of 3.7 g (90 mmol) of acetonitrile in 85 mL of THF over 45 min. After addition was complete, the mixture was stirred at −70 °C for 1 h, and then a solution of 16.3 g (45 mmol) of NPBDP (3)[1] in 85 mL of THF was added dropwise over 30 min. After the addition was complete, the mixture was stirred at −70 °C for 30 min and then allowed to warm to room temperature. The mixture was quenched with 125 mL of 1 N hydrobromic acid solution. The organic layer was separated, and the aqueous portion was washed with ether (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated, leaving an oil which consisted of *p*-nitrophenol and the product by TLC. The oil was chromatographed over 400 g of silica gel using chloroform/cyclohexane (5:1) as eluent. The product, which was less polar than *p*-nitrophenol, eluted in fractions 35–105 (12-mL portions) and amounted to 10.9 g (92%) of a white solid: mp 66–68 °C; NMR ($CDCl_3$) δ 3.83 (s, 2 H), 3.7–3.2 (m, 6 H), 1.14 (t, 6 H). Anal. Calcd for $C_9H_{14}BrNO_3$: C, 40.93; H, 5.34; N, 5.30. Found: C, 40.95; H, 5.21; N, 5.40.

Ethyl 2,3-Dihydro-3,3-diethoxy-6-methyl-4-pyrone-5-carboxylate (29). A slurry of 1.06 g (22 mmol) of 50% sodium hydride in 50 mL of tetrahydrofuran (dried over molecular sieves) was stirred at room temperature under a nitrogen atmosphere, and to this was added, dropwise over 15 min, a solution of 2.73 g (21 mmol) of ethyl acetoacetate in 10 mL of tetrahydrofuran. After addition was complete, the mixture was stirred at room temperature for 15 min and then a solution of 3.62 g (10 mmol) of NPBDP (3)[1] in 40 mL of tetrahydrofuran was added dropwise over 5 min. The mixture was heated at reflux for 4 h, and the heterogeneous mixture was cooled and then poured into 200 mL of ice water. The pH of the solution was brought to 7 with dilute hydrobromic acid solution, and the mixture was extracted with chloroform (4 × 30 mL). The combined extracts were dried (Na_2SO_4), filtered and evaporated, leaving an oil which consisted of *p*-nitrophenol and product. Separation was effected by chromatography over silica gel (120 g) using isopropyl ether as eluent. *p*-Nitrophenol eluted first. The second material amounted to 1.58 g (58%) of **29** as a colorless oil; bp 126 °C (0.8 torr); NMR ($CDCl_3$) δ 4.33 (s, 2 H), 4.25 (q, 2 H), 3.65 (q, 4 H), 2.23 (s, 3 H), 1.4–1.0 (m, 9 H). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34, H, 7.40. Found: C, 57.12; H, 7.28.

4-Ethoxy-3-(cyanomethyl)pyrazole (30). A mixture of 2.64 g (10 mmol) of 5-bromo-4,4-diethoxy-3-oxovaleronitrile (**28**), 0.51 mL of 99% hydrazine hydrate, and 40 mL of absolute ethanol was heated at reflux for 1 h. Another equivalent of hydrazine hydrate was added at this point, and refluxing was continued for another hour. The mixture was cooled, insolubles were removed by filtration, and the filtrate was concentrated, leaving a viscous oil. This was chromatographed over 70 g of silica gel using 2:1 ethyl acetate/hexane as eluent. The product amounted to 845 mg (56%) of an off-white solid: mp 78–81 °C; NMR (Me_2SO-d_6) δ 7.45 (s, 1 H), 3.90 (q, 2 H), 3.80 (s, 2 H), 1.25 (t, 3 H); IR (KBr) 2449 cm^{-1} (CN). An analytical sample was prepared by recrystallization from 1:1 ethyl acetate/hexane, mp 80–82 °C. Anal. Calcd for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 56.00; H, 5.99; N, 27.64.

***N*-(2-Anilino)-3-bromo-2,2-diethoxypropionamide (31).** A mixture of 7.2 g (20 mmol) of NPBDP (3),[1] 2.4 g (22 mmol) of *o*-phenylenediamine, and 60 mL of dimethylformamide was heated at 150 °C (external) for 3 h. At this point, another 0.5 g (4.6 mmol) of *o*-phenylenediamine was added to the mixture, and heating was continued for another 1.5 h. The mixture was cooled and then concentrated. The residue was dissolved in 75 mL of ethyl acetate, and the organic solution was washed with 5% sodium hydroxide solution (3 × 25 mL). The organic solution was dried (Na_2SO_4), filtered, and evaporated, leaving 6 g of a crude solid. This was purified by chromatography over 130 g of silica gel using 19:1 isopropyl ether/ethyl acetate as eluent to give an off-white solid. Recrystallization from cyclohexane afforded 3.64 g (55%) of **31** as a white crystalline solid: mp 91–92 °C; NMR ($CDCl_3$) δ 8.40 (b, 1 H), 7.3–6.6 (m, 4 H), 4.0–3.4 (m, 8 H), 1.32 (t, 6 H). Anal. Calcd for $C_{13}H_{19}BrN_2O_3$: C, 47.15; H, 5.78; N, 8.46. Found: C, 47.63; H, 5.78; N, 8.07.

2-(2-Bromo-1,1-diethoxy-1-ethyl)benzimidazole (32). A mixture of 3.2 g (9.7 mmol) of *N*-(2-anilino)-3-bromo-2,2-diethoxypropionamide (**31**) and 50 mL of 97% formic acid was warmed to 80 °C and heated at this temperature for 2.5 h. The dark solution was concentrated, and the solid residue was triturated with saturated $NaHCO_3$ and then extracted into ether (4 × 50 mL). The ether extracts were dried (Na_2SO_4), filtered, and evaporated, leaving an oil. Chromatography over 75 g of silica gel using 9:1 ether/ethyl acetate as eluent afforded 2.36 g (78%) of **32** as a tan solid: mp 124–127 °C; NMR ($CDCl_3$) δ 7.6–7.0 (m, 4 H), 3.69 (s, 2 H), 3.61 (q, 4 H), 1.26 (t, 6 H). Anal. Calcd for $C_{13}H_{17}BrN_2O_2$: C, 49.85; H, 5.47; N, 8.94. Found: C, 49.38; H, 5.10; N, 8.51.

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Registry No. **3**, 87224-03-1; **4**, 7476-20-2; **5**, 92845-55-1; **6**, 92845-56-2; **7**, 92845-57-3; **8**, 92845-58-4; **8** (oxime), 92845-71-1; **10**, 87224-04-2; **11**, 87224-05-3; **12**, 87224-09-7; **13**, 87224-10-0; **14**, 92900-60-2; **15**, 87224-11-1; **16**, 87246-24-0; **17**, 92845-59-5; **18**, 92845-60-8; **18** (ketone), 92845-72-2; **19**, 92845-61-9; **20**, 92845-62-0; **21**, 92845-63-1; **22**, 92845-64-2; **23**, 92845-65-3; **24**, 92845-66-4; **25**, 92845-67-5; **25** (ketone), 92845-73-3; **26**, 92845-68-6; **27**, 87246-23-9; **28**, 87224-07-5; **29**, 87224-06-4; **30**, 87224-08-6; **31**, 92845-69-7; **32**, 92845-70-0; $CH_3COCO_2C_2H_5$, 617-35-6; $CH(OC_2H_5)_3$, 122-51-0; $CH_3C(OCH_3)_2N(CH_3)_2$, 18871-66-4; $NH_2OH{\cdot}HCl$, 5470-11-1; $CH_3C(NH_2)=NOH$, 22059-22-9; $H_2NCSN=C(NH_2)_2$, 2114-02-5; Ph_2PS_2H, 1015-38-9; $HC(OC_2H_5)_2N(CH_3)_2$, 1188-33-6; H_2NOSO_3H, 2950-43-8; Cl_3CCO_2H, 76-03-9; $H_2NC(NH_2)=NH{\cdot}HCl$, 50-01-1; H_2NCSNH_2, 62-56-6; $NH_4^+CH_3CO_2^-$, 631-61-8; $CH_2(CO_2CH_3)_2$, 108-59-8; CH_3CN, 75-05-8; $CH_3COCH_2CO_2C_2H_5$, 141-97-9; N_2H_4, 302-01-2; *o*-$H_2NC_6H_4NH_2$, 95-54-5.

Functionalized 13-Crown-4, 14-Crown-4, 15-Crown-4, and 16-Crown-4 Compounds: Synthesis and Lithium Ion Complexation[1]

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Seven novel (benzyloxy)methyl-substituted crown ethers with four ring oxygens and 13-, 14-, 15-, and 16-membered polyether rings are synthesized and their lithium and sodium cation-binding abilities are assessed by solvent extraction of the aqueous alkali metal picrates. Strongest lithium ion complexation is observed with [(benzyloxy)methyl]-14-crown-4 compounds.

The design and synthesis of selective lithium ion complexing agents has recently received considerable attention. Among the crown ethers, benzo-13-crown-4 and dibenzo-14-crown-4 were found to exhibit efficient and selective

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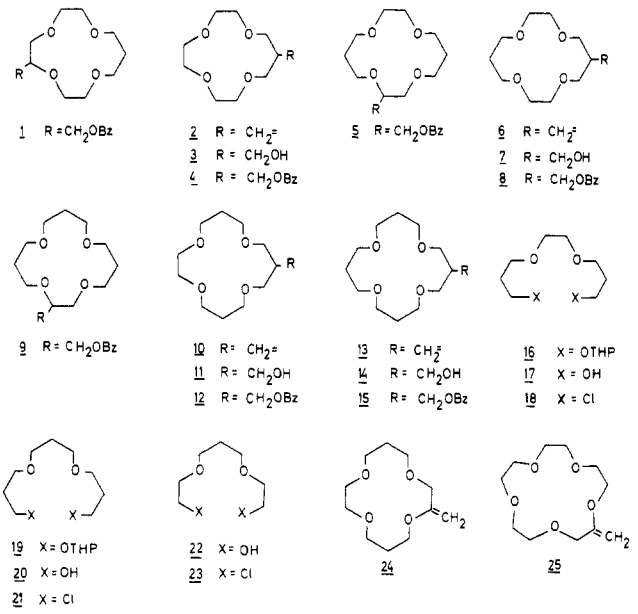
Chart I

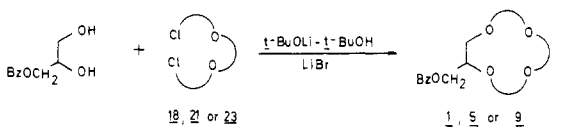


complexation of lithium ions.[2-4] Also, a number of acyclic ionophores have been synthesized and studied for their ability to transport lithium.[5-9] To date the best lithium selectivity has been achieved with lipophilic hexafunctional dioxa diamides.[9]

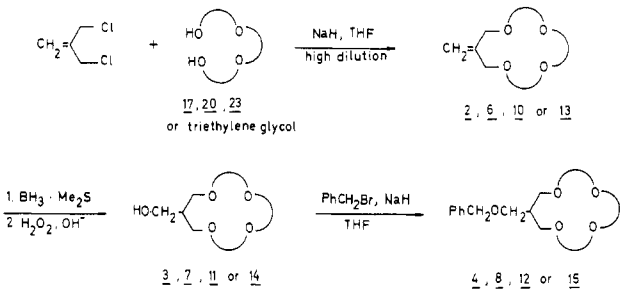
Although [(benzyloxy)methyl]-12-crown-4[10,11] and -15-crown-5[10-13] have been synthesized, lithium complexation by these functionalized, small-ring crowns was not reported. Attainment of lithium selectivity with this type of crown compound would be extremely important since after benzyl-group hydrogenolysis the corresponding hydroxymethyl crown ethers could be readily incorporated into lariat crowns,[14] bis-crowns,[15] ionizable crowns,[16] and polymers with pendant crown units.[17,18]

In this paper, we describe the synthesis of seven new (benzyloxy)methyl-substituted crown ethers **1**, **4**, **5**, **8**, **9**, **12**, and **15**, which have four ring oxygens and ring sizes ranging from 13 to 16 members (Chart I). For the 13-, 14-, and 15-membered crown compounds, two positional isomers which differ in the functional group attachment site are included. Lithium and sodium cation-binding abilities of these seven functionalized crown ethers, as well as [(benzyloxy)methyl]-12-crown-4 and [(benzyloxy)-methyl]-15-crown-5, are assessed by solvent extraction of the aqueous alkali metal picrates.

Scheme I



Scheme II



Results and Discussion

Compounds **1** and **4**, **5** and **8**, and **9** and **12** are pairs of positional isomers in which the (benzyloxy)methyl group is attached to a two or three carbon bridge, respectively. Within the series, the cavity size is systematically varied from that of a 13-crown-4 ring to that for a 16-crown-4 ring.

Synthesis. The 2-(benzyloxy)methyl crown ethers **1**, **5**, and **9** were prepared by Okahara condensation[11] of 3-(benzyloxy)-1,2-propanediol[19,20] with the appropriate dichlorides in a *t*-BuOLi/LiBr/*t*-BuOH reaction mixture (Scheme I). Isolated yields of **1**, **5**, and **9** were 80%, 75%, and 49%, respectively.

The 3-methylene crown compounds **2**, **6**, **10**, and **13** were produced by reactions of the corresponding diols with 3-chloro-2-(chloromethyl)-1-propene under high dilution (Scheme II) using the method reported by Tomoi[21] for the synthesis of 3-methylene-16-crown-5 and 19-crown-6 compounds. Isolated yields of **2**, **6**, **10**, and **13** were 26%, 43%, 58%, and 48%, respectively. These methylene crowns were transformed into the corresponding hydroxymethyl crowns **3**, **7**, **11**, and **14** by treatment with borane–dimethyl sulfide complex followed by oxidative workup. The isolated yields were nearly quantitative except for **14** in which the yield was only 55%. The 3-(benzyloxy)methyl crown ethers **4**, **8**, **12**, and **15** were obtained in yields of 69–90% from the corresponding hydroxymethyl crowns by treatment with sodium hydride and benzyl bromide in THF.

In another project[22] the 2-methylene crown compounds **24** and **25** were isolated as elimination byproducts which accompanied substitution reactions of the corresponding (tosyloxy)methyl crown ethers with phenoxides. Details of these reactions will be provided elsewhere.

Requisite diols **17** and **20** were obtained by reactions of ethylene glycol or 1,3-propanediol with sodium hydride and the monotetrahydropyranyl ether of 3-chloropropanol[23] in DMF. Isolated yields of the ditetrahydropyranyl ethers

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Table I. Extraction Constants (K_{ex}) and Association Constants (K_a) for Cation Complexation by Several Crown Ethers

crown ether: ring size	crown ether: no.	crown ether: attachmt site[a]	K_{ex}[b,c]: Li^+	K_{ex}[b,c]: Na^+	$K_{ex}(Li^+)^b / K_{ex}(Na^+)^b$	K_a for Li^+[d]	K_{ex} for Li^+[c,e]
12C4	**26**	2	<1	9 ± 1			<1
13C4	**1**	2	39 ± 4	8 ± 1	5	27 100	870 ± 20
13C4	**4**	3	9 ± 4	3 ± 1	3	6 300	70 ± 20
14C4	**5**	2	119 ± 2	12 ± 2	10	80 900	1950 ± 30
14C4	**8**	3	200 ± 7	8 ± 4	25	140 000	490 ± 90
15C4	**9**	2	6 ± 1	6 ± 1	1	4 500	23 ± 5
15C4	**12**	3	11 ± 1	7 ± 1	2	7 800	81 ± 20
16C4	**15**	3	<1	<1			<1
15C5	**27**	2	122 ± 16	6760 ± 340	0.02	86 700	ND
benzo-12C4			ND	ND			41[g]
benzo-13C4			ND	ND			1510[g]
dibenzo-14C4			ND	ND			930[g]
benzo-15C5			ND	ND			160 ± 9 (200[g])

[a] 2 = (benzyloxy)methyl group attached to a two-carbon bridge; 3 = (benzyloxy)methyl group attached to the central carbon of a three-carbon bridge. [b] Deuteriochloroform–water system at room temperature (22–23 °C). [c] The crown ether–cation complexes were 1:1 (see Experimental Section). [d] In deuteriochloroform. [e] Tricresyl phosphate and 1,2-dichloroethane–water system at room temperature (22–23 °C). [f] ND = not determined. [g] Data from ref 2.

16 (32%) and **19** (19%) were rather low due to competitive elimination reactions. Acid-catalyzed deprotection of **16** and **19** gave diols **17** and **20** in almost quantitative yields. Standard reactions[24] of **17** and **20** with thionyl chloride produced dichlorides **18** and **21** in 70% and 85% yields, respectively.

The structures of all new compounds were verified by infrared (IR) and proton magnetic resonance (^1H NMR) spectroscopy and by elemental analysis.

Extraction Studies. The lithium and sodium ion-binding abilities of the functionalized crown compounds were assessed by solvent extraction[25,26] of aqueous solutions of lithium and sodium picrates with deuteriochloroform solutions of the crown ethers at room temperature (22–23 °C). Extraction constants, K_{ex}, for lithium and sodium picrates and association constants, K_a, for lithium picrate were evaluated in the customary manner.[25,26] Data for the seven new (benzyloxy)methyl-substituted crown ethers **1**, **4**, **5**, **8**, **9**, **12**, and **15**, as well as [(benzyloxy)methyl]-12-crown-4 (**26**) and [(benzyloxy)methyl]-15-crown-5 (**27**), are presented in Table I.

For the (benzyloxy)methyl-substituted crown-4 compounds, the efficiency of lithium binding is influenced by the number of atoms in the polyether ring and decreases in the order 14-crown-4 > 13-crown-4 ≳ 15-crown-4 with not detectable extraction of lithium picrate by the 12-crown-4 and 16-crown-4 derivatives. In contrast, extraction equilibrium constants for sodium are uniformly low and rather insensitive to the polyether ring size with the exception of the 16-crown-4 compound for which no extraction of sodium picrate was evident. For the three best lithium ion complexing agents **8**, **5**, and **1**, this produces a parallel between K_{ex} for lithium and the Li^+/Na^+ selectivity. The Li^+/Na^+ selectivity achieved with **8** in a deuteriochloroform–water system approaches the ratio of slightly more than 40 which was reported for complexation of lithium and sodium picrates by a lipophilic dioxa diamide in a methylene chloride–water system.[9]

Change of the (benzyloxy)methyl group attachment site from a two-carbon bridge to a three-carbon bridge diminishes lithium ion complexation in the 13-crown-4 couple of **1** and **4** but enhances lithium ion binding for the 14-crown-4 pair (**5** and **8**) and the 15-crown-4 isomers (**9** and **12**).

Comparison of the K_{ex} value for lithium extraction by the most lithium selective crown-4 compound **8** with that for sodium extraction by [(benzyloxy)methyl]-15-crown-5 (**26**) reveals that extraction of lithium ions is relatively inefficient. Presumably this results from the high hydration energy for lithium cations.

Our observation of the high lithium selectivity of functionalized 14-crown-4 compounds in solvent extraction has very recently been confirmed for ion-selective polymeric membrane electrodes by Kimura, Kitazawa, and Shono.[27]

Olsher and Jagur-Grodzinski[2] have studied lithium ion complexation by benzo-12-crown-4, benzo-13-crown-4, and dibenzo-14-crown-4 using extractions of lithium picrate from aqueous media into a 1:1 mixture of 1,2-dichloroethane and tricresyl phosphate. This system produces higher extraction of lithium picrate than does the deuteriochloroform–water system. To allow for comparison with this earlier work, we determined K_{ex} constants for the (benzyloxy)methyl-substituted crown-4 compounds in this system also. Results are recorded in the far right column of Table I.

As was found in the deuteriochloroform–water system, among the (benzyloxy)methyl-substituted crown ethers the best lithium ion extraction is observed with the two 14-crown-4 compounds **5** and **8** and one of the 13-crown-4 derivatives **1**. However, the K_{ex} values decrease in the order **5** > **1** > **8** for the water–(tricresyl phosphate–1,2-dichloroethane) system instead of the order **8** > **5** > **1** which was found for extractions of lithium picrate from water into deuteriochloroform. Reasons for this change in ordering remain uncertain at this time but would seem to involve the presence or absence of tricresyl phosphate. Nevertheless, it is noteworthy that K_{ex} for lithium extraction by the [(benzyloxy)methyl]-14-crown-4 **5** in the water–(tricresyl phosphate–1,2-dichloroethane) system surpases that reported[2] for any of the benzo-substituted crown-4 compounds.

In this project, a variety of methylene-substituted crown compounds were synthetic intermediates for the preparation of the (benzyloxy)methyl crown compounds. Availability of both types of functionalized crowns encouraged a comparison of their cation binding abilities. Extractions of lithium and sodium picrates from aqueous

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Table II. Extraction Constants (K_{ex})[a] and Association Constants (K_a)[b] for Cation Complexation of Methylene-Substituted Crown Ethers

crown ether ring size	crown ether no.	attachmt site[d]	K_{ex}[c] Li+	K_{ex}[c] Na+	$K_{ex}(Li^+)^b / K_{ex}(Na^+)^b$	K_a for Li+	corresponding compd in Table I
14C4	**24**	2	39 ± 4	3 ± 1	13	26800	5
15C5	**25**	2	40 ± 3	126 ± 6	0.32	27500	27
13C4	**2**	3	22 ± 2	2 ± 1	11	15400	4
14C4	**6**	3	445 ± 13	10 ± 2	44	317000	8
15C4	**10**	3	5 ± 1	<1		3600	12
16C4	**13**	3	2 ± 1	<1		1200	15

[a] Deuteriochloroform–water system at room temperature (22–23 °C). [b] In deuteriochloroform. [c] The crown ether–cation complexes were 1:1 (see Experimental Section). [d] 2 = methylene group attached to a two-carbon bridge; 3 = methylene group attached to the central carbon of a three-carbon bridge.

solutions into deuteriochloroform by methylene-substituted crown compounds **2**, **6**, **10**, **13**, **24**, and **25** were conducted as before. Values of K_{ex} and K_a for the methylene-substituted crowns are collected in Table II.

In a control experiment, a 15 mM solution of the methylene-13-crown-4 compound **2** in deuteriochloroform which contained dipentyl ether as an internal standard was analyzed by GLPC and then shaken with an equal volume of 15 mM aqueous lithium chloride solution. GLPC analysis of the deuteriochloroform phase after contact with the aqueous lithium chloride solution revealed that 96.5 ± 1.0% of the crown ether remained. Since **2** should have the lowest lipophilicity of the methylene-substituted and (benzyloxy)methyl-substituted crown-4 compounds examined in this study, crown ether loss to the aqueous phase during the picrate extractions was judged to be unimportant.

The methylene-substituted crown ethers are of two types. In the first variety (compounds **24** and **25**), the methylene group is attached to one carbon of the two-carbon bridge to form a crown ether with one vinyl ether oxygen. Comparison of the K_{ex} values for lithium and sodium extraction by **24** and **25** (Table II) with those for the corresponding (benzyloxy)methyl compounds **5** and **27**, respectively (Table I), reveals substantially reduced metal ion extraction for the methylene-substituted crowns. Presumably this results from the presence of a less basic vinyl ether oxygen in the polyether ring of the former since the concomitant ring carbon hybridization change to sp^2 appears to be a generally favorable structural modification (vide infra).

In the second series (compounds **2**, **6**, **10**, and **13**), the methylene group is attached to the central carbon of a three-carbon bridge. Comparison of K_{ex} values for lithium and sodium extraction by **2** and **6** (Table II) with those for the corresponding (benzyloxy)methyl compounds **4** and **8**, respectively (Table I), shows substantial increases in lithium extraction but no appreciable changes for sodium extraction. Thus, incorporation of a sp^2-hybridized ring carbon which should increase the crown ring rigidity appears to enhance lithium complexation and selectivity in 13-crown-4 and 14-crown-4 compounds. For the methylene-substituted 14-crown-4 compound **6**, the lithium selectivity is very high and equals the record lithium selectivity reported for extractions of lithium and sodium picrates by a lipophilic dioxa diamide in a methylene chloride–water system.[9] For the methylene- and (benzyloxy)methyl-substituted crown compounds in the 15-crown-4 and 16-crown-4 systems, the K_{ex} values are too low to allow a reliable comparison to be made.

Experimental Section

IR spectra were obtained on neat samples (unless specified otherwise) with a Nicolet MX-S or a Beckman Acculab 8 spectrometer and are recorded in reciprocal centimeters. ^1H NMR spectra were recorded with Varian EM 360A or EM 360 spectrometers in deuteriochloroform and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Visible spectra were recorded with a Perkin-Elmer Lambda 5 UV–vis spectrophotometer. GLPC analyses were performed with a Varian Model 3700 capillary gas chromatography with a flame ionization detector. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Chemicals. Unless specified otherwise reagent grade reactants and solvents were obtained from chemical suppliers and used as received. THF was purified by distillation from $LiAlH_4$ under nitrogen. 3-Chloropropyl 2′-tetrahydropyranyl ether,[23] 1,9-dihydroxy-3,7-dioxanonane,[2] 1,9-dichloro-3,7-dioxanonane,[2] 3-(benzyloxy)-1,2-propanediol,[19,20] [(benzyloxy)methyl]-12-crown-4,[11] and [(benzyloxy)methyl]-15-crown-5[13] were prepared by literature methods.

General Procedure for the Synthesis of 2-[(Benzyloxy)methyl]-Substituted Crown Ethers 1, 5, and 9. A published procedure[11] for the synthesis of [(benzyloxy)methyl]-12-crown-4 was adapted. Under nitrogen, lithium metal (1.9 g, 0.27 mol) was added to 500 mL of *tert*-butyl alcohol. After refluxing for 1 h, 3-(benzyloxy)-1,2-propanediol (16.3 g, 89 mmol) was added dropwise. To the cloudy, heterogeneous mixture, the appropriate dichloride (89 mmol) was added followed by LiBr (7.7 g, 89 mmol) and water (1.6 mL). The reaction mixture was refluxed and stirred for 2 weeks. After the solvent had been removed in vacuo, water (50 mL) was added to the residue and the mixture was neutralized with 6 N HCl. Extraction with methylene chloride (3 × 50 mL) afforded the crude product which was purified by column chromatography.

2-[(Benzyloxy)methyl]-13-crown-4 (1). With use of the general procedure and 1,9-dichloro-3,7-dioxanonane (18.0 g, 89 mmol), crude **1** was formed and purified by column chromatography on alumina with petroleum ether/ethyl acetate (4:1) as eluent to give **1** (22.2 g, 80%) as a colorless liquid: IR 1130 (C–O); ^1H NMR δ 1.75 (pentet, 2), 3.3–4.1 (m, 17), 4.53 (s, 2), 7.30 (s, 5). Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.64; H, 8.69.

2-[(Benzyloxy)methyl]-14-crown-4 (5). On a reduced scale, 1,10-dichloro-4,7-dioxadecane (**18**) (7.4 g, 34 mmol) was reacted with an equivalent amount of 3-(benzyloxy)-1,2-propanediol by use of the general procedure. Column chromatography (alumina, petroleum ether:ethyl acetate, 5:1) gave colorless liquid **5** (8.2 g, 75%): IR 1122 (C–O); ^1H NMR δ 1.5–2.0 (m, 4), 3.2–4.1 (m, 17), 4.50 (s, 2), 7.27 (s, 5 H). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.84; H, 8.90.

2-[(Benzyloxy)methyl]-15-crown-4 (9). On a reduced scale, 1,11-dichloro-4,8-dioxaundecane (**21**) (5.7 g, 25 mmol) and an equivalent amount of 3-(benzyloxy)-1,2-propanediol were combined by use of the general procedure. The pure **9** was isolated by column chromatography on alumina, with petroleum ether: ethyl acetate (9:1) as eluent, to produce **9** (5.2 g, 49%) as a colorless liquid: IR 1115 (C–O); ^1H NMR δ 1.76 (pentet, 6), 3.3–4.1 (m, 17), 4.52 (s, 2), 7.28 (s, 5). Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C, 67.15; H, 8.97.

General Procedure for the Synthesis of Methylene-Substituted Crown Ethers 2, 6, 10, and 13. A published procedure[21] for the synthesis of methylene-16-crown-5 was adapted. Under nitrogen, sodium hydride (14.4 g, 0.30 mol) was washed with

n-pentane to remove the protecting mineral oil and suspended in 800 mL of dry THF. To this refluxing mixture were added 3-chloro-2-(chloromethyl)-1-propene (12.5 g, 0.10 mol) in THF (200 mL) and the corresponding diol (0.10 mol) in THF (200 mL) slowly (1.64 mL/h) and simultaneously with two syringe pumps. The addition was completed after 5 days, and the refluxing was continued for an additional 2 days. The solvent was evaporated in vacuo, water (100 mL) was added, and the mixture was neutralized with 6 N HCl. Extraction with chloroform (3 × 50 mL) gave the crude product which was purified by column chromatography.

3-Methylene-13-crown-4 (2). With use of the general procedure and triethylene glycol (15.0 g, 0.10 mol), crude **2** was produced. The crude product was chromatographed on alumina with petroleum ether:ethyl acetate (3:1) as eluent to yield 5.2 g (26%) of **2** as a colorless liquid: IR 1655 (C=C), 1118 (C—O); ^{1}H NMR δ 3.65 (br s, 12), 4.20 (s, 4), 5.12 (br s, 2). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.22; H, 8.93.

3-Methylene-14-crown-4 (6). On a reduced scale, 1,9-dihydroxy-3,7-dioxanonane (23.2 g, 0.14 mol) was combined with an equivalent amount of 3-chloro-2-(chloromethyl)-1-propene under the conditions of the general procedure. Column chromatography on alumina with petroleum ether:ethyl acetate (5:1) as eluent afforded **6** (13.2 g, 43%) as a colorless liquid which solidified below room temperature: IR 1656 (C=C), 1118 (C—O); ^{1}H NMR δ 1.78 (pentet, 2), 3.67 (m, 12), 4.15 (s, 4), 5.13 (br s, 2). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.82; H, 9.06.

3-Methylene-15-crown-4 (10). On a reduced scale, 1,10-dihydroxy-4,7-dioxadecane (**17**) (10.0 g, 56 mmol) and 3-chloro-2-(chloromethyl)-1-propene (7.0 g, 56 mmol) were reacted under the conditions of the general procedure. Pure **10** (7.6 g, 59%) was isolated as a colorless liquid by column chromatography on alumina with petroleum ether:ethyl acetate (5:1) as eluent as a colorless liquid: IR 1655 (C=C), 1124 (C—O); ^{1}H NMR δ 1.77 (pentet, 4), 3.58 (m, 12), 4.03 (br s, 4), 5.10 (br s, 2). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.37; H, 9.72.

3-Methylene-16-crown-4 (13). On a reduced scale, 1,11-dihydroxy-4,8-dioxaundecane (**20**) (8.0 g, 42 mmol) was combined with an equal amount of 3-chloro-2-(chloromethyl)-1-propene according to the general procedure. The crude product was chromatographed on alumina with petroleum ether:ethyl acetate (9:1) as eluent to produce **13** (4.8 g, 48%) as a colorless liquid: II :52 (C=C), 1122 (C—O); ^{1}H NMR δ 1.79 (pentet, 6), 3.3–3.9 (m, 12), 3.99 (s, 4), 5.16 (s, 2). Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.78; H, 9.80.

General Procedure for the Synthesis of 3-Hydroxymethyl Crown Ethers 3, 7, 11, and 14. To a solution of the appropriate methylene crown ether (24 mmol) in dry THF (30 mL) was added dropwise 10 M BH_3·$(CH_3)_2S$ (70 mmol) under nitrogen at 0 °C. The mixture was stirred at 0 °C for 2 h followed by 2 h at room temperature. Water (10 mL), 3 M NaOH (70 mL), and 5 mL of 30% H_2O_2 were added successively at 20–30 °C. The mixture was stirred at 50 °C for 1 h, cooled, and transferred into a separatory funnel. The water layer was saturated with NaCl and the organic layer was separated. The water layer was extracted with chloroform (2 × 20 mL). The combined chloroform extracts and the organic layer were dried ($MgSO_4$), and the chloroform was evaporated in vacuo to give the pure hydroxymethyl crown ether.

3-(Hydroxymethyl)-13-crown-4 (3). With 3-methylene-13-crown-4 (**2**) (4.8 g, 24 mmol) and the general procedure, **3** (5.0 g, 96%) was obtained as a colorless liquid which solidified during storage to form a white, wax-like solid: IR 3385 (O–H), 1130 (C–O); ^{1}H NMR δ 1.8–2.2 (m, 1), 2.62 (s, 1), 3.4–3.9 (m, 18). Anal. Calcd for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 54.52; H, 9.34.

3-(Hydroxymethyl)-14-crown-4 (7). Hydroboration of 3-methylene-14-crown-4 (9.4 g, 43 mmol) was conducted to afford pure **7** (10.0 g, 98%) as a white solid, mp 69–71 °C: IR (deposit on NaCl) 3346 (O–H), 1120 (C–O); ^{1}H NMR δ 1.5–2.2 (m, 3), 3.2–4.2 (m, 19). Anal. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46. Found: C, 56.20; H, 9.27.

3-(Hydroxymethyl)-15-crown-4 (11). Hydroboration of 3-methylene-15-crown-4 (**10**) (6.3 g, 27 mmol) gave **11** (6.7 g, 99%) as a colorless oil which solidified below room temperature: IR 3454 (O–H), 1126 (C–O); ^{1}H NMR δ 1.5–2.2 (m, 4), 2.6–3.1 (m, 1), 3.2–4.3 (m, 19). Anal. Calcd for $C_{12}H_{24}O_5$: C, 58.04; H, 9.74. Found: C, 57.77; H, 9.59.

3-(Hydroxymethyl)-16-crown-4 (14). Hydroboration of 3-methylene-16-crown-4 (**13**) (4.3 g, 18 mmol) gave crude **14** which was purified by column chromatography on alumina with petroleum ether:ethyl acetate (7:3) as eluent to give 2.6 g (55%) of a colorless liquid: IR 3430 (O–H), 1115 (C–O); ^{1}H NMR δ 1.5–2.3 (m, 7), 2.86 (s, 1), 3.3–4.1 (m, 18). Anal. Calcd for $C_{13}H_{26}O_5$: C, 59.52; H, 9.99. Found: C, 59.26; H, 9.86.

General Procedure for the Synthesis of 3-(Benzyloxy)methyl Crown Ethers 4, 8, 12, and 15. Sodium hydride (50% suspension in mineral oil, 0.22 g, 4.6 mmol) was washed with *n*-pentane and suspended in THF (5 mL). To this mixture was added a solution of the corresponding 3-hydroxymethyl crown ether (2.9 mmol) in THF (5 mL) dropwise under nitrogen. After stirring for 1 h at room temperature, benzyl bromide (0.60 g, 3.5 mmol) was added, and the mixture was stirred overnight at room temperature. Water (60 mL) was added, and the mixture was extracted with chloroform (3 × 20 mL). The combined extracts were dried and the solvent was evaporated in vacuo to give the crude product which was purified by chromatography on a short alumina column.

3-[(Benzyloxy)methyl]-13-crown-4 (4). Benzylation of **3** (0.65 g, 2.9 mmol) was conducted by use of the general procedure. After chromatography with petroleum ether–ethyl acetate (4:1) as eluent, 0.63 g (69%) of **4** was obtained as a colorless liquid: IR 1128 (C–O); ^{1}H NMR δ 1.9–2.4 (m, 1), 3.3–3.8 (m, 18), 4.47 (s, 2), 7.28 (s, 5). Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.96; H, 8.60.

3-[(Benzyloxy)methyl]-14-crown-4 (8). The hydroxymethyl crown **7** (0.70 g, 3.0 mmol) was benzylated according to the general procedure. Chromatography with petroleum ether:ethyl acetate (10:1) as eluent gave 0.78 g (80%) of **8** as a colorless liquid: IR 1126 (C–O); ^{1}H NMR δ 1.5–2.6 (m, 3), 3.2–3.9 (m, 18), 4.45 (s, 2) 7.25 (s, 5). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.87; H, 8.76.

3-[(Benzyloxy)methyl]-15-crown-4 (12). 3-(Hydroxymethyl)-15-crown-4 (**11**) (0.69 g, 2.8 mmol) was reacted under the conditions of the general procedure. Chromatography with petroleum ether:ethyl acetate (10:1) as eluent gave **12** (0.85 g, 90%) as a colorless liquid: IR 1126 (C–O); ^{1}H NMR δ 1.5–2.6 (m, 5), 3.3–3.9 (m, 18), 4.47 (s, 2), 7.28 (s, 5). Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C, 67.51; H, 8.77.

3-[(Benzyloxy)methyl]-16-crown-4 (15). Benzylation of **14** (0.50 g, 1.9 mmol) gave, after chromatography with petroleum ether:ethyl acetate (4:1) as eluent, 0.50 g (69%) of **15** as a colorless liquid: IR 1120 (C–O); ^{1}H NMR δ 1.5–2.5 (m, 7), 3.1–4.2 (m, 18), 4.49 (s, 2) 7.32 (s, 5). Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.32; H, 9.20.

Preparation of Bis Tetrahydropyranyl Ether 16. After removing the protecting mineral oil from 32.3 g (0.67 mol) of 50% NaH suspension in mineral oil by washing with *n*-pentane under nitrogen, 20.5 g (0.33 mmol) of ethylene glycol in 400 mL of dry DMF was added. The mixture was stirred at 70 °C for 3 h and then 3-chloropropyl 2′-tetrahydropyranyl ether[23] (120.0 g, 0.67 mol) was added, and the mixture was stirred for 3 days. A second portion of NaH (32.2 g, of 50% suspension in mineral oil, 0.67 mol, with mineral oil removed by washing with *n*-pentane) and 3-chloropropyl 2′-tetrahydropyranyl ether[23] (60.0 g, 0.34 mol) was added, and the reaction was continued for another 4 days. The solvent was removed by distillation under vacuum, and the residue was dissolved in CH_2Cl_2 (400 mL), mixed with 150 g of silica gel, and filtered. The filtered material was washed with CH_2Cl_2. The combined filtrate and washings were concentrated in vacuo to give a crude product which was purified by vacuum distillation (167–168 °C (0.2 torr)), yielding 36.1 g (32%) of a viscous, colorless liquid: IR 1120 (C–O); ^{1}H NMR δ 1.2–2.2 (m, 16), 3.2–4.1 (m, 16), 4.59 (t, 2). Anal. Calcd for $C_{18}H_{34}O_6$: C, 62.40; H, 9.88. Found: C, 62.38; H, 10.02.

1,10-Dihydroxy-4,7-dioxadecane (17). The bis tetrahydropyranyl ether **16** (41.2 g, 0.12 mmol) was dissolved in a mixture of CH_2Cl_2 (200 mL) and CH_3OH (200 mL), and 4 mL of concentrated HCl was added. The solution was stirred at room temperature for 24 h, and 20.0 g of solid $NaHCO_3$ was added. After filtration the solvent was evaporated in vacuo, and the residue was passed through a short silica gel column by use of

diethyl ether and then acetone as eluents to give diol **17** (19.5 g, 92%) as a colorless, viscous liquid: IR 3370 (OH), 1120–1060 (C–O); ^{1}H NMR δ 2.76 (pentet, 4), 3.2–4.3 (m, 14). Anal. Calcd for $C_8H_{18}O_4$: C, 53.91; H, 10.18. Found: C, 53.64; H, 9.99.

1,10-Dichloro-4,7-dioxadecane (18). A published procedure[24] for the synthesis of tetraethylene glycol dichloride was adapted. A mixture of 9.2 g (52 mmol) of diol **17**, benzene (50 mL), and pyridine (9.5 g, 0.12 mol) was heated to reflux, and 14.3 g (0.12 mol) of $SOCl_2$ was added dropwise with stirring during 40 min. Heating was continued for 25 h and after cooling, 1 mL of concentrated HCl which had been diluted with 4 mL of water was added slowly. The organic layer was separated, and the water layer was extracted with benzene (2 × 50 mL). The combined extracts were dried ($MgSO_4$), and the solvent was evaporated in vacuo, leaving a residue which was vacuum distilled (89–104 °C (0.4 torr)) to give 7.8 g (70%) of **18** as a pale yellow, viscous liquid: IR 1130–1115 (C–O); ^{1}H NMR δ 1.99 (pentet, 4), 3.3–3.9 (m, 12). Anal. Calcd for $C_8H_{16}O_2Cl_2$: C, 44.67; H, 7.50. Found: C, 44.47; H, 7.58.

Preparation of Bis Tetrahydropyranyl Ether 19. 3-Chloropropyl 2′-tetrahydropyranyl ether[23] (119.6 g, 0.67 mol) and 1,3-propanediol (25.0 g 0.33 mol) were reacted in DMF in the presence of NaH (16.1 g, 0.67 mol) by use of the procedure described for the synthesis of **16**. The amounts of reagents added during the second addition were NaH (16.1 g, 0.67 mol) and 3-chloropropyl 2′-tetrahydropyranyl ether (59.8 g, 0.34 mol). After workup, vacuum distillation of the residue (170–180 °C (0.06 torr)) afforded 27.2 g (23%) of pure **19** as a colorless, viscous liquid: IR 1114 (C–O); ^{1}H NMR δ 1.2–2.2 (m, 18), 3.2–4.2 (m, 16), 4.55 (t, 2). Anal. Calcd for $C_{19}H_{36}O_6$: C, 63.31; H, 10.07. Found: C, 63.16; H, 10.23.

1,11-Dihydroxy-4,8-dioxaundecane (20). Deprotection of **19** (27.0 g, 75 mmol) was conducted under conditions described earlier for deprotection of **16**. Purification of the crude product on a short silica gel column with acetone as eluent gave diol **20** (14.2 g, 99%) as a colorless, viscous liquid: IR 3370 (OH), 1108 (C–O); ^{1}H NMR δ 1.6–2.1 (m, 6), 3.0–4.0 (m, 14). Anal. Calcd for $C_9H_{20}O_4$: C, 56.23; H, 10.49. Found: C, 56.09; H, 10.66.

1,11-Dichloro-4,8-dioxaundecane (21). The diol **20** (6.0 g, 31 mmol) and thionyl chloride (8.3 g, 70 mmol) were reacted under conditions described earlier for the preparation of **18**. Vacuum distillation of the crude product (94–103 °C (0.4 torr)) gave **21** (6.1 g, 85%) as a pale yellow, viscous liquid: IR 1110 (C–O); ^{1}H NMR δ 1.6–2.3 (m, 6), 3.4–3.9 (m, 12). Anal. Calcd for $C_9H_{18}O_2Cl_2$: C, 47.17; H, 7.92. Found: C, 47.40; H, 7.92.

Alkali metal picrates were prepared by dissolving picric acid in a minimum amount of boiling distilled, deionized water and slowly adding a stoichiometric amount of the alkali metal carbonate. After allowing the solution to cool to room temperature, it was cooled in an ice bath to promote crystallization. Crystals were collected, air-dried, and recrystallized from distilled, deionized water. The recrystallized alkali metal picrate was collected, air-dried, and dried in a vacuum oven at 100 °C for 4 h. The dry picrate salts were stored under vacuum in the dark.

Picrate Extraction into Deuteriochloroform. Crown ether solutions (15 mM) were prepared in ethanol-free deuteriochloroform. With use of the reported extraction procedure,[25,26] extractions were conducted by adding 0.50 mL of a 15 mM crown ether solution in deuteriochloroform to 0.50 mL of a 15 mM alkali metal picrate solution in a centrifuge tube, and the mixture was agitated with a vortex mixer for 1 min. Five identical samples were run concurrently. The mixtures were centrifuged for 10 min to assure complete layer separation. Precisely measured aliquots were removed from each layer with microsyringes and diluted in acetonitrile. Visible spectra of these solutions were measured in the region of 340–550 nm. In all cases, the picrate absorption maxima at 373–374 nm was characteristic of the tight ion pair present in 1:1 complexes.[28] From the alkali metal picrate concentrations in each phase, the K_{ex} (extraction constant) value was calculated[25,26] and in some instances was converted into the K_a (association constant) value by the reported method.[26]

Picrate Extraction into Tricresyl Phosphate–1,2-Dichloroethane. Crown ether solutions (0.10 mM) were prepared in 1:1 (by volume) solution of tricresyl phosphate (Fluka, practical, mixture of isomers) and 1,2-dichloroethane. Extractions were conducted by adding 1.00 mL of the crown solution to 1.00 mL of an aqueous solution which was 0.10 mM in lithium picrate and 0.10 m in lithium hydroxide in a centrifuge tube and agitating the mixture for 2 min with a vortex mixer. Five identical samples were run concurrently. The resulting mixture was centrifuged for 10 min to separate the layers after which 0.50 mL of the aqueous layer was removed with a syringe and diluted to 5.00 mL with acetonitrile. The visible spectrum was measured in the region of 340–550 nm to determine the concentration of lithium picrate in the aqueous phase. In all cases, the picrate absorption maxima were at 373–374 nm which is characteristic of the tight ion pair in 1:1 complexes.[28] The concentration of lithium picrate in the organic phase was calculated by difference and was used in calculating the K_{ex} (extraction constant) value.[26]

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Registry No. **1**, 92818-15-0; **2**, 92818-16-1; **3**, 92818-17-2; **4**, 92818-18-3; **5**, 92818-19-4; **6**, 92818-20-7; **7**, 92818-21-8; **8**, 92818-22-9; **9**, 92818-23-0; **10**, 92818-24-1; **11**, 92818-25-2; **12**, 92818-26-3; **13**, 92818-27-4; **14**, 92818-28-5; **15**, 92818-29-6; **16**, 92818-30-9; **17**, 92144-80-4; **18**, 24997-21-5; **19**, 92818-31-0; **20**, 4161-32-4; **21**, 92818-32-1; **22**, 67439-82-1; **23**, 67439-83-2; **24**, 92818-33-2; **25**, 92818-34-3; $PhCH_2OCH_2CH(OH)CH_2OH$, 4799-67-1; $(ClCH_2)_2C{=}CH_2$, 1871-57-4; $HO(CH_2)_3OH$, 504-63-2; Li^+, 17341-24-1; Na^+, 17341-25-2; triethylene glycol, 112-27-6; 3-chloropropyl 2-tetrahydropyranyl ether, 42330-88-1; lithium picrate, 18390-55-1; sodium picrate, 3324-58-1.

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