The characteristic ^{1}H NMR signals used to identify 7-*cis*-1 in the mixture were H(7) at δ 5.96, H(11) at δ 6.95, CH$_3$(19) at δ 1.90, and CH$_3$(18) at δ 1.56.

The product esters 1 (0.58 g) in ethanol (2.0 mL) were hydrolyzed by boiling for 2 h with 0.208 g (3.5 mmol) of KOH in 2 mL of ethanol and 0.5 mL of water. The mixture was cooled, diluted with water (10 mL), neutralized with ca. 8 N acetic acid, and extracted with CH$_2$Cl$_2$. The organic layer was washed several times with water, dried, and evaporated to give 0.47 g of the acid. Recrystallization from methanol provided 0.20 g (38% overall yield) of *all-trans*-retinoic acid, mp 179–180 °C (lit.[5d] mp 179–181 °C). From the recrystallization yield, the total yield of two isomers of 1 was $\geq$50%.

B. With Isolation of 3. Wittig olefination conditions were similar to the previous experiment. From 1.52 g (1.67 mequiv) of 3 in THF (15.0 mL), 0.22 g (1.00 mmol) of 5, and 1 mL (1.67 mequiv) of NaOEt was obtained 0.18 g (55%) of crude 1. Mass spectral analysis showed M$^+$ at m/e 328, and the fragmentation pattern agreed with that of the corresponding methyl ester.[18] HPLC analysis showed two peaks in agreement with 7-cis and all-trans isomers of 1 which were further confirmed by the ^{1}H NMR spectrum. The esters 1 (0.10 g) in ether/benzene (4 mL, 1:1) were treated with 0.4 mL of 0.5% iodine in benzene at 0 °C for 3 days. After removal of iodine and solvents as before, HPLC analysis showed two peaks corresponding to 13-*cis*- and *all-trans*-1 in the ratio 25:75.

Acknowledgment. We gratefully acknowledge the U.S. Army Research Office for Grants DAAG-29-79-C-0195 and DAAG-29-82-K-0133 (WTF), the National Institutes of Health for Grant AM 09191 (ECN), the partial support of the National Science Foundation by Grant CHE81-06157 to purchase the XL-300 NMR spectrometer, Dr. Michael Rosenberger of Hoffman-LaRoche, Inc., for a generous sample of aldehyde 5, and Dr. V. Rautenstrauch of Firmenich SA for a generous sample of β-cyclocitral.

Registry No. *all-trans*-1, 3899-20-5; 9-*cis*-1, 86708-67-0; 11-*cis*-1, 51249-34-4; 9,13-di-*cis*-1, 86708-68-1; 13-*cis*-1, 59699-82-0; 11,13-di-*cis*-1, 86708-69-2; 9,11,13-tri-*cis*-1, 86708-70-5; 7(*E*),9(*Z*)-4, 54226-17-4; 7(*E*),9(*E*)-4, 3917-41-7; 5, 63826-41-5; 8, 472-20-8; 11, 79-77-6; 7(*E*),9(*Z*)-12, 5299-99-0; 7(*E*),9(*E*)-12, 5299-98-9; (EtO)$_2$P(O)CH$_2$CN, 2537-48-6.

Supplementary Material Available: ^{1}H chemical shifts and coupling constants of ethyl retinoate isomers and *all-trans*-retinoic acid (Table IV) (1 page). Ordering information is given on any current masthead page.

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Crown Ethers of Low Symmetry. Spiro Crown Ethers and 16-Crown-5 Derivatives

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Spiro crown ethers **3a–c**, spiro bis(crown ethers) **5a–e**, and the related 16-crown-5 derivatives **6a–d** were synthesized and their cation binding abilities were evaluated by study of the extraction of aqueous alkali picrates. Crown ethers carrying 13-crown-4 and 16-crown-5 skeletons showed significant changes in cation selectivity as compared with the corresponding 12-crown-4 and 15-crown-5. Spiro-13-crown-4 **3a** and spiro-bis[4.4] **5a** showed extremely low extractabilities for all cations examined, while the 16-crown-5 derivatives, including spiro-bis[4.5] **5b** and spiro-bis[5.5] **5c**, showed anomalously high Na$^+$ selectivity. In a quantitative study of extraction equilibrium constants (K_{ex}), 16-crown-5 was again found to have much higher selectivity for Na$^+$ than 15-crown-5. This result is attributed to the less symmetrical spatial arrangement of donor oxygen atoms in 16-crown-5; the symmetry–extractability relationship is discussed on the basis of the size–fit concept.

Control of the cation binding ability of crown ethers has been the subject of several recent investigations. A wide variety of highly functionalized crown ethers have been synthesized to control the complexation phenomena, as exemplified by chiral crown ethers,[1] photoresponsive crown ethers,[2] poly- and bis(crown ethers) containing more than one adjacent crown ether unit,[3] polymer-supported crown ethers,[4] and lariat ethers carrying a flexible side chain with a donor group.[5] It has also been shown that even a slight conformational change in dicyclohexano-18-crown-6 alters the complex stability drastically.[6] However, little has been reported on the effects of the decrease in molecular symmetry caused, for example, by extending the methylene chain between two oxygen atoms of a $3m$-crown-m into a $(3m + 1)$-crown-m.

Spiro bis(crown ethers) are of interest because they have an extra methylene group and a bulky spiro substituent, both of which may affect their complexing ability. The first spiro bis(crowh ethers) were synthesized by Weber,[7] but subsequent studies of them have been devoted exclusively to the preparation of 1:2 dicationic complexes where

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(1) For a recent review see: Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* 1981, *98*, 43.

(2) Shinkai, S.; Shigematsu, K.; Sato, M.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* 1982, 2735; Shinkai, S.; Kouno, T.; Kusano, Y.; Manabe, O. *Ibid.* 1982, 2741 and earlier references.

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(4) See, for example, Smid, J. *Ind. Eng. Chem. Prod. Res. Dev.* 1980, *19*, 364 and the references cited therein.

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(7) (a) Weber, E. *Angew. Chem., Int. Ed. Engl.* 1979, *18*, 219. (b) *J. Org. Chem.* 1982, *47*, 3478.

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Table I. Extraction of Alkali Picrates with 3, 5, 6, and 7[a]

entry	crown ether	extractability, %[b]			
		Na^+	K^+	Rb^+	Cs^+
1	12-crown-4 (7a)	3.6	0.8	0.6	0.5
2	spiro-13-crown-4 (3a)	<0.1	<0.1	<0.1	<0.1
3	spiro-bis[4.4] (5a)	0.3	0.5	0.5	0.5
4	15-crown-5 (7b)	40.4	43.6	33.0	10.8
5	spiro-16-crown-5 (3b)	16.4	2.4	1.7	0.8
6	spiro-bis[4.5] (5b)	14.5	3.4	2.9	1.9
7	spiro-bis[5.5] (5c)	24.0	10.2	9.0	7.6
8	16-crown-5 (6a)	45.2	14.6	11.7	4.7
9	dimethyl-16-crown-5 (6b)	39.7	8.2	8.2	4.8
10	bis(methoxymethyl)-16-crown-5 (6c)	32.8	9.6	6.8	4.2
11	bis(octyloxymethyl)-16-crown-5 (6d)	35.6	9.9	10.2	6.2
12	18-crown-6 (7c)	15.4	86.4	80.4	62.8
13	spiro-19-crown-6 (3c)	1.1	33.2	27.3	11.4
14	spiro-bis[5.6] (5d)	10.3	30.8	27.7	16.4
15	sprio-bis[6.6] (5e)	4.8	42.4	34.2	19.2

[a] Temperature 25.0 ± 0.1 °C; aqueous phase (10 mL): [picrate] = 5×10^{-3} M; organic phase (CH_2Cl_2, 10 mL): [crown ether unit] = 1×10^{-2} M. Measurements taken after 40 min of shaking and subsequent 2 h of standing. [b] Defined as % picrate extracted into the organic phase. Average of two experiments is given; error < 0.2.

two cations are accommodated in a single ligand molecule against the electrostatic repulsion between the two cations. Some of these complexes have been isolated as crystals,[7] and the structure of the dicationic complex of spiro-bis[6.6] was established by an X-ray crystallographic study.[8] A recent study by Bonquant et al.[9] using ^{23}Na NMR spectroscopy has also revealed the formation of a dicationic complex in solution. No attempt has been made to relate the cation binding ability with an extended methylene chain, or, more strictly, with the symmetry of the ligand molecule.

We now report the facile syntheses of a series of spiro bis(crown ethers) and some related 16-crown-5 derivatives and discuss their cation binding abilities, evaluated from the picrate extraction experiments, in terms of the reduced symmetry caused by introducing an extra methylene group.

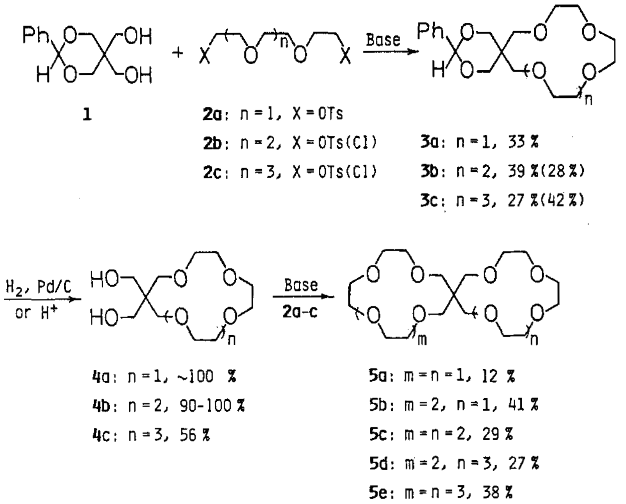
Results and Discussion

Syntheses. The spiro crown ethers (**3**) and spiro bis(crown ethers) (**5**), some of which are new compounds, were prepared by the route (Scheme I) employed by Weber.[7] Spiro crown ethers **3a–c** were synthesized by reactions of 2-phenyl-5,5-bis(hydroxymethyl)-1,3-dioxane (**1**) with oligoethylene glycol ditosylates or dichlorides **2a–c** in the presence of NaH, NaOH, NaOH/NaI, or KOH as a base in dioxane or tetrahydrofuran in 27–42% yields.

Likewise a series of spiro bis(crown ethers) **5a–e** were synthesized by reactions of bis(hydroxymethyl) crown ethers **4a–c**, which were prepared from **3a–c** through hydrolysis or hydrogenolysis, with **2a–c** (X = OTs or Cl) in 12–41% yields. Little effort was made to optimize yields, which were considered satisfactory without need for high dilution.

For comparison purposes, 15,15-disubstituted and parent 16-crown-5 **6a–d** were also prepared. 1,4,7,10,13-Pentaoxacyclohexadecane (16-crown-5, **6a**) was synthesized by reaction of 1,3-propanediol with **2b** (X = OTs or Cl) in 29% or 14% yield. 15,15-Dimethyl-1,4,7,10,13-pentaoxacyclohexadecane (dimethyl-16-crown-5, **6b**) was prepared from 2,2-dimethyl-1,3-propanediol and **2b** (X = OTs or Cl) in 25% or 15% yield by the same procedure. 15,15-Bis(methoxymethyl)-1,4,7,10,13-pentaoxacyclohexadecane [bis(methoxymethyl)-16-crown-5, **6c**] was prepared by reaction of **4b** with methyl iodide in the presence of sodium hydroxide in tetrahydrofuran in 65% yield. 15,15-Bis(octyloxymethyl)-1,4,7,10,13-pentaoxacyclohexadecane [bis(octyloxymethyl)-16-crown-5, **6d**] was prepared likewise from **4b** and *n*-octyl bromide in tetrahydrofuran in 70% yield.

Scheme I



Extraction Studies. Extraction is a facile and useful method for evaluating the complexing ability of crown ethers with cations. In preliminary experiments, extractions of aqueous alkali picrates (Na^+, K^+, Rb^+, and Cs^+: 5×10^{-3} M) were carried out at 25 °C with dichloromethane solutions of the crown ethers **3**, **5**, and **6** (1×10^{-2} M) in order to survey their cation binding abilities, and the results were compared with those for commercially available 3*m*-crowm-*m* (**7**). The results are shown in Table I.

As can be seen from Table I, 12-crown-4 (**7a**) shows the highest extractability for Na^+, 15-crown-5 (**7b**) for Na^+ and K^+, and 18-crown-6 (**7c**) for K^+ and Rb^+, in good agreement with the generally accepted size–fit concept.[10] Unexpectedly, spiro-13-crown-4 (**3a**) and spiro-bis[4.4] (**5a**), which may be compared with 12-crown-4 (**7a**), showed almost negligible extractabilities for any of the alkali cations. A similar observation has been reported by

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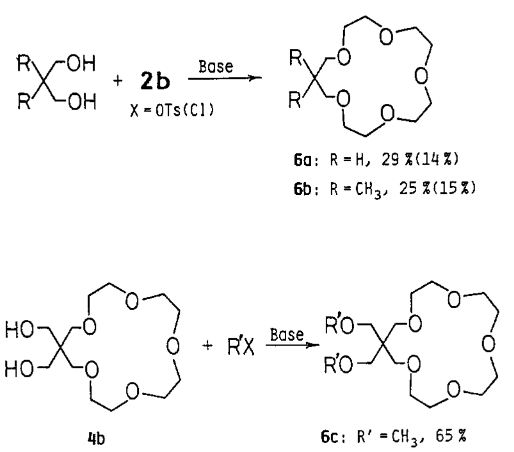
[8] Czugler, M.; Weber, E. *J. Chem. Soc., Chem. Commun.* **1981**, 472.

[9] Bonquant, J.; Delville, A.; Grandjean, J.; Laszlo, P. *J. Am. Chem. Soc.* **1982**, *104*, 686.

[10] For the earliest description of the concept see: Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.

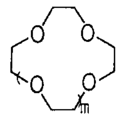
Scheme II



6a: R = H, 29%(14%)
6b: R = CH_3, 25%(15%)

4b

6c: R′ = CH_3, 65%
6d: R′ = n-C_8H_{17}, 70%



7a: m = 1
7b: m = 2
7c: m = 3

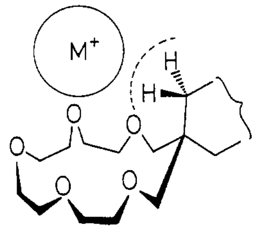


Figure 1. Schematic drawing of "steric hindrance" caused by the spiro-substituent.

Bonquant et al.[9] in the ^{23}Na NMR study of a Na^+ complex with spiro-bis[4.6]; the smaller crown ring, with four oxygen atoms, of the spiro bis(crown ether) does not accommodate the second Na^+ and no detectable dicationic complex is formed. A more interesting result of the present study is that, in spite of its comparable cavity size and the same number of donor oxygen atoms, spiro-16-crown-5 (**3b**) is a much better extractant for Na^+ than for K^+, in sharp contrast to the extraction behavior of 15-crown-5 (**7b**). This preference is also observed with spiro-bis[4.5] (**5b**) and spiro-bis[5.5] (**5c**), and therefore seems characteristic of the 16-crown-5 derivatives. On the other hand, the higher homologues, i.e., spiro-19-crown-6 (**3c**), spiro-bis[5.6] (**5d**), and spiro-bis[6.6] (**5e**), have the same relative extractabilities for the ions as 18-crown-6 (**7c**), $K^+ > Rb^+ > Cs^+ > Na^+$, although their absolute extractabilities are lower.

The selectivity for Na^+ displayed by the 16-crown-5 derivatives **3b**, **5b**, and **5c** may be attributable to the potential steric hindrance of the methylene group adjacent to the spiro carbon which may interfere with the accommodation of larger cations because of the contribution of a conformer shown in Figure 1. However, we think it more probable that the less symmetrical arrangement of donor oxygen atoms caused by introducing an extra spiro carbon atom into the crown ring disrupts the favorable conformation for complexation. Apart from the substantial differences in extractabilities, no difference in cation selectivity was, however, observed between 18-crown-6 (**7c**) and the 19-membered spiro crown ethers **3c**, **5d**, and **5e**. This might be explained by the "steric hindrance" hypothesis by assuming that bulkiness of the spiro substituent is no longer sufficient to reduce the cavity size effectively, although it appears that the reduced symmetry must be responsible for the lower extractabilities of the enlarged crown ethers.

In order to differentiate between these two possibilities, extractions of alkali picrates with 15,15-disubstituted 16-crown-5 (**6b–d**) and the parent 16-crown-5 (**6a**) were carried out under the same conditions.

As can be seen from Table I (entries 4 and 9–11), all the 15,15-disubstituted 16-crown-5 (**6b–d**) have higher selectivity for Na^+ than does 15-crown-5, which resembles spiro-16-crown-5 **3b** in this respect. These results may be taken as evidence in support of the "steric hindrance" hypothesis, since these 16-crown-5 derivatives still have substituents on C-15. Definitive evidence against this hypothesis, however, emerged from the picrate extraction by the parent 16-crown-5 (**6a**). The unsubstituted 16-crown-5 (**6a**) gave exactly the same trend in cation selectivity as the 15,15-disubstituted 16-crown-5 (**6b–d**), suggesting that the anomalously high Na^+ selectivity is inherent in the 16-crown-5 skeleton.

One might, however, assume that the unusual extraction behavior of the 16-crown-5 derivatives could be attributed in part to formation of 2:1 sandwich complexes under the extraction conditions where the [crown ether]/[picrate] ratio is 2. In order to obtain convincing evidence on this point, we carried out extraction studies under a variety of conditions to determine the extraction equilibrium constants (K_{ex}) for 15-crown-5 and 16-crown-5 and to assess their cation selectivities from a more quantitative point of view.

The overall extraction equilibrium between an aqueous solution of alkali picrate (M^+A^-) and a dichloromethane solution of crown ether (CE) can be described for an n:1 crown ether–cation complex (n = 1, 2) as follows:[11]

$$K_{ex} = [M(CE)_nA]_{org}/[M^+]_{aq}[A^-]_{aq}[CE]^n{}_{org} \qquad (1)$$

The substripts aq and org refer to the aqueous and organic phases, respectively. The distribution ratio (D_M) of a metal cation is expressed as follows:

$$D_M = [M(CE)_nA]_{org}/[M^+]_{aq} \qquad (2)$$

From eq 1 and 2, we obtain

$$K_{ex} = D_M/[A^-]_{aq}[CE]^n{}_{org} \qquad (3)$$

Modification of eq 3 results in the following equation:

$$\log (D_M/[A^-]_{aq}) = n \log [CE]_{org} + \log K_{ex} \qquad (4)$$

Equation 4 indicates that the plot of log ($D_M/[A^-]_{aq}$) as a function of log $[CE]_{org}$ should give a straight line with a slope of n (n = 1 or 2) and with log K_{ex} as the intercept.

The plots for 15- and 16-crown-5 are shown in Figure 2a,b. For 16-crown-5, the plots gave straight lines with a slope of unity for all alkali cations over the entire concentration range, indicating that 16-crown-5 forms 1:1 complexes under the conditions employed. For 15-crown-5, the plots for K^+ and Rb^+ gave bent lines of two components, one of which has a slope of unity in the low [crown ether]/[picrate] region, and the other a slope of nearly 2.

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(11) We neglected the formation of crown ether–cation complexes in the aqueous phase throughout this work, since the distribution of these crown ethers into water is minimal and the complex association constants (K_a) of 15-crown-5 in water have been shown to be around 5, which are 3–4 orders of magnitude lower than those in organic solvents. See, for example: de Jong, F.; Reinhoubt, D. N. "Stability and Reactivity of Crown Ether Complexes"; Academic Press: London, 1981; p 25 and the references cited therin.

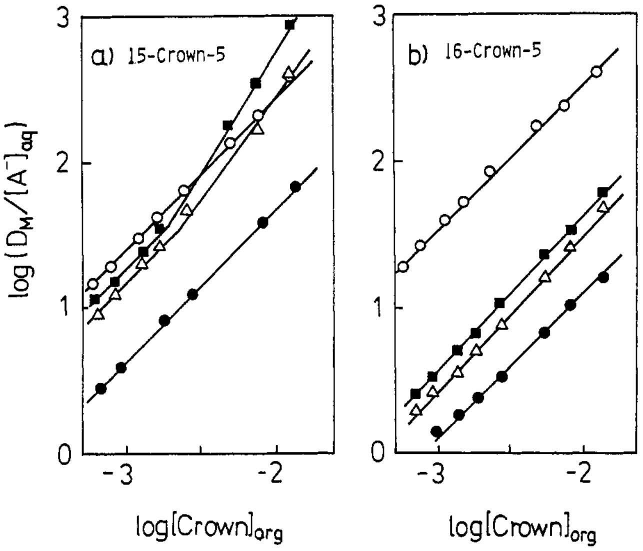

Figure 2. Plots of log (D_M/[A$^-$]$_{aq}$) vs. log [CE]$_{org}$ obtained in extraction experiments on 15-crown-5 (a) and 16-crown-5 (b) with sodium (○), potassium (■), rubidium (△), and cesium (●) picrates.

Table II. Extraction Equilibrium Constants (K_{ex}) of 15- and 16-Crown-5 with Alkali Picrates[a]

	log K_{ex}[b]			
crown ether	Na^+	K^+	Rb^+	Cs^+
15-crown-5	4.52	4.40	4.29	3.74
16-crown-5	4.55	3.65	3.52	3.14

[a] Dichloromethane-water system; temperature 25.0 ± 0.1 °C. [b] Values for 1:1 crown ether-cation complexes.

This indicates that 15-crown-5 tends to form a 2:1 sandwich complex with K^+ and Rb^+ only in the region where the [crown ether]/[picrate] ratio exceeds 1.[12] We calculated the K_{ex} for these two complexes by extrapolating the straight lines at the low [crown ether]/[picrate] ratios, less than 1, while, in the other cases, all points are used. The K_{ex} values thus obtained are given in Table II.

As was shown in the semiquantitative experiments (Table I), 15- and 16-crown-5 exhibit quite different cation selectivities, although the sequences of K_{ex} are the same for these two crown ethers, i.e., $Na^+ > K^+ > Rb^+ > Cs^+$. Most surprising is the anomalously high preference for Na^+ shown by 16-crown-5, which does not reflect a higher K_{ex} for Na^+ but rather lower K_{ex} for the larger cations, K^+, Rb^+, and Cs^+.

This unusual extraction behavior of 16-crown-5, i.e., the invariant K_{ex} for Na^+ and the drastically lower K_{ex} for the larger cations, may be accounted for in terms of the size–fit concept and molecular symmetry. According to the widely accepted size–fit concept,[10] it is likely that both 15- and 16-crown-5 can accommodate Na^+ (cation diameter 1.90 Å)[13] in their cavities (1.7–2.2 Å),[14] and the cation enjoys full coordination by five oxygen atoms. The high and comparable K_{ex} values for Na^+ shown by both 15- and 16-crown-5 support this explanation. It is further suggested that, when a cation is fully accommodated in the crown cavity as is the case with Na^+, the effect of an extra methylene group in the crown ether ring is minimized in spite of the resulting less symmetrical arrangement of donor oxygen atoms in 16-crown-5.

The situation is, however, different with the larger cations. As can be readily understood from their cation diameters, the larger cations K^+ (2.66 Å), Rb^+ (2.96 Å), and Cs^+ (3.38 Å),[13] are too large to fit in the cavity of 15- and 16-crown-5. They consequently lie *above*, not in, the ligand cavity, forming less stable 1:1 complexes with 15- and 16-crown-5. The cation may be regarded as a ball on a tray with a shallow cavity. The formation of 2:1 sandwich complexes with the larger cations in the presence of an excess amount of 15-crown-5 may also support the "ball-on-tray" interaction in the 1:1 complexes with the larger cations. Under these circumstances, it is not unreasonable to assume that the less symmetrical oxygen arrangement of 16-crown-5 must lower its complexing ability for the larger cations in comparison with the symmetrical 15-crown-5. Thus the 16-crown-5 derivatives have anomalously high selectivity for Na^+. The same argument is also applicable to the unexpected extraction behavior of 13-crown-4 derivatives **3a** and **5a**, the extractabilities of which are extremely low even for Na^+. The cation diameter of Na^+ (1.90 Å)[13] is somewhat larger than the cavity of 12-crown-4 (1.2–1.5 Å)[14] and therefore the 1:1 complex of 12-crown-4 with Na^+ is considered to be of the "ball-on-tray" type. We would then anticipate that the introduction of an extra spiro carbon into 12-crown-4 should reduce the extractability for Na^+, and for the larger cations as well, of the resulting 13-crown-4 derivatives **3a** and **5a**. This accords with the observed results and further suggests that 13-crown-4 might exhibit anomalous Li^+ selectivity.

We conclude that the introduction of an extra methylene group into a common 3*m*-crown-*m* has drastic and different effects on its binding ability toward individual cations and, in some instances, endows the enlarged crown ether with an unusual cation selectivity.

Studies of 14- to 17-crown-5 and 17- to 22-crown-6 are in progress.

Experimental Section

General. Infrared spectra were obtained on a JASCO A-100 grating spectrophotometer. Melting points were measured with YANACO Micro melting point apparatus and are uncorrected. Mass spectra were measured at 20 or 70 eV with an Hitachi RM-50GC or RMU-6E instrument. ^1H and ^{13}C NMR spectra were obtained in chloroform-*d* solution containing 1% tetramethylsilane as an internal standard with a JEOL PMX-60 and FX-60 spectrometers. UV-VIS spectra were recorded on a Shimazu UV-300 spectrophotometer. Gas chromatographic analyses were performed on a YANACO G-180 instrument equipped with a 75-cm column of 3% SE-30 or 10% Apiezon grease L and 10% Carbowax 20M (4:1). Liquid chromatographic analyses were performed on a Waters 204 liquid chromatograph using a μBondapak C_{18} column with 5% H_2O-CH_3OH eluent.

Synthesis. 3-Phenyl-2,4,8,11,14,17-hexaoxaspiro[5.12]octadecane (Spiro-13-crown-4, 3a). Sodium hydride (2.4 g, 0.1 mol) and dioxane (200 mL) were introduced into a 1-L three-necked flask equipped with a magnetic stirrer, reflux condenser, dropping funnel, and a nitrogen inlet tube. To the stirred suspension at 70 °C was added 2-phenyl-5,5-bis(hydroxymethyl)-1,3-dioxane[15] (1) (9.0 g, 0.04 mol). Triethylene glycol ditosylate (**2a**)[16] (18.3 g, 0.04 mol) in dioxane (300 mL) was than added dropwise to the stirred mixture over 6 h, and the stirring was continued for 72 h at 70 °C under a nitrogen atmosphere. The solvent was evaporated and the residue was extracted with

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[12] These plots were made by assuming the formation of 1:1 complexes (n = 1), and, nevertheless, the stoichiometry of the crown ether–cation complex is discussed on the basis of these plots. Although the [CE]$_{org}$ depends on the stoichiometry of the complex, i.e., n = 1 or 2 (eq 7), under the extraction conditions employed the actual difference in the log [CE]$_{org}$ value between n = 1 and 2 is quite small; Δ log [CE]$_{org}$ < 0.08. We can therefore discuss the change of complex stoichiometry from the slopes of Figures 2a and 2b.

[13] Pauling, L. "The Nature of the Chemical Bond", 3rd ed; Cornell University Press: Ithaca, NY, 1960; Chapter 13.

[14] Pedersen, C. J. *J. Am. Chem. Soc.* **1970**, *92*, 386.

[15] Issidorides, C. H; Gulen, R. "Organic Synthesis"; Wiley: New York, 1963; Collect. Vol. IV, p 679.

[16] Dale, J.; Kristiansen, P. O. *Acta Chem. Scand.* **1972**, *26*, 1471.

chloroform. The chloroform extract was dried over magnesium sulfate and the solvent was evaporated. The yellow oil obtained was distilled under reduced pressure to give 4.5 g (33%) of the product **3a**: mp 180–185 °C (0.2 torr); MS, *m/e* 338 (M$^+$); ^{1}H NMR δ 7.33 (m, 5 H), 5.36 (s, 1 H, PhC*H*), 3.90 (s, 2 H), 3.60 (m, 16 H), 3.30 (s, 2 H); ^{13}C NMR δ 139.5 (s),129.8 (d), 129.2 (d), 127.1 (d), 102.8 (d, PhC*H*), 70.5 (t), 39.6 (s, spiro-C); IR (neat) 3025, 2860, 1450, 1380, 1100, 740, 690 cm^{-1}. The ^{1}H NMR spectrum was in agreement with published data.[7b]

3-Phenyl-2,4,8,11,14,17,20-heptaoxaspiro[5.15]heneicosane (spiro-16-crown-5, 3b) was prepared in 39% or 28% yield by the reaction of **1** with tetraethylene glycol ditosylate[16] (**2b**, X = OTs) or dichloride[10] (**2b**, X = Cl) in the presence of sodium hydroxide or a sodium hydroxide–sodium iodide mixture in tetrahydrofuran or in dioxane, respectively, according to the procedure described above. The products from both methods showed essentially identical spectra: bp 180–183 °C (0.12 torr); MS, *m/e* 382 (M$^+$); ^{1}H NMR δ 7.23 (m, 5 H), 5.36 (s, 1 H, PhC*H*), 3.80 (s, 2 H), 3.63 (m, 20 H), 3.40 (s, 2 H); ^{13}C NMR δ 139.8 (s), 129.9 (d), 129.4 (d), 127.3 (d), 102.9 (d, PhC*H*), 72.5 (t), 71.6 (t), 70.6 (t), 40.0 (s, spiro-C); IR (neat) 3020, 2860, 1460, 1360, 1100, 750, 700 cm^{-1}. The ^{1}H NMR spectrum was in agreement with published data.[7b]

3-Phenyl-2,4,8,11,14,17,20,23-octaoxaspiro[5.18]tetracosane (spiro-19-crown-6, 3c) was prepared likewise in 27% or 42% yield by the reaction of **1** with pentaethylene glycol ditosylate[16] (**2c**, X = OTs) or dichloride[10] (**2c**, X = Cl) in the presence of potassium hydroxide in tetrahydrofuran or in dioxane, respectively: bp 180–185 °C (0.15 torr); MS, *m/e* 426 (M$^+$); ^{1}H NMR δ 7.30 (m, 5 H), 5.33 (s, 1 H, PhC*H*), 3.73 (s, 2 H), 3.61 (m, 24 H), 3.30 (s, 2 H); ^{13}C NMR δ 139.7 (s), 129.9 (d), 129.3 (d), 127.3 (d), 102.8 (d, PhC*H*), 71.9 (t), 70.7 (t), 40.2 (s, spiro-C); IR (neat) 3030, 2860, 1450, 1380, 1100, 760, 700 cm^{-1}. The ^{1}H NMR spectrum was in agreement with published data.[7b]

12,12-Bis(hydroxymethyl)-1,4,7,10-tetraoxacyclotridecane (bis(hydroxymethyl)-13-crown-4, 4a) was prepared by hydrolysis or by hydrogenolysis of spiro-13-crown-4, **3a**. The hydrolysis of **3a** was performed under conditions described by Krespan.[17] A mixture of **3a** (8.4 g, 0.025 mol) and 50 mL of aqueous 0.1 N H$_2$SO$_4$ was refluxed for 6 h. The solution was neutralized with aqueous barium hydroxide, filtered, and evaporated to dryness. The crude product was extracted with chloroform and then recrystalized twice from benzene–hexane to give 3.7 g (60%) of **4a**.

The hydrogenolysis of **3a** (7.7 g, 0.02 mol) was carried out at 60 °C over 10% Pd/C (200 mg) in an ethanol solution (40 mL) containing *p*-toluenesulfonic acid (40 mg) at a hydrogen pressure of 5 atm to give 5.9 g (~100%) of **4a**. The products obtained by both methods showed essentially identical spectra: mp 80–81 °C (lit. 80–81 °C;[17] 85–86 °C[7b]); MS, *m/e* 251 (M$^+$ + 1); ^{1}H NMR δ 3.70 (m, 20 H), 3.17 (br s, 2 H, O*H*); ^{13}C NMR δ 71.7 (t), 70.9 (t), 66.0 (t), 46.1 (s, spiro-C); IR (nujol) 3400, 2850, 1120 cm^{-1}.

15,15-Bis(hydroxymethyl)-1,4,7,10,13-pentaoxacyclohexadecane (bis(hydroxymethyl)-16-crown-5, 4b) was obtained likewise from **3b** by hydrolysis or hydrogenolysis in 90–100% yield: bp 145–150 °C (0.2 torr); MS, *m/e* 295 (M$^+$ + 1); ^{1}H NMR δ 3.68 (m, 24 H), 2.84 (br s, 2 H, OH); ^{13}C NMR δ 72.9 (t), 71.9 (t), 65.2 (t), 46.5 (s, spiro-C); IR (neat) 3360, 2870, 1110 cm^{-1}.

18,18-Bis(hydroxymethyl)-1,4,7,10,13,16-hexaoxacyclononadecane (bis(hydroxymethyl)-19-crown-6, 4c) was obtained likewise by hydrolysis of **3c** in 56% yield: bp 168–172 °C (0.11 torr); MS, *m/e* 320 (M$^+$ − 18); ^{1}H NMR δ 3.67 (m, 28 H), 3.36 (br s, 2 H, O*H*); ^{13}C NMR δ 72.0 (t), 70.8 (t), 65.3 (t), 64.6 (t), 46.5 (s, spiro-C); IR (neat) 3370, 2860, 1110 cm^{-1}.

2,5,8,11,15,18,21,24-Octaoxaspiro[12.12]pentacosane (Spiro-bis[4.4], 5a). Lithium metal (0.28 g, 0.04 mol) was dissolved in *tert*-butyl alcohol (800 mL) at 82 °C to which bis(hydroxymethyl)-13-crown-4 (**4a**, 4.0 g, 0.016 mol) in *tert*-butyl alcohol (100 mL) was added. After 2 h of stirring at 82 °C, **2a** (X = OTs, 7.33 g, 0.016 mol) in *tert*-butyl alcohol (200 mL) was added dropwise over 30 min and the mixture was stirred at the temperature for 72 h. The solvent was evaporated and the residue was extracted with chloroform. Workup and column chromatography over silica gel with petroleum ether–chloroform eluent gave 0.7 g (12%) of **5a**: mp 78–79 °C (from benzene–hexane) (lit.[7b] 79 °C); MS, *m/e* 364 (M$^+$); ^{1}H NMR δ 3.70 (m);^{13} NMR δ 71.6 (t), 68.4 (t), 46.3 (s, spiro-C); IR (Nujol) 2850, 1120 cm^{-1}. The ^{1}H NMR spectrum was in agreement with published data.[7b]

2,5,8,11,15,18,21,24,27-Nonaoxaspiro[12.15]octacosane (spiro-bis[4.5], 5b) was prepared from **4a** (2.9 g, 0.012 mol) and **2b** (X = Cl, 3.5 g, 0.015 mol) in the presence of sodium *tert*-butoxide in *tert*-butyl alcohol according to the procedure described above. Distillation of the product gave 2.0 g (41%) of **5b**: bp 120–125 °C 0.08 torr); MS, *m/e* 408 (M$^+$); ^{1}H NMR δ 3.68 (m, 2 H), 3.53 (s, 8 H); ^{13}H NMR δ 71.8 (t), 71.3 (t), 71.1 (t), 69.9 (t), 46.2 (s, spiro-C); IR (neat) 2870, 1120 cm^{-1}; Anal. Calcd for $C_{19}H_{36}O_9$: C, 55.87; H, 8.88. Found: C, 56.12; H, 9.13.

2,5,8,11,14,18,21,24,27,30-Decaoxaspiro[15.15]hentriacontane (spiro-bis[5.5], 5c) was prepared from **4b** (5.7 g, 0.012 mol) and **2b** (X = Cl, 6.7 g, 0.03 mol) in the presence of sodium hydroxide in dioxane according to the procedure described above. Distillation of the product gave 2.5 g (29%) of **5c**: bp 168–170 °C (0.18 torr); MS, *m/e* 452 (M$^+$); ^{1}H NMR δ 3.66 (m); ^{13}C NMR δ 71.9 (t), 71.4 (t), 46.7 (s, spiro-C); IR (neat) 2860, 1110 cm^{-1}. The ^{1}H NMR spectrum was in agreement with published data.[7b]

2,5,8,11,14,18,21,24,27,30,33-Undecaoxaspiro[15.18]tetratriacontane (spiro-bis[5.6], 5d) was prepared from **4b** (3.5 g, 0.012 mol) and **2c** (X = OTs, 6.5 g, 0.012 mol) in the presence of potassium hydroxide in tetrahydrofuran according to the procedure described above. Distillation of the product gave 1.6 g (27%) of **5d**: bp 174–184 °C (0.15 torr); MS, *m/e* 496 (M$^+$); ^{1}H NMR δ 3.67 (m, 36 H), 3.50 (s, 8 H); ^{13}C NMR δ 72.0 (t), 46.4 (s, spiro-C); IR (neat) 2850, 1110 cm^{-1}; Anal. Calcd for $C_{23}H_{44}O_{11}$: C, 55.63; H, 8.93. Found: C, 56.00; H, 9.19.

2,5,8,11,14,17,21,24,27,30,33,36-Dodecaoxaspiro[18.18]heptatriacontane (spiro-bis[6.6], 5e) was prepared from **4c** (2.5 g, 0.008 mol) and **2c** (X = Cl, 3.1 g, 0.01 mol) in the presence of potassium hydroxide in dioxane according to the procedure described above. Distillation of the product gave 1.6 g (38%) of **5e**: bp 185–193 °C (0.18 torr); MS, *m/e* 540 (M$^+$); ^{1}H NMR δ 3.70 (m); ^{13}C NMR δ 72.0 (t), 46.5 (s, spiro-C); IR (neat) 2860, 1120 cm^{-1}. The ^{1}H NMR spectrum was in agreement with published data.[7b]

1,4,7,10,13-Pentaoxacyclohexadecane (16-Crown-5, 6a). 1,3-Propanediol (3.8 g, 0.05 mol) was added to a stirred suspension of sodium hydroxide (5.0 g, 0.125 mol) in tetrahydrofuran (200 mL) at 66 °C, and stirring was continued for 1 h. To the mixture was added **2b** (X = OTs, 25.1 g, 0.05 mol) in tetrahydrofuran (100 mL) over 2 h, and stirring was continued for 24 h at 66 °C. Similar workup procedures and distillation gave 3.3 g (29%) of **6a**: by 104–108 °C (0.18 torr). Use of dichloride **2b** (X = Cl) resulted in a lower yield (14%). The products obtained by both methods showed essentially identical spectra: MS, *m/e* 234 (M$^+$); ^{1}H NMR δ 3.68 (m, 20 H), 1.83 (quintet, 2 H, $OCH_2CH_2CH_2O$); ^{13}C NMR δ 71.7 (t), 71.1 (t), 69.0 (t), 31.5 (t, $OCH_2CH_2CH_2O$); IR (neat) 2950, 2850, 1450, 1350, 1120, 940 cm^{-1}. Anal. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.47. Found: C, 56.16; H, 9.50.

15,15-Dimethyl-1,4,7,10,13-pentaoxacyclohexadecane (dimethyl-16-crown-5, 6b) was prepared likewise from 2,2-dimethyl-1,3-propanediol (5.2 g, 0.05 mol) and **2b** (X = OTs, 25.1 g, 0.05 mol) in the presence of sodium hydroxide in tetrahydrofuran. Distillation of the product gave 3.0 g (25%) of **6b**, bp 97–104 °C (0.04 torr). Use of dichloride **2b** (X = Cl) resulted in a lower yield (15%). The product obtained by both methods showed essentially the same spectra: MS, *m/e* 262 (M$^+$); ^{1}H NMR δ 3.65 (m, 16 H), 3.27 (s, 4 H), 0.87 (s, 6 H); ^{13}C NMR δ 78.0 (t), 72.0 (t), 37.3 (s, spiro-C), 23.4 (q, CH$_3$); IR (neat) 2860, 1480, 1450, 1120, 950 cm^{-1}. Anal. Calcd for $C_{13}H_{26}O_5$: C, 59.52; H, 9.99. Found: C, 59.28; H, 9.70.

15,15-Bis(methoxymethyl)-1,4,7,10,13-pentaoxacyclohexadecane (Bis(methoxymethyl)-16-crown-5, 6c). Bis(hydroxymethyl)-16-crown-5 **4b** (3.2 g, 0.011 mol) was added to a stirred suspension of sodium hydroxide (1.3 g, 0.03 mol) in tetrahydrofuran (150 mL) at 66 °C. After cooling to 40 °C, methyl iodide (4.7 g, 0.033 mol) in tetrahydrofuran (50 mL) was added dropwise to the mixture over 30 min, and stirring was continued for 24 h at 40 °C. Distillation of the product gave 2.3 g (65%) of **6c**: bp 122–127 °C (0.07 torr); MS, *m/e* 290 (M$^+$–32); ^{1}H NMR δ 3.66 (m, 16 H), 3.53 (s, 4 H), 3.40 (s, 4 H), 3.32 (s, 6 H, CH$_3$O); ^{13}C

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[17] Krespan, C. G. U.S. Patent 3 860 611, 1975.

NMR δ 73.1 (t), 71.9 (t), 71.3 (t), 60.3 (q, CH_3O), 46.5 (s, spiro-C); IR (neat) 2860, 2810, 1480, 1450, 1120, 940 cm^{-1}. Anal. Calcd for $C_{15}H_{30}O_7$: C, 55.88; H, 9.38. Found: C, 55.94; H, 9.54.

15,15-Bis(octyloxymethyl)-1,4,7,10,13-pentaoxacyclohexadecane (Bis(octyloxymethyl)-16-crown-5, 6d) was prepared from **4b** (1.5 g, 5.1×10^{-3} mol) and *n*-octyl bromide (5.8 g, 0.03 mol) in the presence of sodium hydroxide in tetrahydrofuran according to the procedure described above. Distillation of the product gave 1.85 g (70%) of **6d**: bp 205–210 °C (0.12 torr); MS, *m/e* 518 (M^+); ^1H NMR δ 3.68 (m, 20 H), 3.52 (s, 4 H), 3.40 (s, 4 H), 1.30 (m, 24 H), 0.88 (t, 6 H, CH_3); ^{13}C NMR δ 72.5 (t), 71.9 (t), 70.8 (t), 46.5 (s, spiro-C), 33.0 (t), 30.5 (t), 27.3 (t), 23.8 (t), 15.2 (q, CH_3); IR (neat) 2860, 2810, 1470, 1360, 1300, 1250, 1110, 990, 950 cm^{-1}. Anal. Calcd for $C_{29}H_{58}O_7$: C, 67.14; H, 11.27. Found: C, 66.92; H, 11.09.

The purities of the crown ethers synthesized were determined to be >95% by gas chromatographic or liquid chromatographic analyses. The major impurity, if any, was the unreacted oligoethylene glycol dichloride. No correlation was, however, made for the impurities in the extraction studies.

Extraction. Sodium, potassium, rubidium, and cesium picrates were prepared according to Wong's method.[18,19] Commercially available 12-crown-4 (Merck), 15-crown-5, and 18-crown-6 (Nisso Co.) were used without further purification. The extraction procedures were similar to those reported by Kimura et al.[3] Equal volumes (10 mL) of a dichloromethane solution of the crown ether (1×10^{-2} M in crown ether unit) and of the aqueous alkali picrate (5×10^{-3} M) were introduced into an Erlenmeyer flask, which was then stoppered and shaken for 40 min at 25.0 ± 0.1 °C in a TAIYO M100L incubator. This period of shaking was long enough to establish the equilibrium between the two phases, since shaking periods as short as 10 or 20 min gave the same results. The mixture was then allowed to stand for at least 2 h at that temperature in order to complete the phase separation, and the picrate concentration in the aqueous phase was determined from its absorption at 354 nm. (ϵ 14 600 M^{-1} cm^{-1}).

In the experiments to determine extraction equilibrium constants (K_{ex}), dichloromethane solutions of the crown ether of various concentrations (0.75×10^{-3} to 1.5×10^{-2} M) and aqueous alkali picrates (3×10^{-3} M) were brought to equilibrium by the same procedures.

The free crown ether concentration in the organic phase, $[CE]_{org}$, was calculated by eq 5, where $[CE]_i$ is the initial concentration

$$[CE]_{org} = [CE]_i - n[M(CE)_nA]_{org} - [CE]_{aq} \qquad (5)$$

of crown ether dissolved in the organic phase. The distribution of free crown ether between the two phases is expressed as follows:

$$CE_{org} \underset{}{\overset{K_D}{\rightleftharpoons}} CE_{aq}$$

$$K_D = \frac{[CE]_{aq}}{[CE]_{org}} \qquad (6)$$

Substitution of $[CE]_{aq}$ in eq 5 by eq 6 gives eq 7, which was actually used to calculate the $[CE]_{org}$ values.

$$[CE]_{org} = ([CE]_1 - n[M(CE)_nA]_{org})/(1 + K_D) \qquad (7)$$

In control experiments, detectable amounts of picrates were not extracted into the organic phase in the absence of crown ethers.

Distribution of 15-Crown-5 and 16-Crown-5. Equal volumes (10 mL) of dichloromethane solutions of the crown ethers (1×10^{-2} and 3×10^{-3} M) and distilled water were brought to equilibrium under the conditions used for extraction. The concentration of the crown ether in the organic phase was determined by gas chromatographic analysis with cyclododecane as an internal standard. The average distribution coefficients, $K_D = [CE]_{aq}/[CE]_{org}$, for 15-crown-5 and 16-crown-5 were determined in several runs to be 0.31 and 0.18, respectively.

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Registry No. 1, 2425-41-4; **2a**, 19249-03-7; **2b** (X = OTs), 37860-51-8; **2b** (X = Cl), 638-56-2; **2c** (X = OTs), 41024-91-3; **2c** (X = Cl), 5197-65-9; **3a**, 69502-28-9; **3b**, 82264-98-0; **3c**, 69502-29-0; **4a**, 55067-00-0; **4b**, 55063-81-5; **4c**, 55063-79-1; **5a**, 69502-43-8; **5b**, 86766-55-4; **5c**, 69502-44-9; **5d**, 86766-59-8; **5e**, 69502-15-4; **6a**, 55471-28-8; **6b**, 86766-56-5; **6c**, 86766-57-6; **6d**, 86766-58-7; **7a**, 294-93-9; **7b**, 33100-27-5; **7c**, 17455-13-9; Na^+, 17341-25-2; K^+, 24203-36-9; Rb^+, 22537-38-8; Cs^+, 18459-37-5; sodium picrate, 3324-58-1; potassium picrate, 573-83-1; rubidium picrate, 23296-29-9; cesium picrate, 3638-61-7; 1,3-propanediol, 504-63-2; 2,2-dimethyl-1,3-propanediol, 126-30-7.

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(18) Wong, K. H.; Ng, H. L. *J. Coord. Chem.* **1981**, *11*, 49.

(19) Caution should be taken in working with the picrate salts since they are heat and shock sensitive when dry, as is picric acid itself.