J. Org. Chem. **1992**, *57*, 725-728

A Lipophilic Lariat Ether with Different Intraannular and Pendent Acidic Functions: Synthesis and Metal Ion Extraction

Bronislaw P. Czech,[†] Hwang Huh,[‡,§] and Richard A. Bartsch*[,‡]

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061

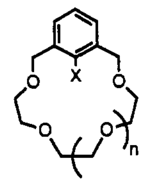
Received June 4, 1991

A novel resorcinol-based, 25-crown-8 compound with an intraannular oxyacetic acid group and a pendent, lipophilic phosphonic acid monoethyl ester function has been synthesized. Competitive solvent extractions of alkali-metal, alkaline-earth, and mixed alkali-metal and alkaline-earth cations from aqueous solutions into chloroform by this lipophilic lariat ether with two different proton-ionizable groups were investigated. The lipophilic diionizable lariat ether exhibits markedly different efficiencies in the extraction of alkali-metal cations and of alkaline-earth cations from basic aqueous solutions.

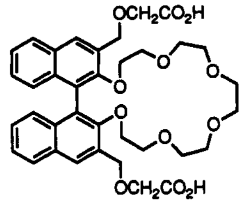
Introduction

The potential of crown ethers as a new generation of specific extracting agents for metal ions was markedly enhanced by the introduction of crown ethers which bear a carboxylic acid group.[1-5] The proton-ionizable group allows the extractant to function both as a cation exchanger and a coordinator.[6] This eliminates the need to transfer hard aqueous phase anions, such as chloride, nitrate, and sulfate, into the organic medium.[7]

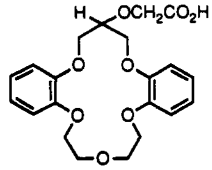
In addition to carboxylic acid functions, other strongly acidic groups such as phosphonic acid monoalkyl ester,[8] phosphonic acid,[5] and sulfenic acid[4] groups have been utilized.[9] These strongly acidic groups may be in intraannular (e.g., **1**[2,4] and **2**[4]) or pendent units (e.g., **3**,[1] **4**,[3] **5**,[10] **6**[8] which are lariat ethers[11]). Crown ethers with weakly acidic proton-ionizable groups (e.g. 4-pyridono,[12-15] triazolo,[15] and bissulfonamido functions[13,16]) as constituents of the macrocyclic ring itself have also been reported.



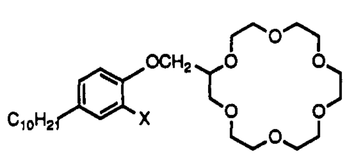
X
1 CO_2H
2 SO_2H



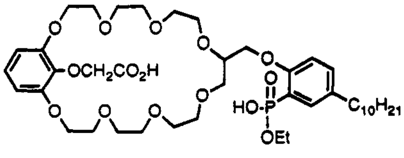
3



4



X
5 CO_2H
6 PO(OH)(OEt)



7

We wished to investigate the extraction behavior of a lipophilic crown ether which possesses two different proton-ionizable groups that are located in very different environments (i.e., one intraannular and one pendent). To this end, novel compound **7** which has an intraannular oxyacetic acid group and a pendent phosphonic acid monoethyl ester group was designed and synthesized. We now report the preparative route to extractant **7** as well as its extraction behavior toward alkali-metal and alkaline-earth cations.

Results and Discussion

Synthesis. The preparation of lipophilic, diionizable, lariat ether **7** is outlined in Scheme I. Cyclization of ditosylate **8**[17] and diol **9**[18,19] with potassium *tert*-butoxide in THF established the 25-crown-8 ring system in **10** in

---

[†] Present address: Technicon Instruments Corporation, Tarrytown, NY 10591-5097.

[‡] Texas Tech University.

[§] Permanent address: Department of Chemistry, University of Ulsan, Ulsan 690, Republic of Korea.

(1) Helgeson, R. C.; Timko, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 3023.

(2) Newcomb, M.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6405.

(3) Bartsch, R. A.; Heo, G. S.; Kang, S. I.; Liu, Y.; Strzelbicki, J. *J. Org. Chem.* **1982**, *47*, 457.

(4) Skowronska-Ptasinska, M.; Arts, V. M. L.; Egberink, R. J. M.; van Eerden, J.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1988**, *53*, 5485.

(5) Bartsch, R. A. *Solv. Extr. Ion Exch.* **1989**, *7*, 829.

(6) McDowell, W. J. *Sep. Sci. Technol.* **1988**, *23*, 1251.

(7) Strzelbicki, J.; Bartsch, R. A. *Anal. Chem.* **1981**, *53*, 1984.

(8) Koszuk, J. F.; Czech, B. P.; Walkowiak, W.; Babb, D. A.; Bartsch, R. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1504.

(9) We are excluding macrocycles in which one or more proton-ionizable groups are attached to one or more ring nitrogens of azacrown ethers.

(10) Bartsch, R. A.; Czech, B. P.; Kang, S. I.; Stewart, L. E.; Walkowiak, W.; Charewicz, W. A.; Heo, G. S.; Son, B. *J. Am. Chem. Soc.* **1985**, *107*, 4997.

(11) Gokel, G. W.; Trafton, J. E. *Cation Binding by Macrocycles*; Inoue, Y., Gokel, G. W., Eds.; Marcel Dekker: New York, 1990; pp 253-310.

(12) Izatt, R. M.; LindH, G. C.; Clark, G. A.; Bradshaw, J. S.; Nakatsuji, Y.; Lamb, J. D.; Christensen, J. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1676.

(13) Biernat, J. F.; Bochenska, M.; Bradshaw, J. S.; Koyama, H.; LindH, G.; Lamb, J. D.; Christensen, J. J.; Izatt, R. M. *J. Inclusion Phenom.* **1987**, *5*, 729.

(14) Izatt, R. M.; LindH, G. C.; Bruening, R. L.; Huszthy, P.; Lamb, J. D.; Brandshaw, J. S.; Christensen, J. J. *J. Inclusion Phenom.* **1987**, *5*, 739.

(15) Bradshaw, J. S.; McDaniel, C. W.; Skidmore, B. D.; Nielsen, R. B.; Wilson, B. E.; Dalley, N. K.; Izatt, R. M. *J. Heterocycl. Chem.* **1987**, *24*, 1085.

(16) Izatt, R. M.; LindH, G. C.; Biernat, J. F.; Bochenska, M.; Bruening, R. L.; Bradshaw, J. S.; Christensen, J. J. *J. Inclusion Phenom. Molecular Recog. Chem.* **1989**, *7*, 487.

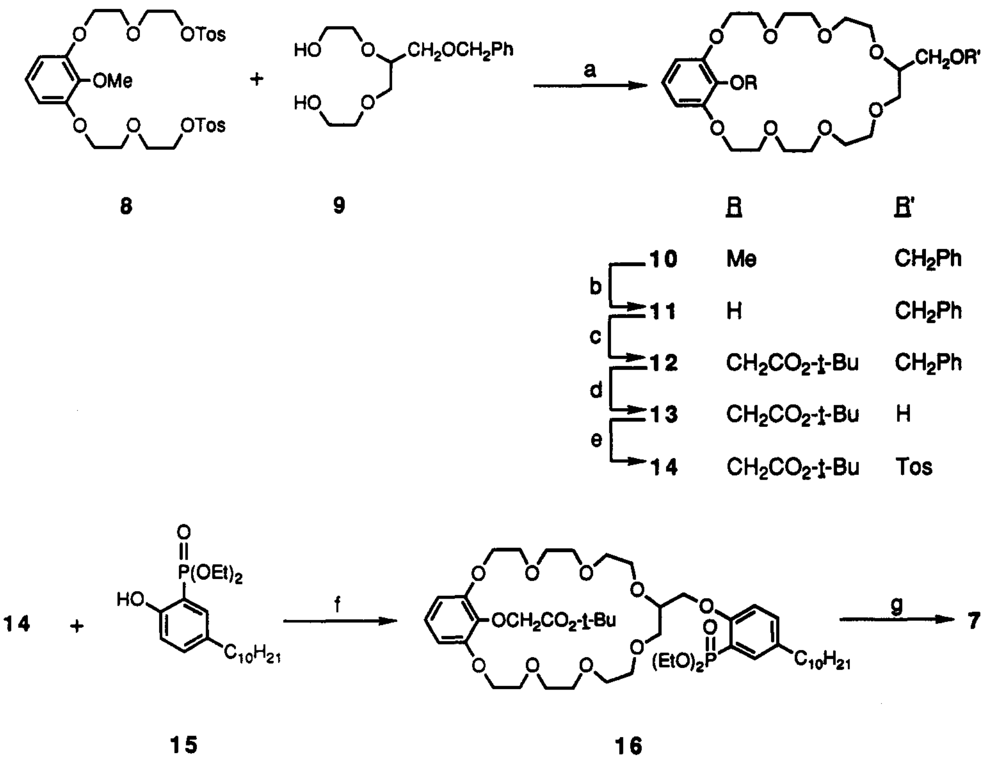
(17) Chapoteau, E.; Czech, B. P.; Kumar, A.; Pose, A.; Bartsch, R. A.; Holwerda, R. A.; Dalley, N. K.; Wilson, B. E.; Weining, J. *J. Org. Chem.* **1989**, *54*, 861.

(18) Manecke, G.; Kramer, A. *Makromol. Chem.* **1981**, *182*, 3017.

(19) Czech, B.; Babb, D. A.; Bartsch, R. A. *Org. Proc. Prep. Int.* **1983**, *15*, 39.

0022-3263/92/1957-0725$03.00/0

Scheme I[a]



[a] (a) *t*-BuOK, THF; (b) $LiAlH_4$, THF; (c) $BrCH_2CO_2$-*t*-Bu, K_2CO_3, acetone; (d) H_2, Pd/C, EtOH; (e) TosCl, pyridine; (f) NaH, THF; (g) 10% aqueous NaOH, EtOH; then aqueous HCl.

24% yield. Demethylation of the anisole unit in **10** was accomplished by refluxing with lithium aluminum hydride in THF[20] to give phenol **11** in 67% yield. Alkylation of **11** with *tert*-butyl bromoacetate and potassium carbonate in acetone yielded ester **12** quantitatively. Debenzylation of the attachment site for the pendent group by catalytic hydrogenolysis provided a 99% yield of crown ether alcohol **13**. Crown ether tosylate **14** was obtained in 82% yield by reaction with tosyl chloride in pyridine. Reaction of diethyl (2-hydroxy-5-decylphenyl)phosphonate[8] (**15**) with NaH and coupling with tosylate **14** afforded a 74% yield of crown ether **16** which has an intraannular carboxylic ester group and a diethyl phosphonate function on a lipophilic side arm. Basic hydrolysis of **16** followed by acidification gave a 96% yield of the target lipophilic, diionizable lariat ether **7**. To our knowledge, **7** is the first example of a lariat ether with different intraannular and pendent acidic groups.

Intermediates **10**–**14** and final product **7** were fully characterized by ^1H NMR and IR spectral analysis and by elemental analysis. Compound **16**, the immediate precursor to **7** by hydrolysis, was characterized only by ^1H NMR and IR spectroscopy.

Solvent Extraction of Alkali-Metal and Alkaline-Earth Cations. Due to the differing acidities of the two proton-ionizable groups in **7**, the selectivity and efficiency of alkali-metal and alkaline-earth cation extraction from aqueous solutions into chloroform were studied as a function of the aqueous phase pH. It is anticipated that the carboxylic acid function would give an effective extractant when the contacting aqueous phase was neutral or basic,[21,22] whereas the phosphonic acid monoethyl ester group would be ionized when contacted with all aqueous solutions except those of very low pH.[5,22]

The competitive extraction experiments involved aqueous chloride and hydroxide solutions of (i) five alkali-metal cations (Li^+, Na^+, K^+, Rb^+, and Cs^+), (ii) four alkaline-earth cations (Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+}), or (iii) a mixed monovalent and divalent cation system of the five alkali-metal cations and the four alkaline-earth cations. A 0.050 M chloroform solution of **7** was shaken with the aqueous solution of alkali-metal cations (0.05 M in each), alkaline-earth cations (0.25 M in each), or the mixed monovalent and divalent cations (0.25 M in each of the alkali-metal cations and 0.125 M in each of the alkaline-earth cations) for 30 min. The layers were separated, and the equilibrium pH of the aqueous phase was measured. A sample of the organic phase was shaken with 0.20 M HCl for 30 min to strip the metal ions from the organic phase into an aqueous medium for analysis by ion chromatography.

For competitive solvent extractions of alkali-metal cations into chloroform, data for the metal cation concentrations in the chloroform phase vs the equilibrium pH of the aqueous phase are shown in Figure 1. Transfer of alkali-metal cations into the chloroform solution of **7** commences at an aqueous phase pH of about 4 and then rises steadily until pH 7. At this pH the metal ion loading of the chloroform phase reached 97%, assuming a one-to-one metal ion–extractant complex. The extraction selectivity order in the acidic–neutral pH region is $K^+ > Rb^+ > Na^+ > Li^+, Cs^+$. The selectivity for K^+ indicates a distortion of the lariat ether ring from planarity as would be expected if the benzene ring tilts to relieve steric interactions between the intraannular carboxylic acid group

---

[20] Czech, A.; Czech, B. P.; Desai, D. H.; Hallman, J. L.; Phillips, J. B.; Bartsch, R. A. *J. Heterocycl. Chem.* **1986**, *23*, 1355.

[21] Walkowiak, W.; Charewicz, W. A.; Kang, S. I.; Yang, I.-W.; Pugia, M. J.; Bartsch, R. A. *Anal. Chem.* **1990**, *62*, 2018.

[22] The interfacial pK_a's of acidic groups attached to highly lipophilic extractant molecules are anticipated to be somewhat higher than those of nonlipophilic analogues in aqueous solution.

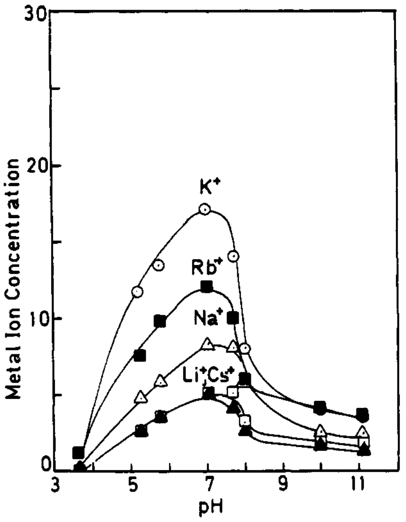


Figure 1. Molar concentrations of metal ions (×10^3) in the chloroform phase vs the equilibrium pH of the aqueous phase for competitive extraction of 0.50 M alkali-metal cations by 0.050 M 7.

and a polyether-coordinated alkali metal cation. In sharp contrast to the extraction efficiency behavior when the pH of contacting aqueous solution is 4–7, metal ion concentrations in the chloroform phase drop precipitously when the aqueous phase is basic. The observed bell-shaped extraction curves are indicative of extractant loss from the chloroform phase into contacting basic aqueous solutions.[7] In agreement, it was determined by ultraviolet spectroscopic examination of the diluted organic phase that at pH 11.2 loss of the extractant from the chloroform phase into the contacting aqueous solution was 62% of the initial concentration.

The alkali-metal cation extraction behavior of 7 may be rationalized in terms of the differing acidities of the two proton-ionizable groups. Below neutral pH, the pendent phosphonic acid monoethyl ester group is ionized, but the oxyacetic acid unit is not.[22] The monoionized extractant is sufficiently lipophilic to be retained in the chloroform phase. However, when the aqueous phase becomes basic and the carboxylic acid group is also deprotonated, the complex of the diionized extractant with two alkali-metal cations has enhanced hydrophilicity and transfers readily into the aqueous phase.

For competitive solvent extractions of alkaline-earth cations into chloroform, data for the metal cation concentrations in the chloroform phase vs the equilibrium phase pH of the aqueous phase are shown in Figure 2. The profile for alkaline-earth cation extraction by 7 is markedly different from that obtained in alkali-metal cation extraction. Transport of alkaline-earth cations into the chloroform phase commences above pH 4 and increases to the most alkaline pH studied. When the pH is approximately 10, there is quantitative metal loading of the organic phase, assuming a one-to-one extraction complex of divalent metal ion-diionized lariat ether. Retention of the extraction complex in the organic phase, even when contacted with a highly basic aqueous solution, reveals that the complex has a much greater lipophilicity than that formed from the diionized lariat ether and two alkali-metal cations. This suggests that when both ionized groups as well as some of the polyether oxygens coordinate with a single metal cation, the overall hydrophilicity of the complex is decreased.

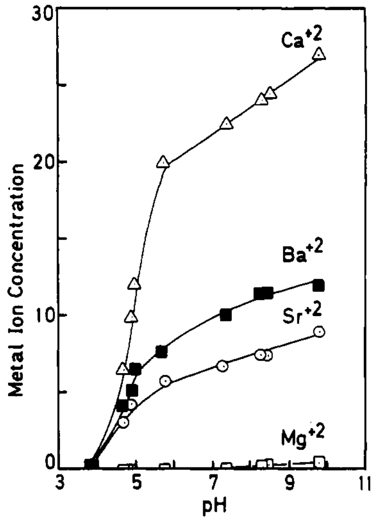


Figure 2. Molar concentrations of metal ions (×10^3) in the chloroform phase vs the equilibrium pH of the aqueous phase for competitive extractions of 0.25 M alkaline-earth cations by 0.050 M 7.

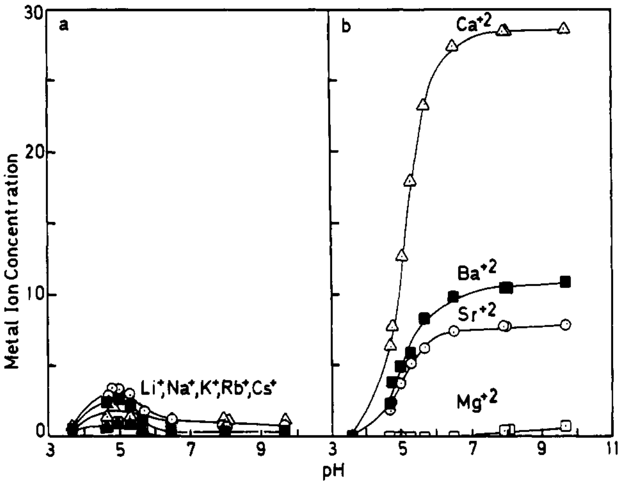


Figure 3. Molar concentrations of metal ions (×10^3) in the chloroform phase vs the equilibrium pH of the aqueous phase for competitive extractions of 0.50 M alkali-metal cations and 0.25 M alkaline-earth cations by 0.050 M 7. For the alkali-metal cation: (□) Li, (△) Na, (○) K, (■) Rb, (▲) Cs.

The alkaline-earth cation extraction selectivity is $Ca^{2+} > Ba^{2+} > Sr^{2+} \gg Mg^{2+}$. In view of the preference for K^+ extraction among the alkali-metal cations, the preferred extraction of Ca^{2+}, a considerably smaller cation, is unexpected. This may result from even further distortion of the crown ether ring from planarity to allow for simultaneous coordination of both ionized groups with a divalent cation.

Data for competitive extractions of mixed alkali-metal and alkaline-earth cations from aqueous solutions into chloroform by 7 are presented in Figure 3. For clarity, the curves for alkali-metal cation and alkaline-earth cation concentrations in the chloroform phase vs the equilibrium pH of the aqueous phase have been separated into Figure 3, parts a and b, respectively. A strong preference for alkaline-earth cation extraction over alkali-metal cation extraction is noted. At pH 9.7, metal ion loading of the chloroform phase is quantitative and the extraction selectivity order is $Ca^{2+} > Ba^{2+} > Sr^{2+} \gg Mg^{2+}$, Li^+, Na^+, K^+, Rb^+, Cs^+.

In summary, a novel lariat ether with different intraannular and pendent proton-ionizable groups has been synthesized, and its extraction behavior toward alkali-metal and alkaline-earth cations has been examined. For alkali-metal cation extraction there is a marked loss of the extractant from chloroform into a contacting aqueous layer when both acid functions of **7** are ionized. Such loss does not occur in alkaline-earth cation extraction which demonstrates the formation of a more lipophilic extractant-metal ion complex.

Experimental Section

IR spectra were obtained on neat samples. ^{1}H NMR spectra were measured at 60 MHz in $CDCl_3$.

Materials. Unless specified otherwise, reagent-grade reactants and solvents were used as received from chemical suppliers. Acetone was stored over anhydrous K_2CO_3. THF was distilled before use from sodium benzophenone ketyl. Pyridine was kept over solid KOH.

Crown Ether 10. Potassium *tert*-butoxide (3.14 g, 28.0 mmol) was added to a solution of diol **9**[18,19] (3.50 g, 13.0 mmol) in THF (130 mL), and the mixture was stirred at rt under N_2 for 1 h. A solution of ditosylate **8**[17] (8.10 g, 13.0 mmol) in THF (50 mL) was added, and the mixture was stirred at 65 °C for 3 days. The solvent was removed in vacuo, and the residue was chromatographed on alumina with EtOAc–petroleum ether (2:1) as eluent to give **10** (1.73 g, 24%) as a colorless liquid: IR 1110 (CO) cm^{-1}; ^{1}H NMR δ 3.40–4.30 (m, 32 H), 4.50 (s, 2 H), 6.40–7.05 (m, 3 H), 7.30 (s, 5 H). Anal. Calcd for $C_{29}H_{42}O_{10}$: C, 63.26; H, 7.69. Found: C, 63.03; H, 7.56.

Phenol 11. A solution of crown ether **10** (1.63 g, 3.0 mmol) in THF (30 mL) was added to a suspension of $LiAlH_4$ (0.87 g, 30.0 mmol) in THF (20 mL). The mixture was refluxed under N_2 for 20 h, cooled, carefully acidified with 6 N HCl and saturated with NaCl. The organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (15 mL), the combined organic layers were dried ($MgSO_4$), and the solvent was evaporated in vacuo. The residue was chromatographed on alumina with EtOAc–MeOH (20:1) as eluent to afford **11** (1.06 g, 67%) as a colorless, hygroscopic liquid: IR 3400 (OH), 1100 (CO) cm^{-1}; ^{1}H NMR δ 3.40–4.30 (m, 29 H), 4.50 (s, 2 H), 6.69 (s, 3 H), 7.05 (s, 1 H), 7.35 (s, 5 H). Anal. Calcd for $C_{28}H_{40}O_1 \cdot 0.5H_2O$: C, 61.64; H, 7.57. Found: C, 61.32; H, 7.76.

Ester 12. *tert*-Butyl bromoacetate (0.78 g, 4.00 mmol) was added to a solution of **11** (1.00 g, 1.86 mmol) in acetone (10 mL) containing anhydrous K_2CO_3 (0.61 g, 4.40 mmol). The mixture was refluxed for 48 h, the solvent was removed in vacuo, and the residue was chromatographed on alumina with petroleum ether–EtOAc (1:1) to give **12** (1.26 g, 100%) as a colorless liquid: IR 1760, 1730 (C=O), 1160–1100 (CO) cm^{-1}; ^{1}H NMR δ 1.48 (s, 9 H), 3.40–4.30 (m, 29 H), 4.51 (s, 2 H), 4.68 (s, 2 H), 6.40–7.05 (m, 3 H), 7.32 (s, 5 H). Anal. Calcd for $C_{34}H_{50}O_{12}$: C, 62.75; H, 7.74. Found: C, 62.72; H, 7.87.

Compound 13. A mixture of the benzyl-protected crown ether **12** (1.20 g, 1.84 mmol) and 10% Pd–C (0.12 g) in EtOH (15 mL) was hydrogenated under 50 psi of hydrogen for 48 h at rt. The catalyst was removed by filtration and the solvent was evaporated in vacuo to produce **13** (1.02 g, 99%) as a colorless, hygroscopic oil: IR 3480 (OH), 1760, 1730 (C=O), 1160–1100 (CO) cm^{-1}; ^{1}H NMR δ 1.50 (s, 9 H), 2.95 (br s, 1 H), 3.40–4.35 (m, 29 H), 4.68 (s, 2 H), 6.45–7.05 (m, 3 H). Anal. Calcd for $C_{27}H_{44}O_{12} \cdot 0.5H_2O$: C, 56.93; H, 7.96. Found: C, 56.80; H, 8.07.

Tosylate 14. A solution of **13** (1.02 g, 1.82 mmol) in pyridine (15 mL) was cooled to −10 °C and tosyl chloride (0.44 g, 2.31 mmol) in pyridine (5 mL) was added dropwise. The reaction mixture was kept overnight at 4 °C, poured over ice, acidified with cold 6 M HCl, and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and evaporated in vacuo to give a residue which was chromatographed on alumina with petroleum ether–EtOAc (1:1) as eluent to afford **14** (1.06 g, 82%) as a colorless oil: IR 1755, 1740 (C=O), 1365, 1180 (S=O), 1160–1100 (CO) cm^{-1}; ^{1}H NMR δ 1.48 (s, 9 H), 2.45 (s, 3 H), 3.35–4.35 (m, 29 H), 4.62 (s, 2 H), 6.45–7.05 (m, 3 H), 7.30 (d, J = 8 Hz, 2 H), 7.77 (d, J = 8 Hz, 2 H). Anal. Calcd for $C_{34}H_{50}O_{14}S$: C, 57.13; H, 7.05. Found: C, 57.34; H, 7.00.

Compound 16. To a suspension of sodium hydride (42 mg, 1.40 mmol) in THF (2 mL) was added **15**[8] (0.44 g, 1.19 mmol) in THF (2.5 mL). After stirring for 1 h at rt under N_2, a solution of tosylate **14** (1.00 g, 1.40 mmol) in THF (2.5 mL) was added and the mixture was refluxed for 4 days. The solvent was removed in vacuo, and the residue was chromatographed on alumina with EtOAc as eluent to produce crown ether **16** (0.80 g, 74%) as a colorless, viscous oil which was used directly in the next step: IR (neat) 1758, 1727, (C=), 1255 (P=O), 1110 (CO) cm^{-1}; ^{1}H NMR δ 0.70–1.90 (m, 34 H), 2.53 (t, J = 7 Hz, 2 H), 3.40–4.35 (m, 33 H), 4.62 (s, 2 H, $ArOCH_2CO_2$-*t*-Bu), 6.45–7.80 (m, 6 H).

Crown Ether 7. A solution of **16** (0.60 g, 0.66 mmol) in a mixture of aqueous 10% NaOH (20 mL) and EtOH (20 mL) was refluxed overnight, the solvent was removed in vacuo and the residue was acidified with concentrated HCl and extracted with CH_2Cl_2. The extract was washed with deionized water, the solvent was evaporated in vacuo and the product was dried at 130 °C (0.01 Torr) for 48 h to afford **7** (0.52 g, 96%) as a colorless, hygroscopic oil: IR 3600–2500 (COOH), 1770–1750 (C=O), 1253 (P=O), 1110 (CO) cm^{-1}; ^{1}H NMR δ 0.65–1.70 (m, 24 H), 2.53 (t, J = 7 Hz, 2 H), 3.30–4.40 (m, 31 H), 4.69 (s, 2 H, $ArOCH_2CO_2H$), 6.40–7.80 (m, 6 H), 8.15 (br s, 2 H). Anal. Calcd for $C_{41}H_{65}O_{15}P \cdot 0.5H_2O$: C, 58.77; H, 7.94. Found: C, 58.41; H, 8.11.

Extraction Procedure. A 0.050 M $CHCl_3$[23] solution (4.0 mL) of **7** was shaken with 4.0 mL of an aqueous solution of the metal chlorides and hydroxides [0.50 M each in Li^+, Na^+, K^+, Rb^+, Cs^+; or 0.25 M each in Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}; or a mixture of the five alkali metal cations (0.25 M in each) and the four alkaline-earth cations (0.125 M in each)] for 30 min in a 30-mL separatory funnel at room temperature with a Burrell Wrist-Action shaker. The two layers were allowed to separate, and the equilibrium pH of the aqueous phase was measured. A small sample (10–20 μL) of the organic phase was diluted with $CHCl_3$ in a 5.0-mL volumetric flask, and the UV–visible spectrum was measured to determine if there had been any loss of **7** from the chloroform phase during the extraction experiment. A portion (2.0 mL) of the organic phase was shaken with 2.0 mL of 0.20 M HCl to strip the metal ions into an aqueous solution for analysis after appropriate dilution, by ion chromatography with a Dionex Model 2000i ion chromatograph.

Acknowledgment. This research was supported by the Division of Chemical Sciences of the Office of Basic Energy Sciences of the U.S. Department of Energy (Grant DE-FG05-88ER13832).

Registry No. 7, 137743-84-1; 8, 118356-86-8; 9, 80525-60-6; 10, 137743-85-2; 11, 137743-86-3; 12, 137743-87-4; 13, 137743-88-5; 14, 137743-89-6; 15, 95206-54-5; 16, 137743-90-9; Li, 7439-93-2; Na, 7440-23-5; K, 7440-09-7; Rb, 7440-17-7; Cs, 7440-46-2; Mg, 7439-95-4; Ca, 7440-70-2; Sr, 7440-24-6; Ba, 7440-39-3.

---

[23] Reagent-grade chloroform was skaken with distilled, deionized water to remove the stabilizing ethanol and saturate the chloroform with water.