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New Molecular Receptors with Cyclophosphazene Subunits: Synthesis, Reactivity, and Structure-Property Relationships

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Abstract. A series of hydrophopic **(2** and **3)** and new hydrophilic (**4**–**7**) molecular receptors of the PNP-lariat ether with tetra-substituted cyclotriphosphazene subunits have been prepared by the complete nucleophilic substitution of chlorine atoms in the reactive PNP-crown precursor **1** with the respective sodium cation-paired oxyanions (phenoxy → **2**, β-naphthoxy → **3**, and methoxytrioxyethylenoxy → **4**) and aliphatic amines (n-propylamine → **5** aziridine → **6,** and pyrrolidine → **7**). Their structures were established by MS and ^{31}P NMR spectroscopy and their metal ion complexing properties tested by a TLC method. Comparison of the complexation behaviour for ligands **1**–**7** shows that the affinity for particular cations is strongly substituent-dependent and, in general, is significantly enhanced by cooperation of the side arm donor atoms (O or N) with the parent PNP-crown structure in the binding process. The remarkable affinity of some ligands for selected cations, in particular lithium, cesium, and silver ions, is interpreted in terms of structure-property relationships.

Key words: P-pivot lariat ethers, synthesis, nucleophilic substitution, metal ion complexation, molecular receptors.

1. Introduction

One of the most promising and rapidly developing aspects in the research on new ligands is the design and synthesis of *lariat ethers*, which are side-armed crown ethers with pendant groups attached to the so-called *pivot* atoms (C, N, or P). The side arms contain atoms with lone-pair electrons which may cooperate with the *n*-electrons of the heteroatoms in the macrocyclic polyether skeleton to provide a third dimension of coordination for a ring-bound cation [1, 2].

Intensive development of the lariat ether concept has led to the synthesis of hundreds of side-armed crown ethers. Uses of lariat ethers range from routine

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(polymer-supported PTC catalysts, separation/extraction reagents, etc.) to sophisticated applications (redox switches for membrane transport, synthetic cation-conducting channels, and nucleotide-based molecular boxes [1, 3], as well as enzyme mimics [4–6]). The present work is aimed at the synthesis and study of the complexing properties of a new family of macrocyclic ligands, cyclophosphazene P-pivot lariat ethers with various side arms, to help elucidate structural factors which control the complexation behavior of lariat ether ligands.

2. Experimental

2.1. MATERIALS

Sodium hydride, 60% dispersion in mineral oil (Aldrich), was used as received. Triethylene glycol, monomethyl ether (Sigma) was dried over 4 Å molecular sieves. Phenol (POCh, Gliwice) was distilled under an argon atmosphere, m.p. 41 °C. β-Naphthol (2-naphthol) (Aldrich) was crystallized from heptane-chloroform (1:1), m.p. 123 °C. *n*-Propylamine (98%) and aziridine (99%) from Fluka AG and pyrrolidine (99%) from Aldrich were distilled over KOH pellets under an argon atmosphere before use.

THF (POCh Gliwice) was distilled over cuprous chloride, then over calcium hydride, and then twice over sodium-potassium alloy under an argon atmosphere. *n*-Hexane (Merck) was used without purification. Benzene was dried over KOH pellets, then over calcium hydride, and distilled from sodium metal. For column chromatography, silica gel 60 (230–400 mesh, Merck) was used. All reactions were performed under an argon atmosphere.

2.2. EQUIPMENT

^{1}H NMR spectra were recorded with a Varian VXR 300 spectrometer operating at 300 MHz using solutions in $CDCl_3$ with TMS as an internal standard. ^{31}P NMR spectra were recorded on the same spectrometer operating at 121 MHz using solutions in $CDCl_3$ with 85% H_3PO_4 as an external standard and with positive shifts recorded downfield from the reference. In most cases, both proton-coupled and proton-decoupled ^{31}P NMR spectra were obtained. Mass spectra were recorded on a Finnigan Mat SSQ 700 spectrometer by chemical ionization (positive and negative) with an isobutane matrix and/or liquid secondary ion mass spectrometry (LSIMS) on an Intectra (Germany) AMD 604 two-sector mass spectrometer with glycerol and *m*-nitrobenzyl alcohol (NBA) matrices; the latter technique was used to examine the metal complexes. Flash column chromatography was performed with silica gel (100-200 mesh, Merck) with hexane-THF (2:3) as eluent. The TLC complexation experiments were performed on Merck precoated silica gel 60 plates and were carried out as previously described [12, 13].

2.3. SYNTHESES OF LIGANDS **1**–**7**

2.3.1. *Preparation of Ligands* **1-3**

Synthesis of 1,1-(oxytetraethylenoxy)-3,3,5,5-tetrachlorocyclotriphosphazene (**1**) was performed as previously reported [7, 8], **1** was separated on silica with hexane-THF (2:1). The syntheses of 1,3-(oxytetraethylenoxy)-1,3,5,5-tetraphenoxycyclotriphosphazatriene (**2**) and of 1,3-(oxytetraethylenoxy)-1,3,5,5-tetra(β-naphthoxy-cyclotriphosphazatriene (**3**) were performed according to the procedure reported previously [8] and the products **2** and **3** were separated as given above for **1**.

2.3.2. *Preparation of 1,3-(Oxytetraethylenoxy)-1,3,5,5-tetra[methyloxy(trioxyethylenoxy)] – cyclotriphosphazatriene* (**4**)

In a 100 mL, 4-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser and argon inlet was added **1** (0.94 g, 2.0 mmol), the monomethyl ether of triethylene glycol (1.75 g, ∼10 mmol), 60% NaH (0.43 g, ∼10 mmol) and 200 mL of dry THF. The mixture was stirred at 20 °C for 6 hours until full substitution of the chlorine atoms with oligooxyethylenoxy groups was achieved, as followed by TLC. The yield of **4** in the crude reaction mixture according to the ^{31}P NMR results was ∼55%. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel with chloroform-methanol (20:1) as eluent to provide **4** as a colourless oil (1,72 g, 88%), R_f = 0.44 [(chloroform-methanol (15:1)]; MS, m/e 980 (M_{calc} for $C_{36}H_{76}O_{21}N_3P_3$, 979); ^{1}H NMR δ_H, $(CH_2)OC$ (3.77–3.35) (4 m, 64H); $(CH_2)OP$ (m, 12H). ^{31}P NMR δ_P, $P(OCH_2\text{-})_2$18.9 (s).

3. Preparation of 1,3-(Oxytetraethylenoxy)-1,3,5,5-tetra(n-propylamino)cyclotriphosphazatriene (5)

In a 100 mL, 3-necked round-bottomed flask was added **1**, (0.235 g, 0.50 mmol) and n-propylamine (1.02 mL, 4.8 mmol) dissolved in 20 mL of dry benzene. The solution was stirred at room temperature for 3 hours, after which the combined TLC/^{31}P NMR data indicated the formation of the amino-disubstituted derivative (∼53%) and tetrasubstituted derivative **5**. The reaction mixture was refluxed for another 2 hours which increased the yield of **5** to ∼82%. The reaction mixture was filtered and solvent was evaporated at reduced pressure. The resultant colourless oil was extracted with benzene (50 mL), concentrated to 5 mL and chromatographed on silica gel with THF-hexane (1:1) as eluent, yielding **5**, $C_{36}H_{48}O_5N_7P_3$, R_f = 0.175 [THF-hexane (2:1)] as a viscous, colourless oil. The MS and ^{1}H and ^{31}P NMR results are given in Table I.

Table I. MS, ^{31}P and ^{1}H NMR data for tetraamino-derivatives of PNP-crown **1** of general formula $N_3P_3R_4[O(C_2H_4O)_4]$

Compound	*R*	^{31}P NMR[a] spin system A_2X; δ_P				^{1}H NMR;[a]; δ_H				
		M^{+} [b]	P $(OCH_2)R$ (A)	PR_2 (X)	$\lvert J_{P-P}\rvert$	$(CH_3)C$	$(CH_2)C$	$(CH_2)N$	$(CH_2)OC$	$(CH_2)OP$
		(m/e)	[ppm]	[ppm]	[Hz]	[ppm]	[ppm]	[ppm]	[ppm]	[ppm]
5	$CH_3(CH_2)_2NH$–	559/560	20.4 doublet[c]	18.0 triplet[e]	43.8	0.94–0.85 (m 12H)	1.58–1.42 (m, 8H)	2.95–2.60 (2m, 8H)	3.78–3.58 (2m, 12H)	4.14–3,95 (m, 4H)
6	$[CH_2]_2N$–	495/496	29.7 doubletd	39.9 triplet[f]	40.7	–	–	2.14–1.97 (m, 16H)	3.79–3.59 (m, 12H)	4.20–4.13 (m, 4H)
7	$[CH_2]_4N$–	609/608	21.8 doublet[c]	18.6 triplet[e]	45.7	–	1.90–1.70 (m, 16H)	3.28–3.02 (m, 16H)	3.80–3.60 (2m, 12H)	4.15–3.90 (m, 4H)

[a] In $CDCl_3$.
[b] Molecular ion in the mass spectrum (calculated/found).
[c] Strong proton coupling causes broadening of the doublet lines.
[d] Doublet broadened due to overlapping of the particular signals.
[e] Proton coupling results in signals overlapping with formation of a broad triplet.
[f] Each line of triplet is intensively split by proton coupling.

3.1. PREPARATION OF 1,3-(OXYTETRAETHYLENOXY)-1,3,5,5-TETRA(AZIRIDINYLO)CYCLOTRIPHOSPHAZATRIENE (**6**)

In a 100 mL, 3-necked round-bottomed flask was placed **1** (0.469 g, 1.0 mmol) and aziridine (0.6 mL, ∼10 mmol) dissolved in 50 mL of dry benzene with small amounts of activated carbon and NaOH being added to prevent the ring opening and polymerization reactions of aziridine. The reaction was carried out in similar manner to that given above for **5**. The main product (96% yield according to ^{31}P NMR) was crystallized from hexane to provide **6**, $C_{36}H_{48}O_5N_7P_3$, as colourless needles with m.p. 85–87 °C, which was well soluble in water and most of organic solvents and stable on storage in air atmosphere for at least 1 year. The MS and ^{1}H and ^{31}P NMR results for **6** are given in Table I.

3.1.1. *Preparation of 1,3-(Oxytetraethylenoxy)-1,3,5,5-tetra(pyrrolidinylo)cyclotriphosphazatriene* (**7**)

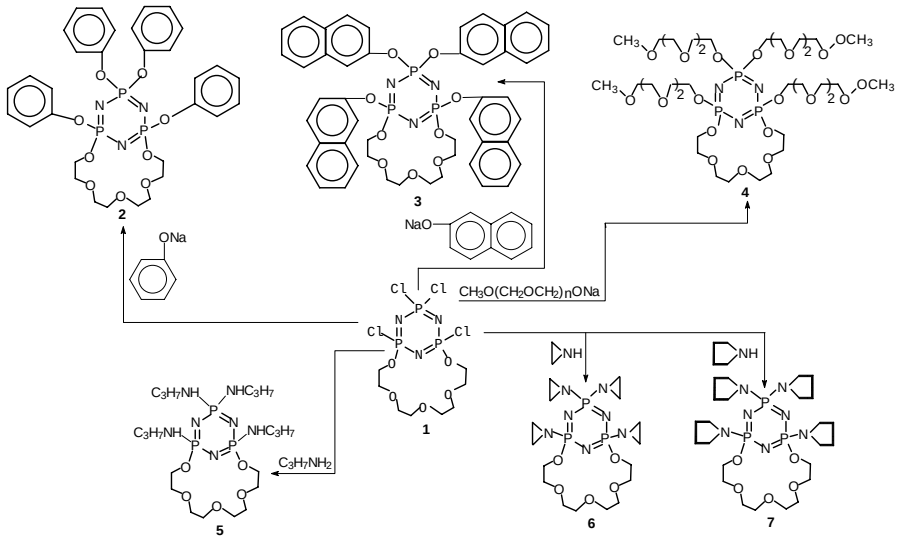
The reaction was conducted by the same method as given above for **5**, with replacement of *n*-propylamine by pyrrolidine in 40 mL of benzene. The main product 86% yield according to ^{31}P NMR was crystallized from hexane to form **7**, $C_{32}H_{48}O_5N_7P_3$, in the form of colourless crystals with m.p. 109–112 °C, which was well soluble in water and most organic solvents and stable on storage in air for at least 1 year. The MS, ^{1}H and ^{31}P NMR results for **7** are given in Table I.

4. Results and Discussion

4.1. SYNTHESIS OF PNP-LARIAT ETHERS

We described previously the synthesis of the reactive tetrachloro-PNP-crown ether **1** [7, 8] and its hydrophobic tetraaryloxy-substituted P-pivot lariat ether derivatives **2** and **3** [8], but without providing any data on their complexation behavior. In this paper, we report the preparation of four new hydrophilic derivatives **4**–**7** from precursor **1** by the complete substitution of its reactive chlorine atoms with the respective nucleophiles (Scheme 1): the sodium salt of trioxyethylene glycol monomethyl ether (→ **4**); a primary aliphatic amine: (*n*-propylamine → **5**), and two cyclic secondary amines (aziridine → **6**, and pyrrolidine → **7**), as well as the metal ion complexation properties of ligands **1–7**.

We reported previously that the presence of the macrocyclic substituent in **1** allows complexation of the sodium counterion of oxyanions [8–10] or entire amino reagents [11] which facilitates the substitution of **1** with aryloxy [8], dioxyarylene [9–10], and diamino [11] nucleophiles due to cation- [8–10] or amino-assistance [11]. Presumably the same factors influence the nucleophilic substitutions reported herein. The new PNP-lariat ethers **4**–**7** are formed quickly in high yields under mild conditions at room temperature. Due to the presence of the oligoether substituents in **4** and the amino substituents in **5**–**7**, all of the new PNP-lariat ether compounds



Scheme 1. Synthesis of PNP-Lariat Ethers.

4–**7** are water-soluble, which makes them potentially useful as flotation agents, as well as for various *in vivo* applications.

4.2. METAL ION COMPLEXATION PROPERTIES OF PNP-LARIAT ETHERS **2**–**7**

The metal cation complexing properties of tetra-substituted PNP-lariats **2**–**7** with different substituents at the P-atoms (hydrophobic in **2** and **3** [8] and hydrophilic in **4**–**7**), have been investigated using a simple test, which is based on the different rates of migration of the free ligand and its complex in TLC experiments [12, 13]. The differences in the R_f values are related to the complex stability constants. Therefore, the sequence of the B coefficients reflects the order of the corresponding Ks values. In many cases, complex formation was confirmed by mass spectrometric investigations (LSIMS), which showed the presence of the molecular ion peaks for the $(\text{metal-ligand})^+$ complexes (Table II).

Comparison of the TLC data in Table II reveals that in all cases the complexing properties of the PNP-lariat derivatives **2**–**7** are equal or exceed those of the precursor **1**, which contains only chlorine substituents. This may be ascribed to the presence of additional *hard* oxygen or *softer* nitrogen donor atoms [14] in **2**-**4** and **5**–**7**, respectively, which can cooperate with the basic PNP-crown structure to enhance the affinity of the parent ligand **1** towards the specified cations.

The small Li cation is complexed well only by polypodand oligoether crown derivative **4**. Owing to the presence of both oxygen and nitrogen binding sites, *hard* (alkali and alkali earth) as well as *soft* (transition) metal cations are complexed by the amino-substituted ligands **5**–**7**.

Table II. TLC[a] and LSIMS[d] results for complexation of metal ions by the tetra-R-substituted PNP-lariat ethers **2**–**7**

Compound	R	B[b] = $(R_{F2} - R_{F1})/R_{F2}$ [%] in hexane – THF (2 : 3)											
		Li^+	Na^+	K^+	Rb^+	Cs^+	Ag^+	Cu^+	Ca^{2+}	Mg^{2+}	Co^{2+}	Ni^{2+}	Cd^{2+}
1[c]	Cl^-	0	9	16	19	6	4	0	0	0	0	0	0
			*	*	*	*	*						
2	C_6H_5O–	0	8	36	23	3	0	0	0	0	0	0	0
3	β-$C_{10}H_7O$–	0	7	36	25	34	7	0	0	0	0	4	0
4	$CH_3O(C_2H_4O)_3^-$	41	35	17	18	15	45	0	0	0	0	0	0
			*	*	*								
5	$CH_3(CH_2)_2NH$–	−6	53	63	43	40	67	−20	0	29	9	37	0
6	$[CH_2]_2N$–	0	19	68	62	56	52	0	12	0	11	7	9
			*	*	*	*	*						
7	$[CH_2]_4N$–	9	39	90	79	62	79	29	−6	−19	−28	30	0

[a] TLC test [12, 13].
[b] The R_F value difference for the ligand on a silica gel alumina plate and on the silica gel impregnated with the salt containing given metal cation.
[c] The parent reactive tetrachloro-PNP-crown.
[d] An asterisk indicates presence of the $(\text{metal-ligand})^+$ molecular ions in the LSIMS spectra. Not all combinations were examined by LSIMS experiments. In no case were divergent TLC and LSIMS results obtained.

The striking enhancement in cesium complexation by **3** relative to **2** may be due to a π-effect of the β-naphthoxy group which favors complexation of large, easily polarizable metal ions. This could be of importance for the recovery of cesium from radioactive wastes [15].

The water-soluble PNP-ligands **4-7** display a high affinity for the silver cations. Recently the cyclophosphazene ring N_3P_3 itself has been reported to be an excellent host molecule for silver ion due to the contribution of its nitrogen atoms to the formation of the complex [17]. Some stable complexes with strong silver ion recognition have been reported to have potential in cancer ^{111}Ag-based radioimmunotherapy [17]. Taking into account the well known antitumour activity of various aziridinyl cyclophosphazene derivatives [18], the capability of **6** for strongly complexing silver ions may be of interest for combined cancer chemo- and radiotherapy.

Further studies of the complexing abilities of these new ligands, particularly regarding the selectivities of polymeric membrane electrodes containing hydrophobic cyclophosphazene lariat ethers as ionophores, are currently under way and will be reported soon.

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