-dihydroxy-1,1′-binaphthyl in THF.[11] In that case also the coordinative interaction of the polyether crown substituent and the sodium cation-paired nucleophile seems to be the driving force for the regioselective substitution of the chlorine atoms adjacent to the macrocycle ('P-crown') to give the *gem* bis-ansa compound **17** as the main product.[11]

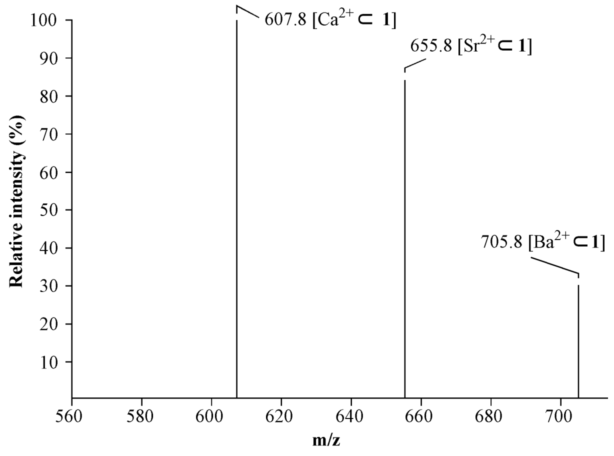


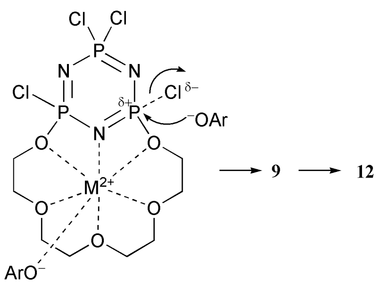
Fig. 2 Liquid secondary ion mass spectrum (LSIMS) of diphosphaza[16]crown-6 (**1**) in the presence of an equimolar mixture of $Ca(ClO_4)_2$, $Sr(ClO_4)_2$ and $Ba(ClO_4)_2$ using *m*-nitrobenzyl alcohol as a matrix.

According to the proposed mechanism (Scheme 2) the cation effect is not observed when: (*i*) the metal ion charge is shielded by a complexing agent as for the salts **6–8** complexed by PHDB18C6 (**14**) or (*ii*) when the bulky non-complexable tetrahexylammonium cation is used. In all cases the kinetically favored products of mono- and di-substitution in the 'P-non crown' position, **10** and **11,** are obtained (reaction 2).

The product distribution found is most likely due to the different anion activation, within the ion pair, on changing the salt **6–8**.[9,10] By decreasing the charge density (defined as the M^{n+} charge–ionic radius ratio) of the cation the reactivity of the ion-paired *p*-nitrophenoxide is expected to increase, in the order $Ca^{2} < Sr^{2+} < Ba^{2+}$.[9,10] Consequently, whereas with the calcium salt **6** the mono-substituted derivative **9** in the 'P-crown' position is the main product, the di-substituted derivative **12** is obtained with the more reactive barium salt **8**, after the same reaction time. Finally, the regiochemistry is in between (mixture of **9** and **12**) with the corresponding strontium salt **7**.

The data of the LSIMS determinations (Fig. 2) reveal that, contrary to previous results with alkali metal ions (only Li^{+} and Na^{+} are complexed), the functional crown ether **1** has good affinity for all the divalent cations, decreasing in the order: $Ca^{2} > Sr^{2+} > Ba^{2+}$. This implies a good extent of complexation and hence high regioselectivity, as experimentally found.

In good agreement with the above results, spectroscopic determinations in chlorobenzene of these complexes show that the absorption maximum wavelength (λ_{max}) increases on going from calcium to the corresponding barium salt. Since bathocromic shifts indicate a more efficient separation in the ion pair, and hence higher reactivity, our data provide additional evidence for increasing anion activation in the same order ($Ca^{2+} < Sr^{2+} < Ba^{2+}$).[14]



Scheme 2

Conclusions

The results clearly indicate that the substitution process (reaction 1) is strongly dependent on the ability of diphosphaza[16]-crown-6 (**1**) to complex the metal cation M^{2+}. The data show the fundamental role of the polyether chain, in the functional crown ether **1**, in determining, *via* host-guest interactions with the alkaline-earth metal *p*-nitrophenoxides **6–8**, (*i*) the solubilization of the salt by complexation in the low polar chlorobenzene, (*ii*) the activation of the ion-paired *p*-nitrophenoxide and (*iii*) the regiocontrol of the chlorine substitution in the phosphazenic ring.

The importance of the complexation on the regiochemistry of reaction 1 is also proved by the comparison with the alkali *p*-nitrophenoxides **2–5**.[13] Indeed, while lithium (**2**) and sodium (**3**) salts give exclusively the product **9**, due to the mono-substitution in the position geminal to the macrocycle, potassium (**4**) and cesium (**5**) salts, which are not appreciably complexed by ligand **1**, only afford the mono- and di-P-non-crown derivatives **10** and **11**, respectively.[13]

It is worth noting that the alkaline-earth *p*-nitrophenoxides **6–8** yield exclusive formation of the mono- and/or di-substituted products **9** and **12** in the 'P-crown' positions (Scheme 2). This allows to gain access to species otherwise unlikely to be obtainable and even to selectively direct the substitution pattern toward the mono- or the di-substituted pathway. As a practical consequence, starting from the crown-bearing phosphazene **1** and the appropriate metal cation M^{2+}, it should be possible to realize the regioselective synthesis of a number of mono- and di-functionalized new PNP-crowns.

Experimental

Materials and solvents

Hexachlorocyclotriphosphazatriene (**17**), perhydrodibenzo-18-crown-6 (**14**), tetrahexylammonium chloride, alkaline-earth metal perchlorates and *m*-nitrobenzyl alcohol were commercial products and were utilized as purchased. Alkaline-earth metal *p*-nitrophenoxides **6–8** were prepared as orange-yellow powders in high yields ($\geqslant 95\%$) by a literature method.[15]

Diphosphaza[16]crown-6 (**1**) was synthesized from **17** following a previously reported procedure.[3] Pure PNP-crown derivatives **9–12** were prepared as previously described.[13]

Tetrahexylammonium *p*-nitrophenoxide (**13**) was prepared *in situ* from tetrahexylammonium chloride by exchange with sodium *p*-nitrophenoxide (**3**), according to the ion-pair extraction technique.[16,17] Dry chlorobenzene ($H_2O \leqslant 20$ ppm) and THF ($H_2O \leqslant 50$ ppm) were used. Petroleum ether (PE, b.p. 40–60 °C) was used as the chromatographic eluant.

Synthesis of tetra *p*-nitrophenoxy-PNP16C6 (16). A solution of **1** (0.193 g, 0.41 mmol) in acetonitrile (20 ml) was stirred for about 21 h with solid 85% sodium *p*-nitrophenoxide **3** (0.624 g, 3.8 mmol) under nitrogen until no starting reagent **1** was detectable by TLC analysis (AcOEt–PE 5:2). The unreacted salt **3** was filtered off and the solvent evaporated. The reaction mixture was diluted with CH_2Cl_2 (20 ml) and washed three times with aqueous 5% NaOH (10 ml) and water (10 ml). The organic layer was dried over anhydrous Na_2SO_4, the solvent removed under vacuum and the crude product purified by flash chromatography (AcOEt–PE 1:1), affording **16** (0.331 g, 92%) as a solid; m.p. = 138.3 °C. Anal. calcd. for $C_{32}H_{32}N_7O_{17}P_3$: C, 43.70; H, 3.67; N, 11.15. Found: C, 42.46, H, 3.88, N, 10.66%.

Methods

^{1}H NMR spectra were recorded on Bruker AC 300 (300.133 MHz) and AMX 300 (300.132 MHz) spectrometers, using TMS as an external reference. $^{31}P\{^1H\}$ NMR spectra were recorded on the same spectrometers operating at 121.496 and 121.5 MHz, respectively, using aqueous 85% H_3PO_4 as an external reference. Potentiometric titrations were performed with a Metrohm 670 Titroprocessor by using a combined glass electrode isolated with a potassium chloride bridge or a combined silver electrode isolated with a potassium nitrate bridge. Karl–Fisher determinations were carried out with a Metrohm 684 KF coulometer. UV-vis spectra were recorded on a Perkin–Elmer LAMBDA 6 spectrophotometer. Liquid secondary ion mass spectrometric (LSIMS) determinations were obtained by using an AMD 604 two-sector spectrometer (AMD Intectra, Germany) of B/E geometry equipped with a cesium ion source (cesium gun), utilizing *m*-nitrobenzyl alcohol (NBA) as the matrix.

UV-vis spectra.. Measurements were performed by stirring at 25 °C a 0.0001–0.001 mol l^{-1} chlorobenzene solution (20 ml) of **1** with 2–3 mol of the appropriate solid alkaline-earth *p*-nitrophenoxide **6–8**. The stirring was stopped at various times for 20–40 s to allow adequate separation and samples (3 ml) were withdrawn and analyzed by UV spectroscopy in a 10 mm quartz cell.

LSIMS spectra. A 0.02 mol l^{-1} solution (1 ml) of **1** in *m*-nitrobenzyl alcohol (NBA) was added to an equal volume of an NBA solution (0.1 mol l^{-1}) containing an equimolar mixture of alkaline-earth perchlorates $M(ClO_4)_2$ (M = Ca, Sr, Ba) and introduced into the FAB probe tip. The mass spectrum was acquired at an acceleration voltage of 8 kV and a post-acceleration of 4 kV in the LSIMS mode. The cesium ion beam was operated at 12 kV and 2 μA. The mass range, from 2000 to 100, was scanned at 2 s per decade with resolution 1000. The relative heights of the $(M^{2+} \subset 1)$ ion peaks were obtained by averaging three different spectra.

Reactions of PNP16C6 (1) with alkaline-earth metal *p*-nitrophenoxides 6–8

A heterogeneous mixture composed of a chlorobenzene solution (0.01 mol l^{-1}) of the functional crown ether **1** and solid alkaline-earth metal *p*-nitrophenoxide **6–8** to give a molar ratio (**6–8**)/**1** = 0.9 was stirred (800 rpm) in a flask thermostated at 60 °C. The reaction was monitored by TLC (AcOEt–PE 2:1, I_2). The reaction was stopped after one week by addition of a few drops of aqueous 36% HCl. The solvent was removed at reduced pressure and the residue was dissolved in CH_2Cl_2(15 ml), dried over anhydrous Na_2SO_4 and, after removal of the solvent, analyzed by ^{31}P NMR spectroscopy.

Reaction of PNP16C6 (1) with alkaline-earth metal *p*-nitrophenoxides 6–8 complexed by PHDB18C6 (14)

A 0.01–0.02 mol l^{-1} standardized (at 60 °C) chlorobenzene solution (10 ml) of **1** was added to a volume of standardized chlorobenzene solution of the preformed complex $(M^{2+} \subset \text{PHDB18C6})\cdot 2X^-$ **14a–c** to obtain a molar ratio (**6–8**)/**1** = 0.9. The reaction was monitored by TLC and stopped after one week as described above. After standard work up, the crude product was analyzed by ^{31}P NMR spectroscopy. The solutions of the preformed complexes **14 a–c** were prepared by magnetically stirring (800 rpm) at 60 °C for 20 h a 0.01 mol l^{-1} standardized chlorobenzene solution of the crown ether **14** with 0.9 mol equiv. of the appropriate solid alkaline-earth salt **6–8** according to a previously reported procedure.[13]

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