High-Pressure Functionalization of Diaza-Crown Ethers: New Synthesis of Ag^+ Ion-Specific Binders

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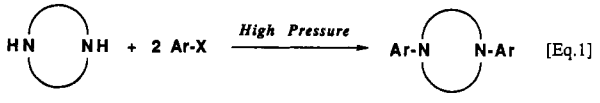
High-pressure S_NAr reaction was first applied to the synthesis of a new crown ether family, which incorporated various heteroaromatics as potential cation binding sites in a unique fashion. In a CH_2Cl_2 liquid membrane transport experiment, several diaza-crown ethers having thiazole, oxazole, pyrazine, and pyridazine rings exhibited a perfect Ag^+ ion selectivity. Cation extraction and ^{13}C NMR titration experiments revealed that attachment of a unique heterocycle to the diaza-crown ring, if in the proper position, significantly offered excellent Ag^+ ion specificity. Since the binding and transport selectivities of these crown ethers were apparently higher than those with conventional crown ethers, the high-pressure technique provided a useful method for synthesis of a new specific crown ether family.

Introduction

Crown ether compounds incorporating heterodonor groups exhibit interesting guest selectivities in cation binding and transport processes which differ greatly from those with conventional crown ethers.[1] For example, nitrogen-heteroaromatics such as pyridine and pyridazine rings have been attached to crown ring in several fashions, and enhanced binding ability toward soft-metal and organic guest cations has been observed.[2] Although many kinds of functionalized crown ethers have been prepared along this line, their syntheses have mostly included common organic reactions and laborious techniques.[3] Thus, there is a need for a new and straightforward method to prepare a variety of functionalized crown ethers.

Here, we report the successful application of the high-pressure technique for the functionalization of diaza-crown ethers with heteroaromatics.[4] Although, high-pressure technique has recently been recognized as a facile and useful methodology in various synthetic reactions,[5,6] few examples have been reported in the synthesis and derivation of crown-type molecules.[7] Under high pressure (0.8 GPa), S_NAr reaction of unsubstituted diaza-crown ethers with haloheteroaromatics gave a new series of functionalized diaza-crown ethers in good yields (eq 1). Furthermore, some crown ethers obtained here showed a perfect Ag^+ ion selectivity in binding, extraction, and transport processes, while common crown ethers rarely distinguished Ag^+ ion from K^+, Ba^{2+}, and Pb^{2+} cations. Since high-pressure reaction is of wide applicability, the present results offer a new synthetic approach to the specific crown-type molecules and a new strategy in molecular design of a metal-specific carrier.



[Eq.1]

Results and Discussion

High-Pressure Functionalization of Diaza-Crown Ethers. The high-pressure reaction used to functionalize the diaza-crown ethers is shown in eq 1. We prepared various diaza-crown ether derivatives of which nitrogen atoms were directly connected to cation-ligating thiazole, oxazole, and other heteroaromatics (Chart I). Because such an aminolysis of haloheteroaromatics rarely occurs under conventional conditions, the preparation of functionalized diaza-crown ethers of this type usually requires

Table I. Preparation of Functionalized Diaza-Crown Ethers and Related Piperazines 2-9 at 0.8 GPa and 100 °C

	time (days)	yield (%)	mp (°C)
2a	5	89	65-66
2b	4	51	163-164
2c	4	92	oil
2d	4	94	244-245
3a	4	100	129-130
3b	4	74	91-92
4a	4	95	158-159
4b	4	64	125-126
5a	4	82	75-76
5b	3	86	113-114
5d	4	96	199-200
6a	4	80	103-104
6b	4	81	155-156
7a	5	95	158-160
7b	3	77	165-166
8a	4	83	127-128
8b	4	85	93-95
8d	3	72	213-214
9a	5	92	oil
9b	6	79	62-63
9d	5	100	179-180

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(1) Lindoy, L. F. In *Cation Binding by Macrocycles*; Inoue, Y.; Gokel, G. W. Ed.; Marcel Dekker; New York, 1990; p 599.
(2) (a) Weber, E.; Vögtle, F. *Chem. Ber.* **1976**, *109*, 1803. (b) Nakatsuji, Y.; Bradshaw, J. S.; Tse, P. K.; Arena, G.; Wilson, B. E.; Dalley, N. K.; Izatt, R. M. *J. Chem. Soc., Chem. Commun.* **1985**, 749. (c) Albrecht-Gary, A. M.; Saad, Z.; Dietrich-Buchecker, C. O.; Sauvage, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3205. (d) Alpha, B.; Lehn, J. M.; Mathis, G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 266. (e) Tsukube, H.; Yamashita, K.; Iwachido, T.; Zenki, M. *J. Org. Chem.* **1991**, *56*, 268. (f) Norante, G. M.; Vaira, M. D.; Mani, F.; Mazzi, S.; Stoppioni, P. *J. Chem. Soc., Chem. Commun.* **1990**, 438. (g) van Eerden, J.; Grootenhuis, P. D. J.; Dijkstra, P. J.; van Staveren, C. J.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1986**, *51*, 3918.
(3) Gokel, G. W.; Korzeniowski, S. H. In *Macrocyclic Polyether Syntheses*; Springer-Verlag; Berlin; 1982, p 1.
(4) Preliminary communication: Matsumoto, K.; Minatogawa, H.; Munakata, M.; Tsukube, H. *Tetrahedron Lett.* **1990**, *31*, 3923.
(5) Noble, W. J.; Kelm, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 841. Matsumoto, K.; Acheson, R. M. In *Organic Synthesis at High Pressure*; John-Wiley and Sons; New York; 1991; p 1.
(6) High-pressure S_NAr reaction with secondary amines as nucleophiles has been demonstrated by Ibata and our group: Ibata, T.; Isogai, Y.; Toyoda, J. *Chem. Lett.* **1987**, 1187. Matsumoto, K.; Hashimoto, S.; Otani, S.; Okamoto, K. *Heterocycles* **1988**, *27*, 319.
(7) Pioneer work: Jurczak, J.; Pietraszkiewicz, M. *Top. Curr. Chem.* **1985**, *130*, 183. Jurczak, J.; Ostaszewski, R.; Salanski, P. *J. Chem. Soc., Chem. Commun.* **1989**, 184.

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Table II. Transport Properties of Functionalized Diaza-Crown Ethers and Related Compounds[a]

carrier	transport rate × 10^6 (mol/h)							
	Li^+	Na^+	K^+	Cs^+	Ag^+	Ca^{2+}	Ba^{2+}	Pb^{2+}
2a	<0.3	<0.3	<0.3	<0.3	(7.9)	<0.3	<0.3	<0.3
2b	<0.3	<0.3	<0.3	<0.3	4.9	<0.3	<0.3	<0.3
2c	<0.3	<0.3	<0.3	<0.3	5.1	<0.3	<0.3	<0.3
2d	<0.3	<0.3	<0.3	<0.3	(<0.3)	<0.3	<0.3	<0.3
3a	<0.3	<0.3	<0.3	<0.3	7.9	<0.3	<0.3	<0.3
3b	<0.3	<0.3	<0.3	<0.3	1.7	<0.3	<0.3	<0.3
4a	<0.3	<0.3	<0.3	<0.3	5.8	<0.3	<0.3	<0.3
4b	<0.3	<0.3	<0.3	<0.3	(1.4)	<0.3	<0.3	<0.3
5a	<0.3	<0.3	<0.3	<0.3	(6.4)	<0.3	<0.3	<0.3
5b	<0.3	<0.3	<0.3	<0.3	(1.4)	<0.3	<0.3	<0.3
5d	<0.3	<0.3	<0.3	<0.3	(<0.3)	<0.3	<0.3	<0.3
6a	<0.3	<0.3	<0.3	<0.3	(12.1)	<0.3	<0.3	<0.3
6b	<0.3	<0.3	<0.3	<0.3	2.9	<0.3	<0.3	<0.3
7a	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
7b	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
8a	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
8b	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
8d	<0.3	<0.3	<0.3	<0.3	(1.6)	<0.3	<0.3	<0.3
9a	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
9b	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
9d	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
10a	7.3	6.4	10.3	1.6	<0.3	6.4	(4.0)	1.6
10b	5.0	10.5	7.9	7.3	<0.3	11.5	3.4	3.2
11b	0.3	3.4	8.7	1.5	<0.3	<0.3	7.0	2.0
12	<0.3	0.4	5.9	3.7	8.2	<0.3	<0.3	<0.3

[a] Conditions. Aq. 1: guest perchlorate, 0.50 mmol/H_2O, 5 mL. Membrane: carrier, 0.0372 mmol/CH_2Cl_2, 12 mL. Aq. 2: H_2O, 5 mL. Parentheses mean precipitation.

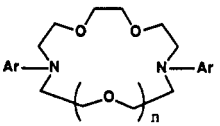
high-dilution conditions and other laborious procedures, and only a few examples have been reported in the literature.[8]

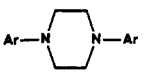
A variety of functionalized diaza-crown ether derivatives were readily prepared from commercially available diaza-crown ethers and corresponding haloheteroaromatics under high pressure. General reaction procedures are as follows: A mixture of diaza-crown (1 mmol), the haloheteroaromatic (4 mmol), and triethylamine (5 mmol) was diluted with THF in a polytetrafluoroethylene capsule (8 mL) which was stored at 0.8 GPa and 100 °C for several days. This high-pressure reaction generally gave 15-, 18-, and 21-membered diaza-crown ethers as well as piperazine derivatives in satisfactory yields. Typical reaction results are summarized in Table I. We conducted this S_NAr reaction under atmospheric pressure for comparison. When a THF solution of diaza-crown **1b**, 2-bromothiazole, and triethylamine was kept at 100 °C for 4 days in a sealed tube, less than 2% yield of **2b** was obtained. High-pressure conditions apparently enhanced this type of crown ether functionalization.

Our developed diaza-crown ethers have unique donor combination and ligand topology and are expected to offer an uncommon cation binding property especially for soft-metal cations. Since we observed Ag^+ ion-specific binding, extraction, and transport properties of new functionalized crown ethers, our high-pressure reaction allowed the facile and effective functionalization of diaza-crown rings.

Cation Transport across a Liquid Membrane. Using new diaza-crown ethers as cation carriers, single cation transport experiments were performed in a CH_2Cl_2 liquid membrane system.[9] Table II summarizes the transport properties of diaza-crown ethers having heteroaromatics, comparing them with those of corresponding piperazine derivatives. Surprisingly, diaza-crown ethers having

Chart I





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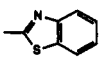
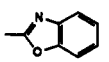
—H	1a	1b	1c	1d
	2a	2b	2c	2d
	3a	3b	—	—
	4a	4b	—	—
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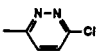
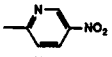
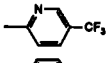
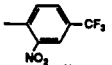
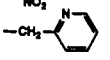
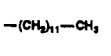
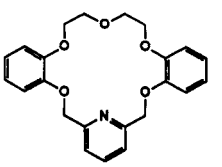
	6a	6b	—	—
	7a	7b	—	—
	8a	8b	—	8d
	9a	9b	—	9d
	10a	10b	—	—
	—	11b	—	—



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thiazole, oxazole, pyrazine, and pyridazine substituents, **2a–c**, **3a,b**, **4a,b**, **5a,b**, and **6a,b** showed a perfect transport

(8) Dix, J. P.; Vögtle, F. *Angew. Chem.* **1978**, *90*, 893.
(9) Tsukube, H.; Adachi, H.; Morosawa, S. *J. Chem. Soc., Perkin Trans.* **1989**, 89.

Table III. Cation Extraction Properties of Functionalized Diaza-Crown Ethers[a]

crown	extraction percentage							
	Li^+	Na^+	K^+	Cs^+	Ag^+	Ca^{2+}	Ba^{2+}	Pb^{2+}
2a	3	<3	<3	<3	39[b]	<3	<3	<3
2b	<3	<3	<3	<3	8	<3	<3	<3
2c	<3	<3	<3	<3	36[b]	<3	<3	<3
9b	<3	<3	<3	<3	<3	<3	<3	<3
10b	<3	38	47	<3	45	5	63	51
11b	<3	<3	11	<3	100	<3	7	45

[a] Conditions. Aq.: guest perchlorate, 0.015 mmol/H_2O, 1.5 mL. Org.: crown, 0.015 mmol/CH_2Cl_2, 1.5 mL. [b] A slight turbidity appeared.

selectivity for Ag^+ ion, while pyridine-containing crown ethers **10a-b**[2e,10,11] and **12**[2e,12] and dialkyl diaza-crown ether **11b** did not exhibit such a high guest selectivity.

Diaza-18-crown-6 ethers **2b**, **3b**, **4b**, **5b**, and **6b** bearing thiazole and related heteroaromatics selectively and efficiently transported Ag^+ ion, while they rarely carried Li^+, Na^+, K^+, Cs^+, Ca^{2+}, Ba^{2+}, or Pb^{2+} ions (Table II). In contrast, diaza-crown ethers **7b**, **8b**, and **9b** could not mediate membrane transport of any examined metal cations, though they had a diaza-18-crown-6 ring and aromatic moieties. The nature of the heteroaromatic introduced had a remarkable influence on the cation transport function of the diaza-18-crown-6 derivatives. Crown ethers **10b** and **12** with a pyridine ring acted as excellent carriers of various metal cations and effectively transported K^+, Ag^+, Ba^{2+}, and Pb^{2+} ions of similar sizes. Dialkyl diaza-18-crown-6 **11b** also exhibited high carrier activity, but its guest selectivity was much lower than those of the present type of crown ethers. Piperazine derivatives **2d**, **5d**, and **9d** were confirmed as being ineffective carriers of the examined metal cations. Thus, the combination of the macroring structure and the heteroaromatic substituent should be carefully chosen when designing a specific carrier of this type.

Table II also indicates that diaza-15-crown-5 and diaza-21-crown-7 derivatives having thiazole, oxazole, pyrazine, and pyridazine rings also transported Ag^+ ion selectively and efficiently. Diaza-15-crown-5 derivatives **2a**, **3a**, **4a**, **5a**, and **6a** exhibited high transport rates of Ag^+ ion, while 21-membered crown **2c** offered relatively slow but selective transport of Ag^+ ion. Other diaza-15-crown-5 derivatives **7a**, **8a**, and **9a** rarely transported any metal cation as observed in corresponding diaza-18-crown-6 systems. This suggests that the coordination character of the heteroaromatic introduced is a more important factor in providing a high Ag^+ ion selectivity than size of the parent crown ring.

Competitive cation transport experiments were carried out by using a mixture of $KClO_4$, $AgClO_4$, and $Pb(ClO_4)_2$ (0.1 mol/L, each) as the Aq. I phase. When thiazole-functionalized diaza-crown ether **2c** was employed as a carrier, Ag^+ ion was specifically and efficiently transported: transport rates were determined as 9.6×10^{-6} mol/h for Ag^+ and $<0.3 \times 10^{-6}$ mol/h for K^+ and Pb^{2+}. Its transport rate for Ag^+ ion was probably enhanced in the presence of excess ClO_4^- ion. On the other hand, the transport properties of diaza-crown ethers **10b** and **11b** were quite different when three kinds of cations were present. Their transport rates were greatly decreased: crown ether **10b** system, $<0.3 \times 10^{-6}$ mol/h for Ag^+ and K^+ and 0.9×10^{-6} mol/h for Pb^{2+}; crown ether **11b** system, $<0.3 \times 10^{-6}$ mol/h for Ag^+, K^+, and Pb^{2+}. Thus, our functionalized diaza-crown ether can be applied as an useful carrier in competitive transport system.

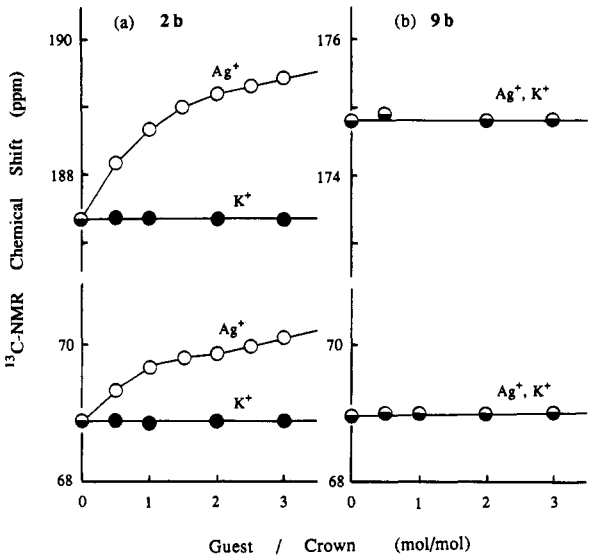


Figure 1. Ag^+- and K^+-induced changes in ^{13}C NMR chemical shifts of crown ethers **2b** and **9b**; carbons as indicated by a and b in Table IV.

Cation Extraction Profile. In order to examine the cation binding property of functionalized diaza-crown ethers, we performed liquid–liquid extraction experiments using a series of alkali, alkaline-earth, and heavy-metal cations. The extraction ability was estimated on the basis of partition of the metal perchlorate between methylene chloride and aqueous solution. Typical extraction results are summarized in Table III.

Table III indicates that thiazole-functionalized diaza-crown ethers of various ring sizes (**2a–c**) predominantly extracted Ag^+ ion among the metal cations examined. Their cation extraction trends are exactly parallel to those of the transport experiments. They specifically bound Ag^+ ion and efficiently transported it across a liquid membrane. Diaza-18-crown-6 ring is known to accommodate a Ag^+ ion more comfortably than diaza-21-crown-7 and diaza-15-crown-5 rings,[13] but the present extraction experiments revealed that no "ion-cavity selectivity" was apparent in our crown ether system and strongly suggested that the heteroaromatic ring introduced was significantly involved in Ag^+ ion-specific binding. Diaza-crown ether having a simple aromatic substituent **9b** was examined for comparison, but this extracted few examined metal cations. Since 2-nitro-4-(trifluoromethyl)benzene ring has no binding site for any metal cations, this electron-withdrawing group seemed to decrease the electron density of nitrogen atoms of diaza-crown ring and then to reduce

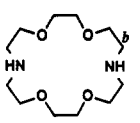
(10) Tsukube, H.; Yamashita, K.; Iwachido, T.; Zenki, M. *Tetrahedron Lett.* **1988**, *29*, 569.
(11) Tsukube, H.; Yamashita, K.; Iwachido, T.; Zenki, M. *Tetrahedron Lett.* **1989**, *30*, 3983; *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1661.
(12) Vögtle, F.; Muller, W. M.; Weber, F. *Chem. Ber.* **1980**, *113*, 1130.
(13) log *K* values of Ag^+ complexes with diaza-15-crown-5 **1a** and diaza-18-crown-6 **1b** have been estimated in water as 5.85 and 7.8. See: Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, *85*, 271.

cation binding ability.[14] Diaza-18-crown-6 ethers **10b** and **11b** effectively extracted several metal cations such as Na^+, K^+, Ba^{2+}, and Pb^{2+} cations as well as Ag^+ ion. Thus, they were confirmed as strong but nonselective carriers. Direct attachment of thiazole moiety to the diaza-crown ring somewhat decreased extraction efficiency for Ag^+ ion but remarkably enhanced extraction selectivity. These observations indicate that the unique molecular structure of our functionalized diaza-crown ether offers a unique and high Ag^+ ion specificity.

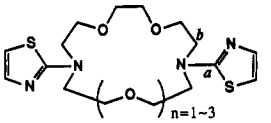
^{13}C NMR Binding Studies. Further detailed information on the cation binding behavior of new diaza-crown ethers was obtained via ^{13}C NMR spectroscopy in DMF/D_2O (4/1) solution. Figure 1 illustrates the K^+- and Ag^+-induced changes in the ^{13}C NMR chemical shifts of selected carbon signals of diaza-crown ethers **2b** and **9b**. The addition of $AgClO_4$ salt to a solution of thiazole-functionalized diaza-crown ether **2b** caused significant and continuous spectral changes, while $KClO_4$ salt offered no spectral change. This indicates that the diaza-crown ether **2b** remarkably discriminates Ag^+ ion from K^+ ion even in a homogeneous solution, though the two are of similar ion sizes. The significant shifts were observed in the signals for carbons of crown ring ($-NCH_2-$) and thiazole ring ($-C{=}N-$) upon complexation. Thus, the nitrogen atoms of crown ring and thiazole substituent were believed to provide the major coordination for Ag^+ ion. Recently we successfully isolated binuclear Ag^+ complex with crown ether **2b**, in which two Ag^+ ions were basically coordinated by two nitrogen atoms of thiazole and crown ring.[15] But the titration curves for the diaza-crown ether **2b**–Ag^+ system offered no direct evidence of binuclear complexation in DMF/D_2O solution. Because 1:2 complex (**2b**:$AgClO_4$) was insoluble in water or CH_2Cl_2, 1:1 complex formation was assumed in the liquid–liquid extraction and liquid membrane transport experiments. Figure 1 indicates that $AgClO_4$ salt induces no spectral change in the diaza-crown ether **9b**, demonstrating the significance of cooperative binding of the diaza-crown ring with the thiazole side arm in the case of the diaza-crown ether **2b**. Since $KClO_4$ salt also offered no spectral change, diaza-crown **9b** was confirmed as an ineffective ligand for these metal cations.

Table IV summarizes the results of ^{13}C NMR binding studies for 15-, 18-, and 21-membered thiazole-functionalized crown ethers **2a–c** and related crowns **1b**, **9b**, and **10b**. The binding selectivity of these diaza-18-crown-6 derivatives was remarkably dependent on the nature of the introduced side arm. Characteristic Ag^+ ion-induced spectral changes were observed in the thiazole-functionalized crown ethers of various ring sizes. This supports that they specifically wrap Ag^+ ion via cooperative binding of two kinds of nitrogen atoms, while they little accomodate alkali and alkaline-earth metal cations of similar ion sizes. Since no spectral change occurred in the crown ether **9b** system, the thiazole moiety was confirmed to play a major role in Ag^+ ion-specific binding. Pyridine-armed diaza-crown ether **10b** and the parent diaza-18-crown-6 **1b** also formed complexes with various metal cations, and their guest specificity was very low. Our developed diaza-crown ethers have more rigid structures than pyridine-armed crown ether **10b**, though both crown ethers incorporate characteristic heteroaromatics as the binding sites. Their rigid junction of the diaza-crown ring with heteroaromatics may organize the ligand topology specific for Ag^+ ion binding.

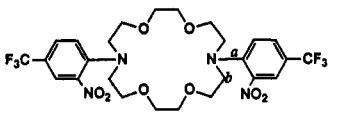
Table IV. Guest-Induced Changes in ^{13}C NMR Chemical Shifts of Functionalized Diaza-Crown Ethers[a]



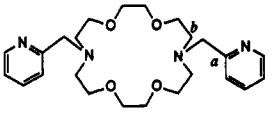
1b



2a - 2c



9b



10b

crown	carbon	induced chemical shift (ppm) K^+	Ag^+	Ba^{2+}	Pb^{2+}
1b	b	0.2	2.2	0.2	−0.4
2a	a	*	2.5	*	*
	b[b]	*	1.5	*	*
2b	a	*	1.3	*	*
	b	*	0.7	*	*
2c	a	*	0.7	*	*
	b	*	0.9	*	*
9b	a	*	*	*	*
	b	*	*	*	*
10b	a	−0.9	−1.7	−1.3	−0.1
	b	0.7	3.6	−0.4	3.7

[a] Conditions. Crown, 0.025 mmol; guest perchlorate, 0.025 mmol in DMF–D_2O (4:1), 0.5 mL. Positive is downfield shift. * $<\pm 0.1$ ppm. [b] The averaged values of two carbon signals were indicated.

We have demonstrated the applicability of the high-pressure technique in the functionalization of crown ether compounds, and the Ag^+ ion-specific binding and transport ability of new functionalized diaza-crown ethers. Their remarkably high Ag^+ ion specificity was based on cooperativity of the crown ring and heteroaromatic substituent. Their unique coordination structures provided selective cation binding and efficient membrane transport properties. Further applications of the high-pressure technique may offer new host molecules having unique structures and excellent functions.

Experimental Section

Solvents and commercially available materials including crown ethers **11b** and **12** and unsubstituted diaza-crown ethers **1a–c** were used without additional purification. Pyridine-armed diaza-18-crown-6 ethers **10a,b** were synthesized by methods described in the literature.[2e] All new compounds had correct elemental compositions determined by microanalysis and high-resolution mass spectroscopy.

Functionalization of Diaza-Crown Ethers. General Procedure. A mixture of the amine (**1a**, 1.37 mmol; **1b**, 1.14 mmol; **1c**, 1.6 mmol; **1d**, 3 mmol), the heteroaromatic chloride[16] (5.48, 4.5, 4.8, and 7 mmol), and triethylamine (10.7, 8.8, 10, and 14 mmol) was diluted with tetrahydrofuran (THF) in a polytetrafluoroethylene tube (8 or 10 mL), which was compressed to 0.8 GPa (8 kbar) and heated to 100 °C for the stated days (Table I). The high-pressure instrument employed has been described before.[5] After cooling and depressurization, triethylamine and THF were removed in vacuo. Benzene (ca. 50 mL) was added, and the quaternary salt was removed by filtration; the filtrate was then subjected to chromatography on silica gel (Wakogel C-200 or C-100), using hexane, hexane/benzene, and benzene/ethyl acetate as eluent in a gradient fashion. Reaction time,

(14) Gustwski, D. A.; Gatto, V. J.; Mallen, J.; Echegoyen, L.; Gokel, G. W. *J. Org. Chem.* **1987**, *52*, 5172.

(15) The structure of **2b**-$(AgOSO_2CF_3)_2$ was determined by X-ray analysis. The details will be reported elsewhere soon.

(16) Bromide was used only in the syntheses of crown ethers **2a–c**.

isolated yield, and melting point of the product are summarized in Table I. Selected spectroscopic data for new compounds are as follows.

7,13-Bis(2′-thiazolyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (2a): ^{1}H NMR ($CDCl_3$) δ 3.59 (s, 4 H), 3.55–3.85 (m, 16 H), 6.38 (d, 2 H, J = 3.5 Hz), 7.04 (d, 2 H, J = 3.5 Hz); ^{13}C NMR ($CDCl_3$) δ 52.9, 53.1, 68.5, 70.1, 70.7, 105.9, 139.3, 171.0. Anal. Calcd for $C_{16}H_{24}N_4O_3S_2$: C, 49.98; H, 6.29; N, 14.57. Found: C, 50.06; H, 6.51; N, 14.57.

7,13-Bis(2′-benzothiazolyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (3a): ^{1}H NMR ($CDCl_3$) δ 3.49 (s, 4 H), 3.55–3.89 (m, 16 H), 6.77–7.51 (m, 8 H), 6.90 (dt, 2 H, J = 1.5, 7.5 Hz), 7.14 (dt, 2 H, J = 1.5, 7.5 Hz), 7.32–7.50 (br d, 4 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 52.7, 52.9, 68.7, 70.0, 70.7, 118.8, 120.4, 120.9, 125.7, 130.7, 152.9, 168.0. Anal. Calcd for $C_{24}H_{28}N_4O_3S_2$: C, 59.48; H, 5.82; N, 11.56. Found: C, 59.42; H, 5.88; N, 11.43.

7,13-Bis(2′-benzoxazolyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (4a): ^{1}H NMR ($CDCl_3$) δ 3.60 (br s, 4 h), 3.79 (m, 16 H), 6.75–7.32 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 49.8, 50.5, 69.2, 70.6, 70.9, 108.7, 116.0, 120.3, 123.9, 143.3, 148.9, 162.4. Anal. Calcd for $C_{24}H_{28}N_4O_5$: C, 63.70; H, 6.24; N, 12.38. Found: C, 63.84; H, 6.23; N, 12.44.

7,13-Bis(2′-pyrazinyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (5a): ^{1}H NMR ($CDCl_3$) δ 3.56 (s, 4 H), 3.45–3.85 (m, 16 H), 7.65 (d, 2 H, J = 3.0 Hz), 7.87 (dd, 2 H, J = 1.7, 3.0 Hz), 8.04 (d, 2 H, J = 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 49.5 (overlapped), 68.7, 69.7, 70.4, 130.3, 131.2, 140.7, 153.7. Anal. Calcd for $C_{18}H_{26}N_6O_3$: C, 57.74; H, 7.00; N, 22.44. Found: C, 57.44; H, 6.90; N, 22.48.

7,13-Bis(3′-chloro-6′-pyridazinyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (6a): ^{1}H NMR ($CDCl_3$) δ 3.50–3.85 (m, 20 H), 6.85 and 6.99 (AB q, 4 H, J = 9.1 Hz); ^{13}C NMR ($CDCl_3$) δ 51.2, 51.4, 69.3, 69.7, 70.5, 115.4, 128.2, 146.0, 158.3. Anal. Calcd for $C_{18}H_{24}N_6O_3Cl_2$: C, 48.77; H, 5.46; N, 18.96. Found: C, 48.49; H, 5.33; N, 18.87.

7,13-Bis(3′-nitro-6′-pyridyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (7a): ^{1}H NMR ($CDCl_3$) δ 3.59 (br s, 4 H), 3.60–3.90 (m, 16 H), 6.60 (d, 2 H, J = 9.4 Hz), 8.09 (dd, 2 H, J = 9.4, 2.9 Hz), 8.95 (d, 2 H, J = 2.9 Hz); ^{13}C NMR ($CDCl_3$) δ 51.4, 51.4, 69.2, 70.0, 70.9, 105.4, 132.5, 135.2, 146.1, 160.7; HRMS m/e calcd for $C_{20}H_{26}N_6O_7$ 462.1862, found 462.1858.

7,13-Bis(3′-(trifluoromethyl)-6′-pyridyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (8a): ^{1}H NMR ($CDCl_3$) δ 3.54 (s, 4 H), 3.57–3.92 (m, 16 H), 6.55 (d, 2 H, J = 9.0 Hz), 7.42 (dd, 2 H, J = 2.6, 9.0 Hz), 8.24 (br d, 2 H, J = 2.6 Hz); ^{13}C NMR ($CDCl_3$) δ 50.5, 50.6, 69.1, 70.1, 70.7, 105.6, 114.3 (J_{CF} = 33 Hz), 124.8 (J_{CF} = 270 Hz), 134.0, 145.3, 159.8. Anal. Calcd for $C_{22}H_{26}N_4O_3F_6$: C, 51.97; H, 5.15; N, 11.02. Found: C, 52.42; H, 5.16; N, 10.95.

7,13-Bis(1′-nitro-3′-(trifluoromethyl)-6′-phenyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (9a): ^{1}H NMR ($CDCl_3$) δ 3.37–3.66 (m, 20 H), 7.31 (d, 2 H, J = 9.2 Hz), 7.54 (dd, 2 H, J = 2.2, 9.2 Hz), 7.89 (br d, 2 H, J = 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 52.7, 53.4, 68.9, 69.5, 70.8, 120.7 (J_{CF} = 34 Hz), 122.0, 123.5 (J_{CF} = 271 Hz), 123.9, 129.3, 140.1, 146.6; HRMS m/e calcd for $C_{24}H_{26}N_4O_7F_6$ 596.1705, found 596.1609.

7,16-Bis(2′-thiazolyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (2b): ^{1}H NMR ($CDCl_3$) δ 3.73 (br s, 16 H), 3.59 (s, 8 H), 6.35 and 7.04 (AB q, 4 H, J = 3.5 Hz); ^{13}C NMR ($CDCl_3$) δ 52.4, 69.1, 70.8, 105.8, 139.5, 170.8. Anal. Calcd for $C_{18}H_{28}N_4O_4S_2$: C, 50.45; H, 6.59; N, 13.07. Found: C, 49.97; H, 6.59; N, 12.56.

7,16-Bis(2′-benzothiazolyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (3b): ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 8 H), 3.78 (br s, 16 H), 6.80–7.04 (dd, 2 H, J = 1.5, 7.2 Hz), 7.05–7.27 (dd, 2 H, J = 7.0, 1.4 Hz), 7.35–7.54 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 52.0, 69.2, 70.7, 118.8, 120.4, 120.8, 125.7, 130.7, 153.1, 167.6. Anal. Calcd for $C_{26}H_{32}N_4O_4S_2$: C, 59.07; H, 6.10; N, 10.60. Found: C, 59.36; H, 6.17; N, 10.58.

7,16-Bis(2′-benzoxazolyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (4b): ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 8 H), 3.79 (br s, 16 H), 6.77–7.33 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 49.6, 69.7, 70.7, 108.5, 116.0, 120.1, 123.8, 143.4, 148.9, 162.3. Anal. Calcd for $C_{26}H_{32}N_4O_6$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.01; H, 6.58; N, 11.21.

7,16-Bis(2′-pyrazinyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (5b): ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 8 H), 3.74 (m, 16 H), 7.69 and 7.90 (AB q, 4 H, J = 2.5 Hz), 7.97 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 49.2, 69.4, 70.9, 130.0, 131.6, 141.5, 153.9. Anal. Calcd for $C_{20}H_{30}N_6O_4$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.40; H, 7.20; N, 19.97.

7,16-Bis(3′-chloro-6′-pyridazinyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (6b): ^{1}H NMR ($CDCl_3$) δ 3.60–3.86 (m, 16 H), 3.60 (s, 8 H), 6.81 and 7.09 (AB q, 4 H, J = 9.5 Hz); ^{13}C NMR ($CDCl_3$) δ 50.3, 69.4, 71.0, 114.6, 128.4, 145.9, 158.1. Anal. Calcd for $C_{20}H_{28}N_6O_4Cl_2$: C, 49.29; H, 5.79; N, 17.24. Found: C, 49.50; H, 5.79; N, 17.04.

7,16-Bis(3′-nitro-6′-pyridyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (7b): ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 8 H), 3.65–4.00 (m, 16 H), 6.48 (d, 2 H, J = 9.4 Hz), 8.09 (dd, 2 H, J = 3.0, 9.4 Hz), 8.92 (d, 2 H, J = 3.0 Hz); ^{13}C NMR ($CDCl_3$) δ 50.4, 69.3, 71.0, 104.6, 132.7, 135.2, 146.3, 160.2. Anal. Calcd for $C_{22}H_{30}N_6O_8$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.28; H, 5.88; N, 16.21.

7,16-Bis(3′-(trifluoromethyl)-6′-pyridyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (8b): ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 8 H), 3.67–3.93 (m, 16 H), 6.50 (d, 2 H, J = 8.9 Hz), 7.50 (dd, 2 H, J = 2.4, 8.9 Hz), 8.28 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 49.7, 69.4, 70.9, 104.9, 114.2 (J_{CF} = 33 Hz), 124.9 (J_{CF} = 270 Hz), 134.0 (J_{CF} = 3 Hz), 145.7 (J_{CF} = 4 Hz), 159.5. Anal. Calcd for $C_{24}H_{30}N_4O_4F_6$: C, 52.17; H, 5.47; N, 10.14. Found: C, 52.23; H, 5.48; N, 10.15.

7,16-Bis(1′-nitro-3′-(trifluoromethyl)-6′-phenyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (9b): ^{1}H NMR ($CDCl_3$) δ 3.36 and 3.83 (m, 24 H), 7.29 and 7.53 (AB q, 4 H, J = 9.3 Hz), 7.85 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 52.6, 69.2, 70.8, 120.9 (J_{CF} = 34 Hz), 123.4 (J_{CF} = 271 Hz), 123.8 (J_{CF} = 4 Hz), 128.2, 129.2 (J_{CF} = 4 Hz), 140.6, 147.0. Anal. Calcd for $C_{26}H_{30}N_4O_8F_6$: C, 48.75; H, 4.72; N, 8.75. Found: C, 49.04; H, 4.60; N, 8.66.

10,19-Bis(2′-thiazolyl)-1,4,7,13,16-pentaoxa-10,19-diazacycloheneicosane (2c): ^{1}H NMR ($CDCl_3$) δ 3.61 (m, 12 H), 3.74 (s, 16 H), 6.43 (d, 2 H, J = 3.5 Hz), 7.11 (d, 2 H, J = 3.5 Hz); ^{13}C NMR ($CDCl_3$) δ 52.2, 52.3, 68.5, 68.7, 70.3, 70.4, 70.6, 105.7, 139.4, 170.4; HRMS m/e calcd for $C_{20}H_{32}N_4O_5S_2$ 472.1813, found 472.1779.

1,4-Bis(2′-thiazolyl)piperazine (2d): ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 8 H), 6.50 (d, 2 H, J = 3.5 Hz), 7.10 (d, 2 H, J = 3.5 Hz); ^{13}C NMR ($CDCl_3$) δ 48.0, 108.0, 139.7, 171.8. Anal. Cacld for $C_{10}H_{12}N_4S_2$: C, 47.60; H, 4.79; N, 22.20. Found: C, 47.70; H, 4.70; N, 22.10.

1,4-Bis(2′-pyrazinyl)piperazine (5d): ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 8 H), 7.76 (d, 2 H, J = 2.6 Hz), 7.95 (dd, 2 H, J = 2.6, 1.6 Hz), 8.04 (d, 2 H, J = 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 44.0, 131.0, 133.5, 141.7, 154.8. Anal. Calcd for $C_{12}H_{14}N_6$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.66; H, 5.83; N, 34.93.

1,4-Bis(3′-(trifluoromethyl)-6′-pyridyl)piperazine (8d): ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 8 H), 6.59 (d, 2 H, J = 8.6 Hz), 7.59 (d, 2 H, J = 8.6 Hz), 8.32 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 44.2, 105.5, 115.8 (J_{CF} = 33 Hz), 124.6 (J_{CF} = 270 Hz), 134.7 (J_{CF} = 4 Hz), 145.9 (J_{CF} = 4 Hz), 160.2. Anal. Calcd for $C_{16}H_{14}N_4F_6$: C, 51.07; H, 3.75; N, 14.89. Found: C, 51.61; H, 3.72; N, 14.94.

1,4-Bis(1′-nitro-3′-(trifluoromethyl)-6′-phenyl)piperazine (9d): ^{1}H NMR ($CDCl_3$) δ 3.32 (s, 8 H), 7.14 (d, 2 H, J = 9.0 Hz), 7.63 (dd, 2 H, J = 2.0, 9.0 Hz), 8.00 (d, 2 H, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 50.8, 121.0, 123.2 (J_{CF} = 272 Hz), 123.6 (J_{CF} = 34 Hz), 124.1 (J_{CF} = 4 Hz), 130.3 (J_{CF} = 4 Hz), 141.6, 147.8; HRMS m/e calcd for $C_{18}H_{14}N_4O_4F_6$ 464.0919, found 464.0974.

Extraction Experiment. Extraction experiments were carried out by adding a methylene chloride solution of diaza-crown ether (0.015 mmol/1.5 mL) to an aqueous solution of metal perchlorate (0.015 mmol/1.5 mL). After the mixture had been stirred for 2 h, the aqueous phase was separated. The concentrations of metal cations were determined by atomic absorption or flame spectroscopic method.

Transport Experiments. Transport experiments were performed at room temperature (ca. 20 °C) in a U-tube glass cell (2.0 cm i.d.).[2e] The carrier, dissolved in methylene chloride, was placed in the base of the U-tube, and two aqueous phases were placed in the tube arms, floating on the organic membrane phase. The membrane phase was constantly stirred with a magnetic stirrer. The transport rates indicated in Table II were calculated from the initial rates of appearance of cotransported ClO_4^- anion into Aq. 2 phase, which was determined by a ClO_4^- ion-selective electrode. The transported amount of each metal cation was also determined by atomic absorption or flame spectroscopic method, and was nearly equal to that of the cotransported anion. We

confirmed that all guest salts were rarely transported in the absence of carrier (transport rate $<0.3 \times 10^{-6}$ mol/h).

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Supplementary Material Available: ^1H and/or ^{13}C NMR spectra for compounds **2c**, **7a**, **9a**, and **9d** (8 pages). Ordering information is given on any current masthead page.

N-[1-(Benzotriazol-1-yl)alkyl]amides, Versatile Amidoalkylation Reagents. 5. A General and Convenient Route to *N*-(α-Alkoxyalkyl)amides[1]

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N-[1-(Benzotriazol-1-yl)alkyl]amides **2**, easily prepared from benzotriazole **1**, an aldehyde, and an amide, react readily with a variety of primary and secondary alcohols under mild conditions to give *N*-(α-alkoxyalkyl)amides **3** in good yield.

N-(α-Alkoxyalkyl)amides are of importance both in natural product chemistry and in industrial synthesis. Pederin, a toxic principle isolated from *Paederus fuscipes* curt, contains an *N*-(α-methoxyalkyl)amide structural feature,[2] and *N*-(α-alkoxyalkyl)amide functionalities also occur in a number of synthetic herbicides.[3] *N*-(α-Alkoxyalkyl)amides are useful synthetic intermediates and have participated in the amidoalkylations of aromatics and of active methylene compounds.[4] They react with enol ethers, isonitriles, and phosphorus compounds to give useful products.[5] *N*-(α-Methoxyalkyl)amides are important starting materials for the preparation of hemithioaminals[6] and *N*-(haloalkyl)amides.[7] α-Methoxylated amides are easily transformed to unsaturated carbamates (enecarbamates) through elimination of methanol.[8]

Several synthetic routes to *N*-(α-alkoxyalkyl)amides **3** are known, but none is both general and convenient. Perhaps the most important method for their preparation is electrochemical:[5,9] anodic oxidation of *N*-alkylamides gave *N*-(α-alkoxyalkyl)amides when carried out in an alcoholic solution;[10] such oxidation in solutions of carboxylic acids gives *N*-(α-acyloxyalkyl)amides.[11] However, the anodic method is inconvenient in many laboratories and most of the results apply to methanol solution and hence to the *N*-(α-methoxyalkyl)amides (**3**: $R^3 = CH_3$).[12-14] Although some *N*-(α-alkoxyalkyl)-, and especially α-methoxylated, amides can be synthesized by conventional chemical methods, the types of α-alkoxylated amides obtainable are severely limited. Nucleophilic additions of alcohols to *N*-benzoylbenzaldimines, prepared by the pyrolysis of benzylidenebisbenzamides, afforded *N*-(α-alkoxybenzyl)benzamides;[15] however, the required *N*-acylimines are unstable;[16] furthermore, the bis-amides can be prepared only from aromatic aldehydes (without α-hydrogen), and finally 2-molar equiv of the amide must be used, so the utility of this route is restricted. Reactions of strongly electron-deficient aldehydes such as chloral or glyoxylic acid with amides form stable carbinol amides, which can be converted to *N*-(α-methoxyalkyl)amides.[6b]

Recently, Lokensgard and co-workers[17] claimed two general routes to *N*-(α-methoxyalkyl)amides from imidates: the first involves N-acylation of the imidate with an acyl chloride followed by reduction with sodium borohydride. In the second, an aldehyde is converted, via its methyl acetal, to an α-chloromethyl ether, which is used to alkylate the imidate, and further treatment with pyridinium chloride in dry DMSO gives the *N*-(α-methoxyalkyl)amide (yield of last step: 20-63%). However, both routes have

(1) For Part 4, see: Katritzky, A. R.; Pernak, J.; Fan, W. Q. *J. Prakt. Chem.*, submitted for publication.
(2) (a) Cardani, C.; Ghiringhelli, D.; Mondelli, R.; Quilico, A. *Tetrahedron Lett.* **1965**, 2537. (b) Matsumoto, T.; Yanagiya, M.; Maeno, S.; Yasuda, S. *Tetrahedron Lett.* **1968**, 6297. (c) Furusaki, A.; Watanabe, T. *Tetrahedron Lett.* **1968**, 6301.
(3) Brian, R. In *Herbicides: Physiology, Biochemistry, Ecology*, 2nd ed.; Audua, L. J., Ed.; Academic Press: New York, 1976; Chapter 1.
(4) (a) Zaugg, H. E. *Synthesis* **1970**, 49. (b) Zaugg, H. E. *Synthesis* **1984**, 85, 181.
(5) Shono, T. *Electroorganic Synthesis*; Academic Press: London, 1991; p 71-74.
(6) (a) Matthies, D.; Bartsch, B.; Richter, H. *Arch. Pharm.* **1981**, *314*, 209. (b) Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863.
(7) Chupp, J. P.; Leschinsky, K. L.; Mischke, D. A. *J. Org. Chem.* **1982**, *47*, 3169.
(8) (a) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264. (b) Nyberg, K. *Synthesis* **1976**, 545. (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y. *Tetrahedron Lett.* **1982**, *23*, 1201.
(9) Shono, T. *Tetrahedron* **1984**, *40*, 811.
(10) Nyberg, K.; Servin, R. *Acta Chem. Scand., Ser. (B)* **1976**, *30*, 640.
(11) Nyberg, K. *Acta Chem. Scand., Ser. (B)* **1974**, *28*, 825.
(12) Ross, S. D.; Finkelstein, M.; Petersen, R. C. *J. Am. Chem. Soc.* **1966**, *88*, 4657.
(13) Rudd, E. J.; Finkelstein, M.; Ross, S. D. *J. Org. Chem.* **1972**, *37*, 1763.
(14) Finkelstein, M.; Ross, S. D. *Tetrahedron* **1972**, *28*, 4497.
(15) Breuer, S. W.; Bernath, T.; Ben-Ishai, D. *Tetrahedron* **1967**, *23*, 2869.
(16) Lasne, M. C.; Ripoll, J. L.; Thuillier, A. *J. Chem. Res., Synop.* **1982**, 214.
(17) Lokensgard, J. P.; Fischer, J. W.; Bartz, W. J.; Meinwald, J. *J. Org. Chem.* **1985**, *50*, 5609.

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