Journal of Inclusion Phenomena and Macrocyclic Chemistry **38:** 435–443, 2000.

Synthesis and Cation Binding Ability of the Phosphonoalkyl- and Phosphinoylalkyl Derivatives of Monoaza-18-Crown-6

TIBOR NOVÁK, PÉTER BAKÓ, TIMEA IMRE and GYÖRGY KEGLEVICH*
Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, Hungary

ANDRÁS DOBÓ
Hungarian Academy of Sciences, Chemical Research Center, 1525 Budapest, Hungary

LÁSZLÓ TÕKE
Research Group of the Hungarian Academy of Sciences, Technical University of Budapest, 1521 Budapest, Hungary

(Received: 10 December 1999; in final form: 3 March 2000)

Abstract. Azacrown ethers with phosphonoalkyl- and phosphinoylalkyl side chains of two to five carbon atoms (**2–4**, **7** and **5–6**, **8**, respectively) were synthesized in acceptable yields. The cation binding ability of the new lariat ethers was evaluated by the picrate extraction method. Introduction of the P-functionalised N-substituent resulted in a decrease in the cation extraction ability in most cases, but the discrimination between the cations examined was, in some instances, significantly increased.

Key words: monoaza-18-crown-6, lariat ether, P-functionalised side chain, extraction ability.

1. Introduction

In the past few years a great number of azacrown macrocycles bearing functionalised pendant arms have been synthesized. These type of compounds, named lariat ethers [1], are known to be effective host molecules for alkali metal and alkaline earth metal cations due to the cooperative coordination function of the crown ring and the electron-donating side arm [1, 2]. The selectivity for the different cations may be affected by the heteroatom(s) in the side chain and by the number of methylene units connecting the functional group with the hetero atom to the azacrown ring [3]. The complex forming ability of the macrocycles having P-functionalized pendant arms is relatively less studied. Some monoaza- and diazacrown ethers with phosphonomethyl side arms have been described [4–6]. These lariat ethers were mainly phosphonic acid derivatives [4, 6], a few examples

* Author for correspondence.

of mono- and diazacrowns incorporating longer side arm(s) with the phosphine function are also known [7].

Recently we have reported the synthesis and cation extracting ability of monoaza-15-crown-5 ether having a phosphonate, phosphine oxide or phosphine function in the side chain [8, 9]. In the light of our favourable experiences with the above lariat ethers, it seemed to be promising to attach P-functionalised side arms to azacrown ethers of larger ring size. In this paper, we report the synthesis and cation binding ability of new lariat ethers with the phosphonic ester or phosphine oxide function based on the monoaza-18-crown-6 hetero ring. We wished to study the effect of the P-function and that of the length of the pendant arm on the cation binding ability of the parent macrocycle.

2. Experimental

The ^{31}P, ^{13}C and ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer operating at 202.4, 125.7 and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. Mass spectra were obtained on an MS-RFA instrument or on a ZAB-2SEQ spectrometer at 70 eV.

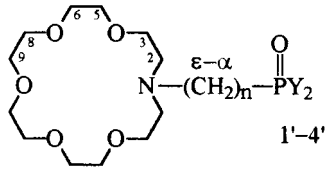
2.1. GENERAL PROCEDURE FOR THE PREPARATION OF LARIAT ETHERS (**2–6**)

A mixture of 1.0 g (3.80 mmol) of monoaza-18-crown-6 (**1**) [10], 5.70 mmol of the corresponding bromoalkylphosphonate [8] (or bromoalkylphosphine oxide [9]), and 0.79 g (5.70 mmol) of dry potassium carbonate in 30 mL of dry acetonitrile was stirred at 82 °C for 8 h. Solid components were removed by filtration and the filtrate concentrated *in vacuo*. The residue was purified by repeated column chromatography (3% methanol in chloroform, silica gel). The following products were thus synthesized.

2.2. DIETHYL (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLPROPYL)PHOSPHONATE (**2**)

Yield: 58%; ^{31}P NMR ($CDCl_3$) δ 32.4; ^{13}C NMR, Table I; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.0, 6H, C(3′)H_3), 1.65–1.81(m, 4H, C(α)H_2, C(β)H_2), 2.66–2.84 (m, 6H, C(2)H_2, C(γ)H_2), 3.52–3.75 (m, 20H, C(2)H_2, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 4.10 (q, J = 6.94, 4H, C(2′)H_2); MS, *m/z* 442 (M+H, 5), 396 (M–EtO, 7), 380 (M–EtO–O, 9), 336 (M–2EtO–O+H, 13), 276 (crown–CH_2, 100), 246 (30), 208 (38); $(M+H)^+_{found}$ = 442.2562, $C_{19}H_{41}NO_8P$ requires 442.2570.

Table I. ^{13}C NMR data for lariat ethers **2–8** in $CDCl_3$ solutions



Comp.	Y	n	δ_C (J_{PC} in Hz)													
			C_α	C_β	C_γ	C_δ	C_ϵ	C_2	C_3	C_5	C_6	C_8	C_9	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$
7	EtO	2	23.0	48.3	–	–	–	53.2	69.4[a]	70.1[a]	70.4[a]	70.4[a]	70.6[a]	–	61.2	16.2	–
			(136.6)												(6.4)	(6.0)	
2	EtO	3	22.6	16.9	51.0	–	–	53.5	69.4[b]	69.5[b]	69.5[b]	69.5[b]	69.6[b]	–	61.4	16.1	–
			(141.2)	(3.8)	(15.4)										(6.1)	(5.9)	
3	EtO	4	24.5	19.9	24.3	50.4	–	53.6	69.3[c]	69.4[c]	69.5[c]	69.6[c]	69.7[c]	–	61.2	16.1	–
			(140.1)	(4.7)	(14.3)										(6.1)	(5.9)	
4	EtO	5	25.3	22.2	28.2	23.9	51.5	54.0	69.9[d]	69.9[d]	69.9[d]	70.0[d]	70.1[d]	–	61.4	16.4	–
			(140.0)	(3.8)	(16.4)										(6.5)	(5.9)	
8	Ph	2	26.9	47.6	–	–	–	53.4	69.2[e]	70.0[e]	70.3[e]	70.4[e]	70.5[e]	132.7	130.5[f]	128.5[f]	131.5
			(69.3)											(99.0)	(9.2)	(11.3)	()
5	Ph	3	26.6	16.8	51.8	–	–	53.8	69.4[g]	69.5[g]	69.7[g]	70.1[g]	70.2[g]	132.3	130.4[h]	128.5[h]	131.5
			(71.9)											(98.7)	(9.2)	(11.6)	(1.5)
6	Ph	4	28.7	19.3	25.5	50.9	–	53.8	69.5[i]	69.8[i]	69.9[i]	70.1[i]	70.2[i]	132.8	130.5[j]	128.4[j]	131.4
			(71.6)	(3.4)	(12.1)	(16.0)								(97.8)	(9.5)	(11.7)	(1.7)

[a–j] Tentative assignments.

2.3. DIETHYL (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLBUTYL)PHOSPHONATE (**3**)

Yield: 45%; ^{31}P NMR ($CDCl_3$) δ 32.4; ^{13}C NMR, Table I; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.0, 6H, C(3′)H_3), 1.52–1.66 (m, 4H, C(β)H_2, C(γ)H_2), 1.72–1.85 (m, 2H, C(α)H_2), 2.55–2.94 (m, 6H, C(2)H_2, C(δ)H_2), 3.48–3.80 (m, 20H, C(2)H_2, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 4.08 (q, J = 7.0, 4H, C(2′)H_2); MS FAB, *m/z* 456 (M+H, 5), 410 (M–EtO, 20), 394 (M–EtO–O, 25), 350 (M–2EtO–O+H, 50), 276 (crown–CH_2, 100), 246 (93), 208 (63); $(M+H)^+_{found}$ = 456.2712, $C_{20}H_{43}NO_8P$ requires 456.2726.

2.4. DIETHYL (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLPENTYL)PHOSPHONATE (**4**)

Yield: 48%; ^{31}P NMR ($CDCl_3$) δ 32.7; ^{13}C NMR, Table I; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.0, 6H, C(3′)H_3), 1.33–2.15 (m, 10H, C(α)H_2, C(β)H_2, C(γ)H_2, C(δ)H_2, C(ϵ)H_2), 2.52–2.78 (m, 4H, C(2)H_2), 3.43–3.76 (m, 20H, C(2)H_2, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 4.07 (q, J = 7.1, 4H, C(2′)H_2); MS, *m/z* 468 (M+H, 5), 424 (M–EtO, 5), 408 (M–EtO–O, 4), 364 (M–2EtO–O+H, 5), 276 (crown–CH_2, 100), 246 (36), 236 (36); $(M-H)^+_{found}$ = 468.2726, $C_{21}H_{43}NO_8P$ requires 468.2707.

2.5. (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLPROPYL)-DIPHENYLPHOSPHINE OXIDE (**5**)

Yield: 46%; ^{31}P NMR ($CDCl_3$) δ 34.1; ^{13}C NMR, Table I; ^{1}H NMR ($CDCl_3$) δ 1.59–1.71 (m, 2H, C(β)H_2), 2.22–2.30 (m, 2H, C(α)H_2), 2.97–3.03 (m, 6H, C(γ)H_2, C(2)H_2), 3.35–3.63 (m, 20H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 7.21–7.65 (m, 10H, Ar); MS, *m/z* 506 (M+H, 5), 444 (M–2CH_2O–H, 5), 400 (9), 311 (96), 276 (crown–CH_2, 53), 243 ((CH_2)$_3$–P(O)PPh_2, 100), 201 (P(O)Ph_2, 42); $(M+H)^+_{found}$ = 506.2640, $C_{27}H_{41}NO_6P$ requires 506.2672.

2.6. (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLBUTYL)-DIPHENYLPHOSPHINE OXIDE (**6**)

Yield: 44%; ^{31}P NMR ($CDCl_3$) δ 33.1; ^{13}C NMR, Table I; ^{1}H NMR ($CDCl_3$) δ 1.40–1.51 (m, 4H, C(β)H_2, C(γ)H_2), 2.20–2.29 (m, 2H, C(α)H_2), 2.45–2.54 (m, 2H, C(δ)H_2), 2.89–2.99 (m, 4H, C(2)H_2), 3.35–3.57 (m, 20H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 7.27–7.67 (m, 10H, Ar); MS, *m/z* 520 (M+H, 4), 458 (M–2CH_2O–H, 6), 414 (10), 276 (crown–CH_2, 80), 257 ((CH_2)$_4$–P(O)PPh_2, 100), 201 (P(O)Ph_2, 71); $(M+H)^+_{found}$ = 520.2830, $C_{28}H_{43}NO_6P$ requires 520.2828.

3. General Procedure for the Preparation of Lariat Ethers (7–8)

A solution of 1.0 g (3.80 mmol) of monoaza-18-crown-6 (**1**), 3.80 mmol of diphenylvinylphosphine oxide [9] (or diphenylvinylphosphonate [8]) 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*. The residue was purified by repeated column chromatography (3% methanol in chloroform, silica gel). The following products were thus synthesized.

3.1. DIETHYL (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLETHYL)PHOSPHONATE (**7**)

Yield: 69%; ^{31}P NMR ($CDCl_3$) δ 31.4; ^{13}C NMR, Table I; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.0, 6H, C(3′)H_3), 1.84–1.90 (m, 2H, C(α)H_2), 2.69–2.80 (m, 4H, C(2)H_2), 2.82–2.92 (m, 2H, C(β)H_2), 3.56–3.70 (m, 20H, C(2)H_2, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 4.09 (q, J = 7.4, 4H, C(2')H_2); MS, *m/z* 428 (M+H, 33), 382 (M–EtO, (22), 366 (M–EtO–O, 25), 322 (M–2EtO–O+H, 41), 276 (crown–CH_2, 100), 220 (95), 208 (95); $(M+H)^+_{found}$ = 428.2415, $C_{18}H_{39}NO_8P$ requires 428.2413.

3.2. (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLETHYL)-DIPHENYLPHOSPHINE OXIDE (**8**)

Yield: 58%; ^{31}P NMR ($CDCl_3$) δ 32.2;^{13}C NMR, Table I; ^{1}H NMR ($CDCl_3$) δ 2.47–2.56 (m, 2H, C(α)H_2), 2.74 (t, J = 5.5, 4H, C(2)H_2), 2.86–2.95 (m, 2H, C(β)H_2), 3.55 (t, J = 5.5, 4H, C(3)H_2), 3.57–3.67 (m, 16H, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 7.45–7.79 (m, 10H, Ar); MS, *m/z* 492 (M+H, 6), 430 (M–2CH_2O–H, 6), 386 (10), 297 (100), 290 (M–P(O)Ph_2, 72), 201 (P(O)Ph_2, 74); $(M+H)^+_{found}$ = 492.2511, $C_{26}H_{39}NO_6P$ requires 492.2515.

3.3. PROCEDURE FOR THE DETERMINATION OF THE EXTRACTION ABILITY IN THE PRESENCE OF AZACROWN ETHERS **1–8**

Equal volumes (5mL) of a dichloromethane solution of the azacrown ether (**1**–**8**) (c = 0.01 mol L^{-1}) and of the aqueous alkali metal picrate (c = 0.005 mol L^{-1}) were introduced into an Erlenmeyer flask, which was then stoppered and shaken for 40 min at 25 °C. The mixture was then allowed to stand for at least 2 h in order to complete the phase separation. The phases were separated and the picrate concentration in the aqueous phase determined from its absorption at 354 nm. (ϵ = 14600 mol^{-1} cm^{-1}). The extraction ability is given as % of the picrate extracted into the organic phase. In the control experiments carried out in the absence of azacrown ethers no detectable amounts of picrates were extracted into the organic phase. According to our experience, azacrowns **2–8** could only be detected in negligible amounts in the aqueous phase.

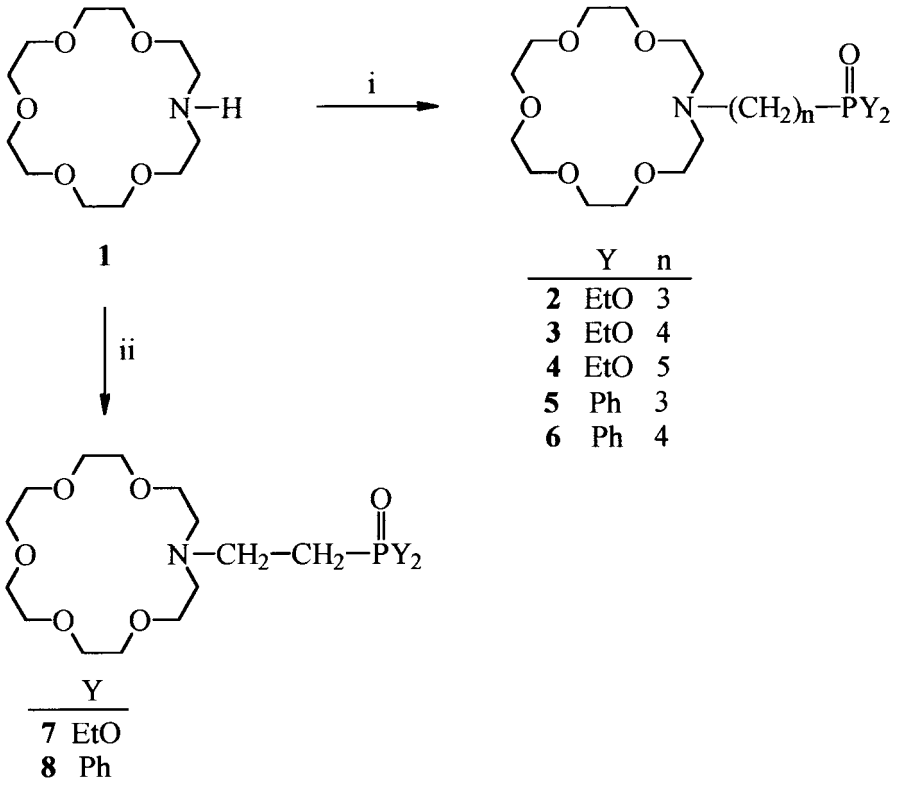
4. Results and Discussion

4.1. SYNTHESIS AND SPECTRAL CHARACTERIZATION OF *N*-PHOSPHONOALKYL- AND *N*-PHOSPHINOYLALKYL-MONOAZA-18-CROWN-6 ETHERS

The monoaza-18-crown-6-based lariat ethers with phosphonyl- or phosphinoyl function were prepared by the N-alkylation of starting material **1**. The azacrown (**1**) was reacted with the bromoalkylphosphonates and bromoalkylphosphine oxides in acetonitrile at 82 °C to give phosphonates **2–4** and phosphine oxides **5** and **6**, respectively in 69–44% yield after purification by column chromatography (Scheme 1). The lariat ethers with an ethylene chain (**7** and **8**) were synthesized by reacting azacrown **1** with diethyl vinylphosphonate and dipenyl-vinylphosphine oxide, respectively (Scheme 1). The structure of the products (**2–8**) was characterised by ^{31}P, ^{13}C and ^{1}H NMR data, as well as MS and HRMS. The ^{13}C NMR spectral parameters listed in Table I, as well as the mass spectroscopic features were similar to those reported for analogous derivatives [8, 9].

4.2. EXTRACTION ABILITY OF THE NEW LARIAT ETHERS (**2–8**)

The complex forming ability of the P-functionalized lariat ethers (**2–8**) was characterized by the extracting ability (EA) of picrate salts (lithium, sodium, potassium and ammonium picrate) from water into dichloromethane by the method of Kimura *et al.* [11]. The use of the EA values has been widely accepted as the indicator of the cation binding ability, since Pedersen introduced this approach [12]. Concentrations of the picrates in water were determined by UV spectroscopy. The experimental data are shown in Table II. The unsubstituted azacrown **1** used as reference compound has a rather good extracting ability with all cations, but it is hardly able to discriminate between them (EA = 86–93%). In the case of the N-substituted compounds, the EA values are either similar to or lower than the values obtained using **1**. Crown ethers **3** and **6**, having four methylene units between the nitrogen atom and the phosphorus function, as well as compound **5** with three methylene units revealed unchanged EA values (84–97%) within the error limit. These compounds did not display any selectivity towards the cations examined. In the case of azacrowns **7** and **8** with a short connecting chain (n = 2), the presence of the N-substituents brought about a remarkable decrease in the extracting properties. At the same time, a significant discrimination could be observed between certain cations: e.g. **7** transports 35% of lithium picrate, while 82% each of potassium or ammonium picrate; **8** extracts 42% of lithium picrate, but 94% of the potassium salt. Thus, the azacrowns with a shorter side arm discriminated between the cations to a higher extent than the compounds with longer side arms. Figure 1 revealing the situation for compounds **2–8** shows how the lone pair of the P=O function may assist in binding a metal cation. The complex effect of the N-substituents is presumably due to steric and electronic reasons. The presence of the N-phosphonoalkyl



Scheme 1. Reagents and conditions: (i) $Br(CH_2)_nP(O)Y_2$, K_2CO_3, acetonitrile, 82 °C; (ii) $CH_2{=}CHP(O)Y_2$, CH_3COOH (catalyst), methyl alcohol, 64 °C.

and N-phosphinoylalkyl substituents in the azacrown results in an increase in the electron density on the nitrogen atom due to the electronreleasing effect of the substituents under discussion. The phosphorus-containing side arm can influence the cation binding ability to a greater extent, when it is nearer to the parent crown ring.

Among the phosphonoalkyl-azacrown ethers (**2–4**, **7**), compound **3** with a four carbon atom connecting chain formed the most stable complexes with all cations examined (84–94%). The EA values for the alkali cations seem to be larger for the azacrowns with a phosphine oxide function (**5**, **6**, **8**) than for those with the phosphinic moiety (**2–4**, **7**). All of the new macrocycles formed the strongest complexes with K^+ and NH_4^+ cation under our circumstances. The sequence for the cation binding ability was generally $K^+ \sim NH_4^+ > Na^+ > Li^+$. The trends discussed above seem to be comparable with those observed by us for the monoaza-15-crown-5 with similar N-substituents [8,9]. In these cases, the substituents had, however, a more significant influence on the EA values. This may be due to the better complexing ability of the azacrown with the 18-membered ring (**1**), incorporating the cations under discussion to a higher extent, as compared to that of the monoaza-15-crown-

Table II. Data for the extraction of alkali metal and ammonium picrates by crown ethers **1–8**[a]

$CH_2CH_2(OCH_2CH_2)_5N–(CH_2)_n–P(O)Y_2$

Compound	Y	n	Extractability (%)[b]			
			Li^+	Na^+	K^+	NH_4^+
1	H		86	88	93	93
7	EtO	2	35	66	82	82
2	EtO	3	69	74	89	91
3	EtO	4	84	85	94	94
4	EtO	5	76	78	87	95
8	Ph	2	42	75	94	85
5	Ph	3	88	91	95	90
6	Ph	4	86	89	97	92

[a] Temperature 25 °C; aqueous phase (5 mL); [picrate] = 5×10^{-3} M; organic phase (CH_2Cl_2, 5 mL); [crown ether] = 1×10^{-2} M.
[b] Defined as % picrate extracted into the organic phase. Determined by UV spectroscopy. Error limit: 5%.

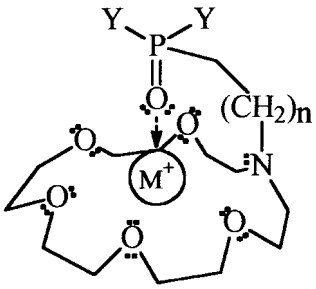


Figure 1. The effect of the P-functionalized side arm on the cation binding ability of the azacrown ring.

5. (The EA values for the cations examined are 86–93% and 56–67%, respectively.) Consequently, the introduction of the side arm is less efficient in the case of the macrocycle with a larger ring size.

In the next part of our work, we shall focus on the synthesis and study of lariat ethers with other P-functions, such as phosphine, thiophosphine and the iminophosphine functional groups.

Acknowledgements

We are grateful for the OTKA-support (T 029253). T. N. thanks the grant from the József Varga Foundation.

References

1. G. W. Gokel: *Chem. Soc. Rev.* **21**, 39 (1992) and references cited therein.
2. (a) H. Tsukube, T. Inoue and K. Hori: *J. Org. Chem.* **59**, 8047 (1994).
   (b) T. Nabeshima, N. Tsukada, K. Nishijima, H. Ohshiro and Y. Yano: *J. Org. Chem.* **61**, 4342 (1996).
   (c) W. Walkowiak, W. A. Charewicz, S. I. Kang, I-W. Yang, M. J. Pugia and R. A Bartsch: *Anal. Chem.* **62**, 2018 (1990).
3. Y. Nakatsuji, T. Nakamura, M. Yonetani, H. Yuya and M. Okahara: *J. Am. Chem. Soc.* **110**, 531 (1988).
4. M. Tazaki, K. Nita, M. Takagi and K. Ueno: *Chem. Lett.* 571 (1982).
5. B. Zhang and A. Clearfield: *J. Am. Chem. Soc.* **119**, 2751 (1997).
6. L. Burai, S. Jakab, R. Király, I. Lázár, I. Tóth and E. Bruecher: *J. Chem. Soc. Dalton Trans.* 1113 (1996).
7. A. Carroy, C. R. Langick, J-M. Lehn, K. E. Matthes and D. Parker: *Helv. Chim. Acta* **69**, 580 (1986).
8. Gy. Keglevich, T. Novák, P. Bakó, K. Újszászy, K. Ludányi, K. Tóth and L. Tõke: *J. Incl. Phenom.* **34**, 299 (1999).
9. Gy. Keglevich, T. Novák, T. Imre, P. Bakó, L. Tõke, K. Újszászy and K. Ludányi: *Heteroatom Chem.* **10**, 573 (1999).
10. R. A. Schultz, B. D. White, D. M. Dishong, K. A. Arnold and G. W. Gokel: *J. Am. Chem. Soc.* **107**, 6659 (1985).
11. K. Kimura, T. Maeda and T. Shono: *Talanta* **26**, 945 (1979).
12. C. J. Pedersen: *J. Am. Chem. Soc.* **92**, 386 (1970).