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Synthesis and Cation Binding Ability of Azacrown Ethers with Phosphine or Phosphine Oxide Side Chain

György Keglevich,[1] Tibor Novák,[1] Tímea Imre,[1] Péter Bakó,[1] László Tőke,[1] Kálmán Újszászy,[2] and Krisztina Ludányi[3]

[1]*Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, Hungary*

[2]*Department of General and Inorganic Chemistry, Eötvös University, 1518 Budapest, Hungary*

[3]*Central Research Institute of Chemistry for Hungarian Academy of Sciences, 1525 Budapest, Hungary*

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ABSTRACT: *The reaction of monoaza-15-crown-5* **1** *with bromoalkylphosphine oxides* **2** *and diphenylvinylphosphine oxide led to a new type of lariat ethers (***3a–d***), one member of which (***3a***) was deoxygenated to the corresponding phosphine (***4***). The substituent at the nitrogen atom had a great impact on the extraction ability of the azacrown.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 573–576, 1999

INTRODUCTION

In continuation of our current interest in the synthesis of macrocycles with phosphorus containing side chains [1,2], we present the preparation of the phosphine and the phosphine oxide derivatives of monoaza-15-crown-5. The few examples of monoaza- and diazacrown ethers with phosphorus containing side arm(s) described include phosphonomethyl- and phosphinoalkyl derivatives [3–5]. We attempted to evaluate the effect of the length of the carbon chain and the *P*-function on the complexing ability of the parent azacrown ring.

RESULTS AND DISCUSSION

The monoaza-15-crown-5-based lariat ethers with *P*-function were synthesized by the *N*-alkylation of azacrown **1.** The reaction of crown **1** with bromoalkyl-diphenylphosphine oxides **2a–d** in dimethylformamide (DMF) in the presence of potassium carbonate at 90°C gave the corresponding lariat ethers (**3a–d**) (Scheme 1). Products **3b–d** were obtained in reasonable yields (47–53%) after column chromatography, and because of side reactions of unknown nature, **3a** was isolated only in 12% yield. The reaction of crown **1** with diphenylvinylphosphine oxide in boiling methanol, in the presence of a catalytic amount of acetic acid, however, led to product **3a** in excellent yield (92%) (Scheme 2). With the exception of **3b** [1], the lariat ethers (**3a,c,d**) that were synthesized are new compounds and have been characterized by ^{31}P, ^{13}C, and ^{1}H NMR, as well as mass spectrometry (MS) and high-resolution mass spectrometry (HRMS) data. The ^{31}P and ^{13}C NMR parameters are listed in Table 1. The chemical shifts, couplings, and mass spectroscopic fragmentation of phosphine oxides **3** showed close resemblance to the

Correspondence to: György Keglevich.
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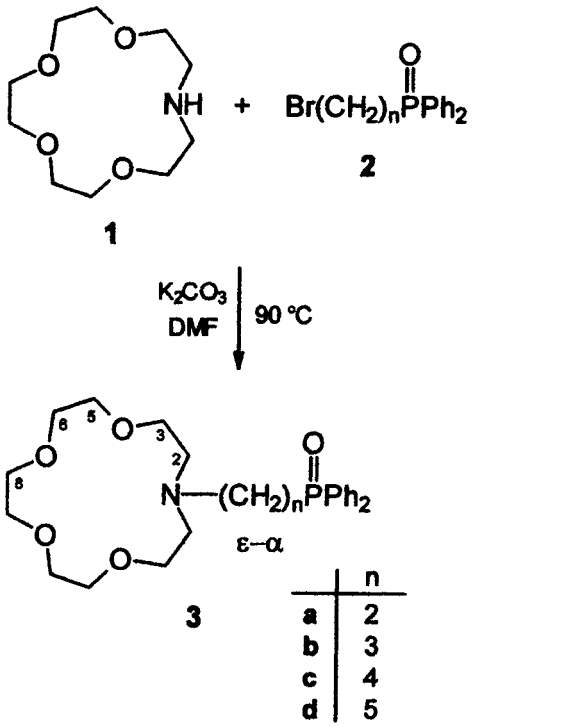
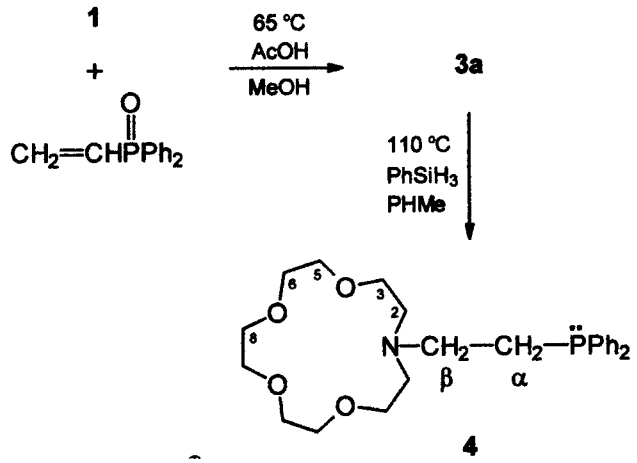


SCHEME 1



SCHEME 2

corresponding features of phosphinic esters described earlier [1].

An additional lariat ether (**4**) with a phosphinoethyl substituent on the N atom was synthesized by the deoxygenation of phosphine oxide **3a** using phenylsilane (Scheme 2). Earlier, phosphine **4** was synthesized by another approach [6]. The ^{31}P and ^{1}H NMR data of product **4** were similar to those reported [6]. In a nitrogen atmosphere, phosphine **4** can be stored for weeks. Oxidation of phosphine **4** by 30% hydrogen peroxide regenerated phosphine oxide **3a.**

Having lariat ethers **3a–d** and **4** in hand, it was possible to evaluate the effect of the length of the carbon chain and *P*-function on the cation binding ability of the azacrown ether (**1**). The complex forming ability of the lariat ethers (**3a–d** and **4**) was characterized by the extracting ability (EA) of lithium, sodium, potassium, and ammonium picrates from water into dichloromethane in the presence of **3** or **4** by the method of Kimura et al. [7]. Concentrations of the picrates in water were determined by UV spectroscopy. The experimental data are shown in Table 2. The unsubstituted azacrown ether (**1**), which is used as the reference compound, transports 56–67% of the picrate salts into the organic phase, but it does not show a notable selectivity with any of the alkali or ammonium ions. As can be seen, the side arms with a diphenylphosphine oxide moiety at their end have a significant influence on the EA of the azacrown ring. In most cases, introduction of the $Ph_2P(O)$-alkyl side arm decreased the EA of the parent azacrown (**1**) (Table 2). In some cases, an increase in the EA, however, was observed (Table 2). The complex effect of the *N*-substituents is presumably due to steric and electronic effects. The length of the side arm is decisive; the highest extraction values (59–75%, except the EA for the lithium cation) were obtained for azacrown **3c**, which incorporated four methylene units between the diphenylphosphine oxide moiety and the nitrogen atom. At the same time, compound **3b** with a chain of three carbon atoms revealed the lowest values (21–50%, except the EA for the ammonium cation). The selectivity of the parent azacrown (**1**) was improved significantly by the introduction of the diphenylphosphine oxide side arm. Azacrown **3a** with a two carbon atom chain showed the best selectivity because it transports two times more lithium picrate and sodium picrate (78% and 71%, respectively,) into the organic phase than potassium picrate or ammonium picrate (33 and 36%, respectively). Compound **3b** distinguishes between lithium and sodium cations because it carries two times more sodium picrate (50%) than lithium picrate (21%) through the phase border. The sequence of selectivity was also changed for the different azacrown ethers (1, 3a–c); in the case of the base azacrown (**1**), the order is $K^+ \sim Li^+ > NH_4^+ > Na^+$. Product **3a** revealed the $Li^+ > Na^+ > NH_4^+ \sim K^+$ order, and **3b** followed the $Na^+ \sim NH_4^+ > K^+ > Li^+$ sequence. For **3c**, an order of $NH_4^+ \sim Na^+ > K^+ > Li^+$ was detected.

It is interesting to compare the cation binding ability of phosphine oxide **3a** with that of phosphine

TABLE 1 ^{31}P and ^{13}C NMR Data for the New Lariat Ethers

		$\delta_C(J_{PC})$													
Compound	δ_P	*C-α*	*C-β*	*C-γ*	*C-δ*	*C-ε*	*C-2*	*C-3*	*C-5*	*C-6*	*C-8*	*C-1′*	*C-2′*	*C-3′*	*C-4′*
3a	31.4	27.7 (69.2)	48.9				54.0	69.7[a]	70.1[a]	70.3[a]	70.9[a]	133.1 (98.8)	130.6[b] (9.4)	128.6[b] (11.5)	131.6 (1.7)
3c	33.4	29.6 (71.8)	19.6 (3.7)	28.4 (14.1)	56.1		54.7	69.7[c]	70.1[c]	70.3[c]	70.9[c]	133.1 (98.1)	130.9[d] (10.1)	128.8[b] (11.3)	131.8 (2.5)
3d	35.0	29.0 (73.1)	21.3 (2.0)	29.8 (8.4)	26.7	56.5	54.5	69.8[e]	70.0[e]	70.3[e]	70.9[e]	132.9 (98.2)	130.7[f] (8.8)	128.6[f] (11.4)	131.7

[a,c,e]Tentative assignment.
[b,d,f]May be reversed.

TABLE 2 Data for the Extraction of Alkali Metal and Ammonium Picrates by Azacrown Ethers **1, 3a–c,** and **4**[a]

	Extractability (%)[b]			
Compound	Li^+	Na^+	K^+	NH_4^+
1	65	56	67	60
3a	78	71	33	36
3b	21	50	30	46 (Ref. [1])
3c	47	72	59	75
4	20	63	47	48

[a]Temperature 20°C; aqueous phase (5 mL); [picrate] = 0.005 M; organic phase (CH_2Cl_2, 5 mL); [crown ether] = 0.01 M.
[b]Defined as % picrate extracted into the organic phase. Determined by UV spectroscopy. Error limit = 5%.

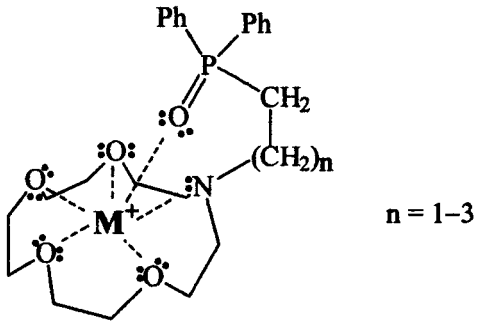


FIGURE 1 The effect of the P-functionalized side arm on the cation binding ability of the aracrown ring.

4. Removal of the oxygen atom from the phosphoryl group of **3a** resulted in a change of the EA values; phosphine **4** forms a weaker complex with the lithium cation than oxide **3a** does, but with the potassium and ammonium cations the complexes are stronger for **4** than for **3a** (Table 2). The selectivity also changed; compound **4** transports three times more sodium picrate than the lithium salt. The low value of 20% obtained for **4** can be explained by assuming that the short side arm cannot promote the complexation of the relatively small lithium cation. If there is an oxygen on the phosphorus atom (compound **3a**), the binding ability toward the lithium cation is improved.

It can be concluded that the *P*-functionalized side arms attached to the nitrogen atom have a significant effect on the cation binding ability of the monoaza-15-crown-5 ring, probably by the lateral discrimination [8] caused by the lone-pair electrons of the heteroatom (oxygen or phosphorus) at the end of the *N*-substituent. This effect is visualized for phosphine oxide **3b** in Figure 1. We plan to perform molecular mechanics calculations to explain the interaction between the complexing cation and the bending side arm. Although the extracting ability generally decreased, the selectivity always improved.

EXPERIMENTAL

^{31}P, ^{1}H, and ^{13}C NMR spectra were obtained on a Bruker DRX-500 spectrometer (at 202.4, 500, and 125.7 MHz, respectively) with 85% phosphoric acid (external) and tetramethylsilene (internal) standards in $CDCl_3$ solutions. Coupling constants are given in Hz. Mass spectra were recorded on a MS 25-RFA instrument at 70 eV.

Diphenylvinylphosphine oxide was prepared from diphenylphosphinic chloride and vinylmagnesium bromide as described earlier [9]. Diphenylvinylphosphine and monoaza-15-crown-5 were purchased from Aldrich.

General Procedure for the Preparation of ω-Bromoalkyl-diphenylphosphine Oxides **2a,c,d**

A mixture of 2.62 g, (11.4 mmol) of ethyl diphenylphosphinite [10] and 56.9 mmol of the corresponding dibromoalkane was heated at 150°C (oil bath) for 3 hours. The excess of dibromoalkane was removed at 20 mmHg, and the residue was purified by column

chromatography (silica gel, 3% methanol in chloroform) to give **2a,c,d.**

(**2a**) Yield 46%; ^{31}P NMR ($CDCl_3$) δ 29.8; ^{13}C NMR ($CDCl_3$) δ 24.0 (C-2), 35.0 (J = 63.5, C-1), 129.1 (J = 11.9, C-3′), 130.8 (J = 9.4, C-2′), 131.9 (J = 99.3, C-1′), 132.4 (J = 2.2, C-4′); MS, m/z (rel. int.) 308 (M^+, 1), 228 (10), 201 (100).

(**2c**) Yield 53%; ^{31}P NMR ($CDCl_3$) δ 33.0; ^{13}C NMR ($CDCl_3$) δ 20.1 (C-2), 28.0 (J = 71.3, C-1), 32.8 (C-4), 33.1 (J = 14.7, C-3), 128.9 (J = 11.8, C-3′), 129.9 (J = 101.2, C-1′), 130.7 (J = 9.6, C-2′), 132.4 (C-4′); MS, m/z (rel. int.) 337 (M + H, 1), 257 (64), 201 (100).

(**2d**) Yield 42%; ^{31}P NMR ($CDCl_3$) δ 32.7; ^{13}C NMR ($CDCl_3$) δ 20.9 (J = 3.4, C-2), 29.5 (J = 14.5, C-3), 29.7 (J = 71.8, C-1), 32.3 (C-4), 33.5 (C-5), 128.8 (J = 11.3, C-3′), 130.8 (J = 9.0, C-2′), 131.8 (J = 1.7, C-4′), 133.1 (J = 98.1, C-1′); MS, m/z (rel. int.) 350 (M^+, 1), 271 (36), 215 (100), 201 (57).

General Procedure for the Preparation of (1,4,7,10-Tetraoxa-13-aza-cyclo-pentadec-13-ylalkyl)-diphenylphosphine Oxides **3a–d**

A mixture of 0.5 g (2.28 mmol) of azacrown **1,** 3.42 mmol of the corresponding bromalkylphosphine oxide, 0.32 g (2.28 mmol) of dry potassium carbonate in 30 mL of DMF was stirred at 85°C for 20 hours. The solid components were removed by filtration and the filtrate concentrated in vacuo. The residue was taken up in a mixture of 50 mL of chloroform and 2 mL of water. Then, the organic phase was dried (Na_2SO_4), and the solvent was evaporated. The remaining oil was purified by repeated column chromatography (silica gel, 3% methanol in chloroform) to give **3a–d.**

(**3c**) Yield 51%; ^{31}P and ^{13}C NMR, Table 1; ^{1}H NMR ($CDCl_3$) δ 1.53–1.63 [m, 4H, C(β)H_2, C(γ)H_2], 2.22–2.31 [m, 2H, C(α)H_2], 2.45–2.51 [m, 2H, C(δ)H_2], 2.67 [t, J = 3.5, 4H, C(2)H_2], 3.53–3.67 [m, 16H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2], 7.51–7.73 (m, 10H, Ar); MS, m/z (rel. int.) 475 (M^+, 3), 474 (M-H, 4), 414 (M-$(CH_2O)_2$-H, 13), 326 [414-$(CH_2CH_2O)_2$,25], 325 (326-H, 33), 312 (326-CH_2, 22), 274 [M-P(O)Ph_2, 24], 257 [$(CH_2)_4$P(O)Ph_2, 95], 232 [M-$(CH_2)_3$P(O)Ph_2, 100], 201 [P(O)Ph_2, 60]: M^+_{found} = 475.2401, $C_{26}H_{38}NO_5P$ requires 475.2488.

(**3d**) Yield 47%; ^{31}P and ^{13}C NMR, Table 1; MS, m/z (rel. int.) 489 (M^+, 3), 488 (M-H, 5), 428 [M-$(CH_2O)_2$-H, 12], 340 [428-$(CH_2CH_2O)_2$, 21], 339 (340-H, 18), 326 (340-CH_2, 37), 288 [M-P(O)Ph_2, 27], 271 [$(CH_2)_5$P(O)Ph_2, 55], 232 [M-$(CH_2)_4$P(O)Ph_2, 100], 201 [P(O)Ph_2, 47]; M^+_{found} = 489.2579, $C_{27}H_{40}NO_5P$ requires 489.2644.

(**3b**) Yield 53%; spectroscopical data were similar to those reported earlier [1].

(**3a**) Yield 12%; preparation of **3a** by the method described below was more efficient. A solution of 0.57 g (2.60 mmol) of azacrown **1,** 0.59 g (2.60 mmol) of diphenylvinylphosphine oxide, and three drops of acetic acid in 30 mL of methanol was stirred at the boiling point for 10 days. Volatile components were removed in vacuo. Column chromatography (as above) of the oily residue led to 1.07 g (92%) of **3a.** ^{31}P and ^{13}C NMR, Table 1; ^{1}H NMR ($CDCl_3$) δ 2.48–2.56 [m, 2H, C(α)H_2], 2.73 [d, J = 5.9, 4H, C(2)H_2], 2.88–2.94 [m, 2H, C(β)H_2], 3.56–3.69 [m, 16H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2], 7.45–7.78 (m, 10H, Ar); MS, m/z (rel. int.) 447 (M^+, 5), 446 (M-H, 3), 386 [M-$(CH_2O)_2$-H, 8], 298 [386-$(CH_2CH_2O)_2$, 30], 297 (298-H, 100), 284 (298-CH_2, 23), 246 [M-P(O)Ph_2, 70], 228 [$(CH_2)_2$P(O)Ph_2-H, 22], 201 [P(O)Ph_2, 94]; M^+_{found} = 447.2093, $C_{24}H_{34}NO_5P$ requires 447.2175.

Preparation of Phosphine **4**

A solution of 0.2 g (0.447 mmol) of azacrown **1** and 0.20 mL (1.622 mmol) of phenylsilane in 5 mL of toluene was heated at 110°C under nitrogen for 4 days. Evaporation of the volatile components in vacuo left 0.20 g (98%) of **4** in a purity of 94%. ^{31}P NMR ($CDCl_3$) δ −19.1 [^{31}P NMR ($CDCl_3$) δ −19.3] [6]; ^{1}H NMR ($CDCl_3$) δ 2.22–2.43 (m, 2H, CH_2P), 2.59–3.09 (m, 6H, NCH_2), 3.46–3.80 (m, 16H, OCH_2), 7.16–7.56 (m, 10H, Ar); MS, m/z (rel. int.) 431 (M^+, 4), 372 [M-$(CH_2O)_2$ + H, 3], 246 (M-PPh_2, 2), 232 (M-CH_2PPh_2, 100), 200 (CH_2PPh_2 + H, 28), 185 (PPh_2, 24).

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