Functional crown ethers with chlorocyclophosphazene sub-units as anion activators and promoters of highly regioselective reactions

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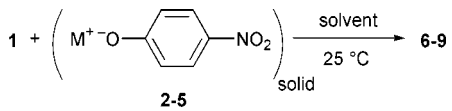
The effect of the metal ion on the regiochemical outcome has been revealed in the nucleophilic substitution reactions of diphosphaza[16]crown-6 with a series of alkali metal *p*-nitrophenoxides in low polarity solvents (chlorobenzene, THF) under solid–liquid heterogeneous conditions. While lithium and sodium salts give exclusively the 'P-crown' substitution product, the preferential formation of mono- and di-'P-non-crown' derivatives was found with the corresponding potassium and caesium salts. The regiochemistry observed on changing the salt has been rationalized in terms of the differing involvement of the cation in the stabilization of the transition state, following a 'push–pull' mechanism. The results provide strong evidence for the key role of the polyether crown substituent in determining, *via* a host–guest interaction with the alkali metal *p*-nitrophenoxide, both the activation of the anion and the regiocontrol of the chlorine substitution in the phosphazenic ring ('P-crown' *vs.* 'P-non-crown' substitution). As a consequence of this supramolecular control, it is possible to switch the reaction pattern toward electronically and sterically unfavored regioselective substitution at the position geminal to the macrocycle ('P-crown' substitution), giving easy access to species otherwise difficult to obtain following the rules of classical phosphazene chemistry.

Crown ethers are particularly interesting synthetic macrocyclic polyethers due to their ability to form stable inclusion complexes with a number of inorganic salts, even in poorly solvating media, and to promote the extraction and transport of the ions in both biological and liquid–liquid membranes.[1,2] Starting from the pioneering work of Pedersen,[3] efforts have continued to modify the properties of these macrocycles in order to increase the stability of the metal ion–ligand complex and to improve the selectivity to cations.[4]

In recent years, much attention has been paid to the synthesis of functional crown ethers due to their relevance to enzyme chemistry. Indeed such ligands can be regarded, as enzyme models because their reactivity is greatly influenced by the cation complexed inside the macrocyclic cavity and the catalytic activity depends on the size fit of the host–guest complex with the interacting substrate. Such a high specificity and cation dependence are known to be typical of enzymatic action.[2]

Recently, some of us have realized the template synthesis of a new class of functional crowns obtained by the incorporation of reactive chlorocyclophosphazene sub-units into the polyether backbone,[5] like 1,3-$[O(C_2H_4O)_4]P_3N_3Cl_4$ (**1**) (Scheme 1), which can be regarded as diphosphaza[16]crown-6 or PNP16C6 following the crown nomenclature rules.[6a] These ligands, which combine the complexing ability of crown ethers[6] with the versatile reactivity of chlorocyclophosphazenes,[7,8] are potential activators of anions and hence could be utilized, more generally, as promoters of nucleophilic substitution reactions in homogeneous and heterogeneous systems.[6,9]

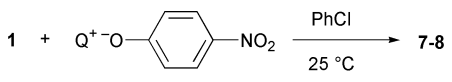
In the complexes of **1**, the metal cation was found to affect not only the nucleophilic reactivity of the ion-paired anion[6,9] (anion activation) but even the distribution of the substitution of the chlorine atoms in the phosphazenic ring.[10] To elucidate the role played by the metal ion in determining the regiochemistry of these reactions we carried out a systematic study of the nucleophilic substitution of **1** with a series of alkali metal *p*-nitrophenoxides **2**–**5** in solvents of low polarity (chlorobenzene, THF), at 25 °C [reaction (1)].



2-5 (1)

$M^+ = Li^+$ (**2**), Na^+ (**3**), K^+ (**4**), Cs^+ (**5**)
solvent = chlorobenzene, THF

A comparative study with non-complexable quaternary onium salts, like tetrahexylammonium *p*-nitrophenoxide (**10**), and classical polyether ligands such as perhydrodibenzo-18-crown-6 (PHDB18C6, **11**) has also been performed [reaction (2)].



10,11a-d (2)

$Q^+ = (C_6H_{13})_4N^+$ (**10**); ($M^+ \subset$ PHDB18C6), $M^+ = Li^+$ (**11a**), Na^+ (**11b**), K^+ (**11c**), Cs^+ (**11d**)

Results

Reactions were performed under solid–liquid heterogeneous conditions by stirring an organic solution of di-

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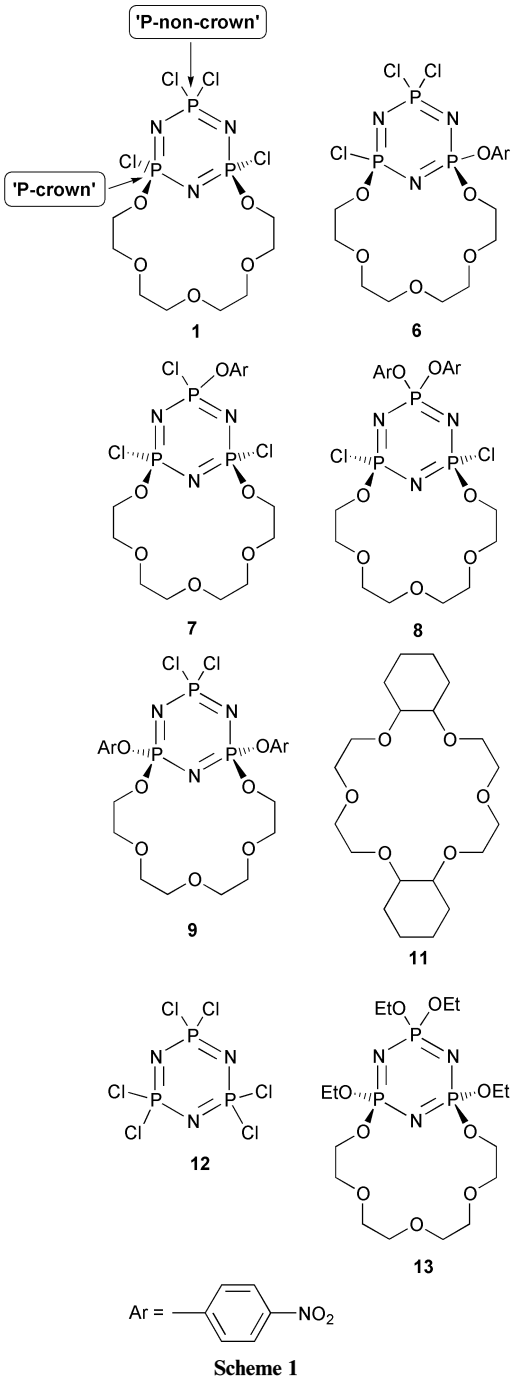


Scheme 1

phosphaza[16]crown-6 (**1**, 0.02 M) at 800 ± 50 rpm with a substoichiometric amount of the appropriate solid *p*-nitrophenoxide **2**–**5** (0.9 mol equiv) in order to obtain mainly mono-substitution products **6** and **7** [reaction (1)]. The crude reaction mixtures were analyzed by ^{31}P NMR spectroscopy and the products identified by comparison with the spectra of the pure compounds **6**–**9** (see Fig. 1, Table 1 and Experimental).

The regiochemical outcome of reaction (1) is quite different depending on the salt **2**–**5** and, the latter being the same, on the polarity of the organic medium. When both lithium (**2**) and sodium (**3**) *p*-nitrophenoxides are used in the low polarity solvent chlorobenzene ($E_T^N = 0.188$)[11] reaction (1) leads to the exclusive formation (80% in 16 h for Li^+, 70% in 20 h for Na^+) of the 'P-crown' **6** [Fig. 2(a)], that is substitutions in the position geminal to the macrocycle. In contrast, the regiochemistry changes remarkably with the corresponding potassium salt **4**. As shown in Fig. 2(c), the reaction mixture is much more complex, revealing, in this case, the preferential formation (60% in 30 h) of the derivative **7**, produced by 'P-non-crown' mono-substitution, that is, in the position more distant from the macrocycle, together with minor quantities of the 'P-non-crown' di-substituted product **8** and traces of the 'P-crown' derivative **6**. Finally, reaction of **1** with the bulky caesium *p*-nitrophenoxide (**5**) was extremely slow and afforded, after prolonged reaction (more than 1 week), minor quan-

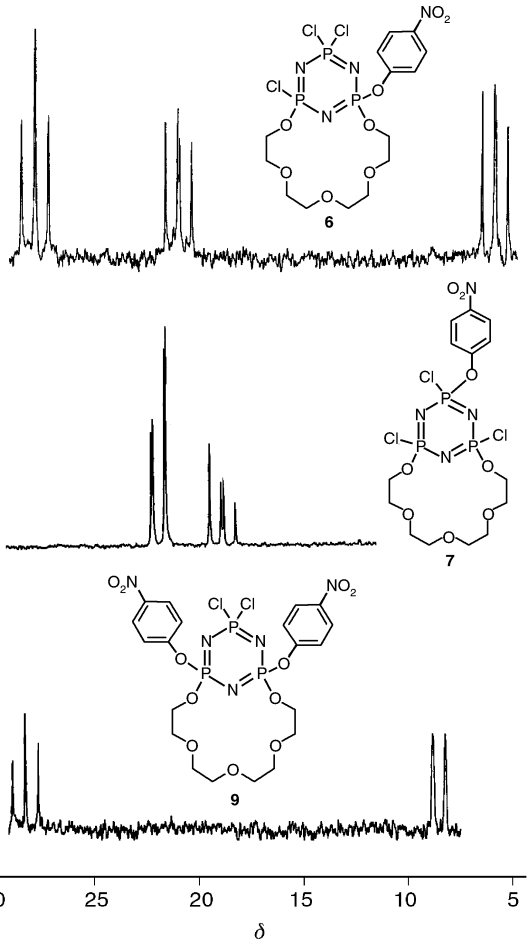


Fig. 1 $^{31}P\{^1H\}$ NMR spectra ($CDCl_3$) of the pure mono-'P-crown' (**6**), mono-'P-non-crown' (**7**) and di-'P-crown' (**9**) derivatives.

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

	δ_{PCl_2}	$\delta_{PCl(OCH_2)}$	$\delta_{PCl(OAr)}$	$\delta_{P(OAr)(OCH_2)}$	$\delta_{P(OAr)_2}$
1	25.1 (t, 1 P)	18.9 (d, 2 P)			
6	27.8 (dd, 1 P)	21.0 (dd, 1 P)		5.8 (dd, 1 P)	
7		AB_2 system; $\upsilon_B = 22.1$ (2 P)	AB_2 system; $\upsilon_A = 19.1$ (1 P)		
8		23.4 (d, 2 P)			4.7 (t, 1 P)
9	27.9 (t, 1 P)			8.0 (d, 2 P)	

[a] Recorded in $CDCl_3$ solution using phosphoric acid as an external reference.

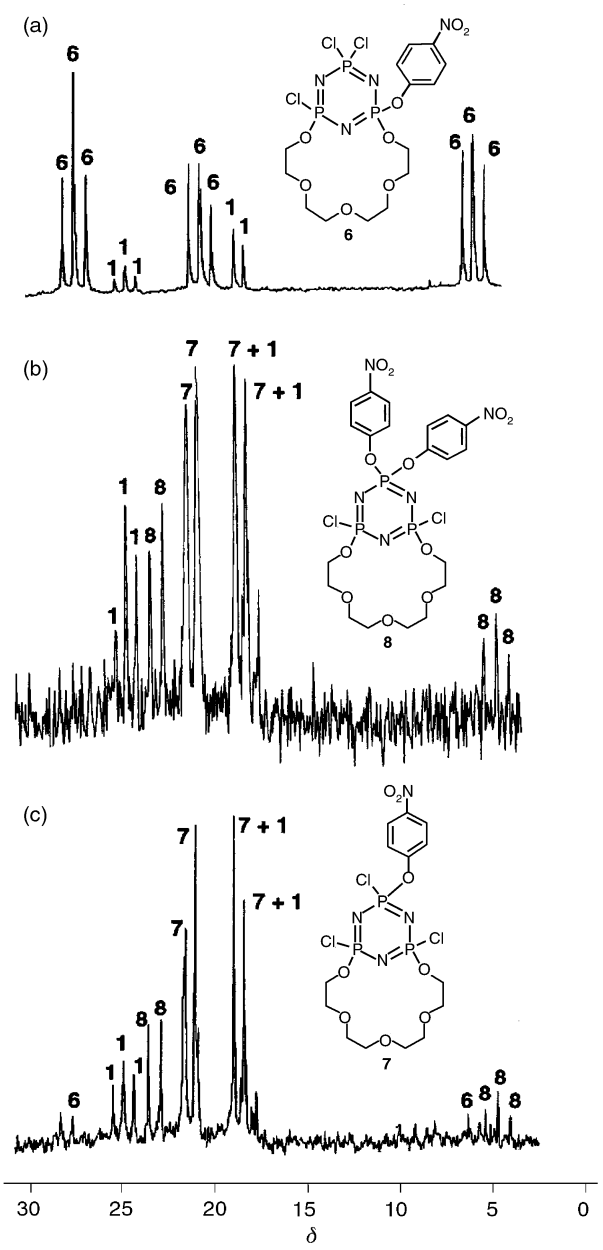


Fig. 2 $^{31}P\{^{1}H\}$ NMR spectra ($CDCl_3$) of the crude reaction mixtures of: diphosphaza[16]crown-6 (**1**) and lithium *p*-nitrophenoxide (**2**) in PhCl (a); **1** and the complex ($Li^+ \subset$ PHDB18C6)4–NO_2–$C_6H_4O^-$ (**11a**) in PhCl (b); **1** and potassium *p*-nitrophenoxide (**4**) in PhCl (c).

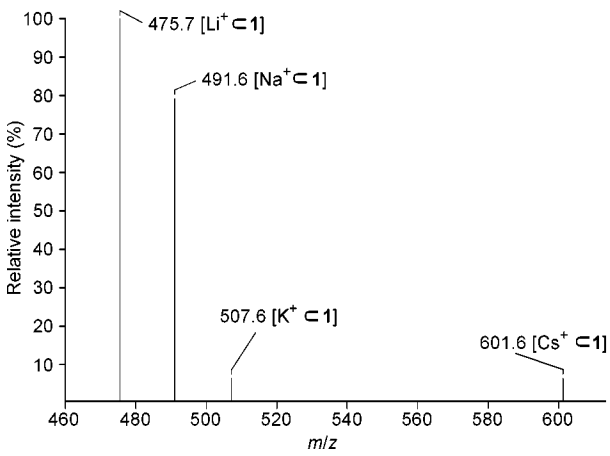


Fig. 3 Liquid secondary ion mass spectrum (LSIMS) of diphosphaza[16]crown-6 (**1**) in the presence of an equimolar mixture of $LiClO_4$, $NaClO_4$, $KClO_4$ and $CsClO_4$ using *m*-nitrobenzyl alcohol as a matrix.

tities of the 'P-non-crown' di-substituted compound **8** together with large amounts of unreacted PNP16C6.

'P-non-crown' derivatives **7** and **8** were obtained after shorter reaction times (1–2 h) as the only products when **1** was reacted with the corresponding lipophilic tetrahexylammonium salt **10** under homogeneous conditions [reaction (2)].

The change to a slightly more polar solvent like THF ($E_T^N = 0.207$),[11] in which the salts **2**, **4** and **5** are partially soluble, was found to affect both the rate and regiochemistry of the reaction. With the lithium salt, the regioselectivity drops remarkably. In this solvent the crude product is composed of a 70 : 30 mixture of mono- (**6**) and di-substituted (**9**) 'P-crown' derivatives. In contrast, with the sodium salt being completely insoluble in THF, the regiochemical outcome is the same as in chlorobenzene. As to the salts **4** and **5**, an increase in rate was observed, but without much change in the product distribution (similar mixtures of **7** and **8** as in chlorobenzene).

The displacement reactions, performed under homogeneous conditions by reacting chlorobenzene solutions of **1** ($1–2 \times 10^{-2}$ M) and of the preformed complexes (**11a–d**) (0.9 mol equiv) of **2–5** with the crown ether **11** [reaction (2)], all afforded, after short reaction times (2–3 h) the same mixture of mono- (**7**) and di-substituted (**8**) 'P-non-crown' derivatives, as indicated by their ^{31}P NMR spectra [*e.g.*, **11a**, see Fig. 2(b)].

Control experiments performed in parallel upon the reaction of the crown-free hexachlorocyclotriphosphazatriene $N_3P_3Cl_6$ (**12**) with lithium *p*-nitrophenoxide (**2**) in chlorobenzene at 25 °C showed, after prolonged reaction (3 days), only the starting reagent **12**. The complexing ability of **1** was independently determined *via* both UV-vis spectroscopy and liquid secondary ion mass spectrometry (LSIMS). UV-vis determinations were carried out by stirring (800 rpm) chlorobenzene solutions ($1–10 \times 10^{-4}$ M) of the tetraethoxy derivative **13** as a ligand with the appropriate solid salt **2–5** (2–3 mol equiv.) at 25 °C. The complexation experiments were performed on **13** in order to avoid the concomitant substitution of the chlorine atoms of the phosphazenic ring by the anionic nucleophile *p*-nitrophenoxide [reaction (1)]. The complex formation was qualitatively monitored by the appearance of an absorbance maximum in the region 380–400 nm where the free ligand **13** was found to be transparent.

In addition, the affinity of the functional crown ether **1** toward the alkali metal cations (Li^+, Na^+, K^+, Cs^+) was measured by LSMIS analysis of solutions of **1** in a *m*-nitrobenzyl alcohol (NBA) matrix in the presence of equimolar mixtures of the corresponding alkali metal perchlorates (Fig. 3).[12] Since the intensities of the LSIMS ion peaks are directly proportional to the concentrations and therefore to the stabilities, from the relative peak heights of the complexes [$M^+ \subset$ **1**] the following complexation percentages were obtained: Li^+(51); Na^+(43); K^+(3.5); Cs^+(2.5%).

Discussion

Our study on the nucleophilic substitution of PNP16C6 (**1**) with a series of alkali metal *p*-nitrophenoxides **2–5** in low polarity solvents [reaction (1)] has revealed the important role played by the metal cation M^+ in determining the regiochemical outcome of the reaction. Whereas the lithium (**2**) and sodium (**3**) salts gave exclusively the product **6** derived from the mono-substitution in the 'P-crown' position, with the corresponding potassium and caesium salts, only mono- (**7**) and di-substituted (**8**) products in the 'P-non-crown' position are obtained. Interestingly, the regiochemistry observed with lithium and sodium *p*-nitrophenoxides (*i.e.* geminal substitution in the 'P-crown' position) is in apparent contrast with classical cyclophosphazene chemistry, in which steric and electronic effects (charge distribution) are found to determine the

substitution patterns.[7] According to these rules, the introduction of electron-releasing substituents in the N_3P_3 ring decreases the electrophilicity of all P atoms, in particular that bearing the electron-donating substituent. As a consequence, the second substituent prefers to link to the most electropositive non-substituted P-atom following a non-geminal substitution pathway.[7]

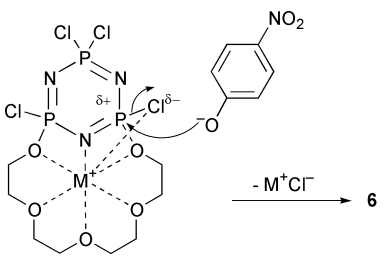
The results may be rationalized on the basis of a transition state in which the alkali metal *p*-nitrophenoxide (guest) interacts with the oxygens of the polyether macrocycle (host) in the functional crown ether **1** to give host–guest complexes stabilized by a combination of coordinative and electrostatic interactions (Scheme 2).

Complexation is a relatively fast step and is most likely the driving force for the entire process. As shown in Scheme 2, in the activation process the metal cation M^+, brought in close 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 *p*-nitrophenoxide simultaneously attacks the adjacent phosphorous atom through a concerted 'push–pull' mechanism.

The regioselectivity observed on changing the salt (**2**–**5**) can be interpreted in terms of the differing involvement of the cation in the stabilization of the transition state of reaction (1). The cation participation in the transition state is expected to be greater the higher its charge density ρ, increasing in the order $Cs^+ < K^+ < Na^+ < Li^+$. The results obtained with lithium and sodium salts, substitution in the 'P-crown' position only, are in line with the proposed mechanism. It is worth noting that the great preference of ligand **1** for these high charge density cations in chlorobenzene is also confirmed by liquid secondary ion mass spectrometry (LSIMS) determinations in a matrix of relatively low polarity, like *m*-nitrobenzyl alcohol (Fig. 3). The order of cation selectivity found with this functional crown ether ($Li^+ > Na^+ \gg K^+$) parallels that previously reported by Izatt *et al.* for 15-crown-5 in propylene carbonate.[6b]

More recently, *ab initio* quantum mechanical studies in the gas phase also predicted a decrease in binding affinity for 18-crown-6 with increasing alkali cation size, in the order: $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$.[13] This trend is in line with our experimental data with PNP16C6. Indeed, changing to cations of lower charge density and greater size, like potassium and caesium, results in a remarkable drop in the extent of complexation (Fig. 3). In these complexes the bulky cation most likely protrudes from the cavity of the polyether moiety, so interacting more effectively with the *p*-nitrophenoxide counteranion in a more intimate ion pair. As a consequence, the substitution of the chlorine atoms in the 'P-crown' position is much less favored and increasing quantities of kinetically preferred 'P-non-crown' derivatives (**7** and **8**) are found.

Interestingly, the same results are obtained, under homogeneous conditions, either by using the bulky non-complexable quaternary onium *p*-nitrophenoxide **10** or when the functional crown **1** is reacted with the salts **2**–**5** previously complexed by PHDB18C6 (**11**) [reaction (2)]. In the latter case, unlike the corresponding intramolecular reaction [reaction (1)], the effect of the metal ion is not observed at all and, whatever the cation may be, mixtures of 'P-non-crown' derivatives **7** and **8** are always obtained [Fig. 2(b)].



Scheme 2

Comparison with the corresponding unfunctionalized hexachlorocyclotriphosphazatriene (**12**) confirms the fundamental role played by the polyether chain of PNP16C6 in determining both the solubilization through complexation of the salts (**2**–**5**) in the low polarity chlorobenzene solvent and the activation of the ion-paired *p*-nitrophenoxides.

Analogous behavior was reported by Okano *et al.* in the cyanation of aryl halides with powdered NaCN catalyzed by crowned phosphine complexes of palladium under solid–liquid two-phase conditions. In this case also, the catalytic efficiency of the crowned complexes was found to be much higher compared with that of the unmodified phosphine complexes and was attributed by the authors to a proximity effect, as in enzyme chemistry.[14]

In addition, complex-induced proximity effects (CIPs) have been used to rationalize many apparently anomalous results in organolithium chemistry. Very recently, the regioselectivity observed in directed aryl and benzylic lithiations was attributed to the formation of a pre-lithiation complex that brings the lithiating agent in close proximity to the acidic hydrogen.[15]

Conclusion

The data as a whole clearly show that functional crown ethers like PNP16C6 (**1**) that combine the complexing ability of macrocycles with the well-known reactivity of chlorocyclophosphazenes behave as new molecular receptors for alkali metal cations. Results provide strong evidence of the key role of the polyether crown substituent in determining, *via* host–guest interaction with the alkali metal *p*-nitrophenoxide, the regiocontrol of the chlorine substitution in the phosphazenic ring ('P-crown' *vs.* 'P-non-crown' substitution), thus mimicking the action of natural enzymes in biological systems.[16] As a consequence of this supramolecular control, it is possible to switch the reaction pattern from kinetically favored ('P-non-crown' substitution) toward electronically and sterically unfavored regioselective substitution at the position adjacent to the macrocycle ('P-crown' substitution), giving easy access to species otherwise difficult to obtain following the rules of classical phosphazene chemistry. This means that, starting from the functional crown ether **1**, and with an appropriate choice of metal cation, nucleophile and solvent, we can realize the synthesis of a wide range of new PNP-crowns with a well-defined regiochemistry, under mild conditions and in high yields.

Experimental

Materials and solvents

Hexachlorocyclotriphosphazatriene (**12**), tetrahexylammonium chloride, alkali metal perchlorates and *m*-nitrobenzyl alcohol were commercial products and were utilized as purchased. Dry chlorobenzene ($H_2O \leqslant 20$ ppm) and THF ($H_2O \leqslant 50$ ppm) from Fluka were used. Diphosphaza[16]crown-6 (**1**) was synthesized from **12** following a previously reported procedure.[5] Alkali metal *p*-nitrophenoxides **2**–**5** were prepared as orange–yellow powders in high yields ($\geqslant$97%) by a literature method.[17] Tetrahexylammonium *p*-nitrophenoxide (**10**) was prepared *in situ* from tetrahexylammonium chloride by exchange with sodium *p*-nitrophenoxide (**3**), according to the ion-pair extraction technique.[18] Petroleum ether (b.p. 40–60 °C) was used as the chromatographic eluant.

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. $^{31}P\{^{1}H\}$ 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 caesium ion source (caesium gun), utilizing an *m*-nitrobenzyl alcohol (NBA) matrix.

UV-vis spectra. Measurements were performed by stirring at 25 °C a chlorobenzene solution (20 mL) of tetraethoxy-PNP16C6 (**13**, 1–10 × 10^{-4} M) with 2–3 mol. equiv. of the alkali metal *p*-nitrophenoxide **2–5**. 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 solution (1 mL) of **1** in *m*-nitrobenzyl alcohol (NBA, 0.02 M) was added to an equal volume of an NBA solution (0.1 M) containing an equimolar mixture of alkali metal perchlorates $MClO_4$ (M = Li, Na, K, Cs) 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 caesium 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 LM^+ ion peaks were obtained by averaging three different spectra.

Reaction of PNP16C6 (1) with alkali metal *p*-nitrophenoxides (2–5) general procedure

A heterogeneous mixture composed of a solution (0.05 M) of the functional crown ether **1** in the appropriate organic solvent (chlorobenzene, THF) and solid alkali metal *p*-nitrophenoxide **2–5** (0.9 mol equiv.) was stirred (800 rpm) in a flask thermostatted at 25 °C. The reaction was monitored by TLC (AcOEt–hexane 2 : 1, I_2). The reaction was stopped after 16–30 h 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), dehydrated over anhydrous Na_2SO_4 and, after removal of the solvent, analyzed by ^{31}P NMR spectroscopy (see Table 1). The reaction products **6–9** were occasionally isolated by flash chromatography (Et_2O–petroleum ether 4 : 1) on silica gel (230–400 mesh). Their physical, ^{1}H and ^{31}P NMR and analytic data are as follows.

Mono-'P-crown' derivative (6). Mp 75–80 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (d, 2 H, J = 9.1), 7.49 (dd, 2 H, J = 9.1, 1.2), 4.53–4.42 (m, 1 H), 4.31 (dt, 2 H, J = 17.1, 4.4 Hz), 4.24–4.17 (m, 1 H), 3.82–3.78 (m, 2 H), 3.77–3.61 (m, 10 H); ^{31}P NMR ($CDCl_3$) δ 27.8 (dd, 1 P, ^{2}J = 79.5, 78.7), 21.0 (dd, 1 P, ^{2}J = 79.5, 71.4), 5.8 (dd, 1 P, ^{2}J = 78.7, 71.4 Hz). Anal. calc. for $C_{14}H_{20}Cl_3N_4O_8P_3$: C, 29.42; H, 3.53; N, 9.80; found: C, 29.35; H, 3.44; N, 9.63%.

Mono-'P-non-crown' derivative (7). Wax; ^{1}H NMR ($CDCl_3$) δ 8.29 (d, 2 H, J = 13.9), 7.49 (dd, 2 H, J = 13.9, 2.5 Hz), 4.44–4.33 (m, 2 H), 4.33–4.22 (m, 2 H), 3.78–3.56 (m, 12 H); ^{31}P NMR ($CDCl_3$) AB_2 system υ_B = 22.1 (2 P), υ_A = 19.1 (1 P), J_{AB} = −75.8 Hz. Anal. calc. for $C_{14}H_{20}Cl_3N_4O_8P_3$: C, 29.42; H, 3.53; N, 9.80; found: C, 29.26; H, 3.40; N, 9.66%.

Di-'P-non-crown' derivative (8). Wax; ^{1}H NMR ($CDCl_3$) δ 8.30 (dd, 2 H, J = 17.1, 1.0), 8.30 (dd, 2 H, J = 10.0, 0.8), 7.44 (d, 2 H, J = 13.6), 7.43 (d, 2 H, J = 13.3 Hz), 4.37–4.21 (m, 2 H), 4.18–4.04 (m, 2 H), 3.73–3.54 (m, 12 H); ^{31}P NMR ($CDCl_3$) δ 23.4 (d, 2 P, ^{2}J = 85.0), 4.7 (t, 1 P, ^{2}J = 85.0 Hz). Anal. calc. for $C_{20}H_{24}Cl_2N_5O_{11}P_3$: C, 35.63; H, 3.59; N, 10.39; found: C, 35.50; H, 3.47; N, 10.21%.

Di-'P-crown' derivative (9). Wax; ^{1}H NMR ($CDCl_3$) δ 8.14 (dd, 4 H, J = 9.1, 2.2), 7.23 (dd, 4 H, J = 9.1, 2.2), 4.32–4.26 (m, 4 H), 3.79 (t, 4 H, J = 5.1 Hz), 3.71–3.65 (m, 8 H); ^{31}P NMR ($CDCl_3$) δ 27.9 (t, 1 P, ^{2}J = 74.2), 8.0 (d, 2 P, ^{2}J = 74.2 Hz). Anal. calc. for $C_{20}H_{24}Cl_2N_5O_{11}P_3$: C, 35.63; H, 3.59; N, 10.39; found: C, 35.48; H, 3.50; N, 10.31%.

Reaction of PNP16C6 (1) with alkali metal *p*-nitrophenoxides 2–5 complexed by PHDB18C6 (11)

A thermostatted (25 °C) chlorobenzene solution (10 mL) of **1** (0.01–0.018 M) was added to a volume of standardized chlorobenzene solution of the preformed complex ($M^+ \subset$ PHDB18C6)X^- (**11a–d**) to keep a molar ratio of *p*-nitrophenoxide/PNP16C6 = 0.9. The reaction was monitored by TLC and stopped after 3–90 h as described above. After standard work up, the crude product was analyzed by ^{31}P NMR spectroscopy (see Table 1).

The solutions of the preformed complexes (**11a–d**) were prepared by magnetically stirring (800 rpm) at 25 °C for 2–3 h a standardized chlorobenzene solution of the ligand **11** (0.02–0.085 M) with 0.9 molar equiv. of the appropriate solid alkali metal phenoxide **2–5**. The heterogeneous mixture was then allowed to stand, without stirring, for an additional 30 min. The organic phase was separated by centrifugation and samples (2–3 mL) were withdrawn and potentiometrically titrated with 0.01 N HCl.

Reaction of hexachlorocyclotriphosphazatriene (12) with lithium *p*-nitrophenoxide (2)

The reaction was carried out by stirring, for 3 days, a chlorobenzene solution of hexachlorocyclotriphosphazatriene (**12**) with 2 mol. equiv. of lithium *p*-nitrophenoxide (**2**), by analogy with the reaction of **1** (see above). The ^{31}P NMR analysis in $CDCl_3$ of the crude reaction mixture showed only a signal due to the starting reagent **12** at δ 20.6.

Synthesis of tetraethoxy-PNP16C6 (13)

NaH (60%, 93 mg, 2.3 mmol) was washed under nitrogen with dry pentane (3 × 5 mL) and added to anhydrous (molecular sieves 3 Å, $H_2O \leqslant 30$ ppm) ethanol (2 mL). To this, sodium ethoxide solution **1** (99.5 mg, 0.21 mmol) in anhydrous ethanol (2.5 mL) was added at 25 °C . The reaction was stirred (20 h) under nitrogen until no starting reagent **1** was detectable by TLC analysis (AcOEt–PE 5 : 2). The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with aqueous 10% HCl (2 × 10 mL) and water (3 × 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, affording **13** (50 mg, 47%) as a viscous oil: n_D^{17} = 1.4770. ^{1}H NMR ($CDCl_3$) δ 4.13–3.89 (m, 12 H), 3.81–3.48 (m, 12 H), 1.28 (t, 12 H, J = 8.9 Hz). ^{31}P NMR ($CDCl_3$) δ 18.0–18.6 (m, 3 P). Anal. calc. for $C_{16}H_{36}N_3O_9P_3$: C, 37.87, H, 7.15, N, 8.28; found: C, 37.67, H, 7.23, N, 8.15%.

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