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THE SYNTHESIS OF SOME AROMATIC CROWN ETHER DERIVATIVES AND THEIR ION-SELECTIVE ELECTRODE PROPERTIES

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Abstract

The synthesis of alkyl, nitro and halogeno derivatives of benzo-15-crown-5, benzo-18-crown-6 and naphtho-15-crown-5 has been reported. Also some novel ester type bis(crown ether)s have been prepared. Some of the compounds have been characterized as electroactive substances in PVC membrane ion-selective electrodes.

INTRODUCTION

Introduction of lipophilic substituents into crown ethers or other ion carriers, applied as electroactive substances in ion-selective membrane electrodes, leads to a decrease of the carrier solubility in water. This is a consequence of an increase in the partition coefficient between water and the membrane of the carrier and especially of its complex with the respective ion.[1] Also, the stability of the membrane and, at the same time, the stability of the electrode increases with the rise in lipophilicity of the carrier.

Mono crown ethers have been applied as electroactive substances in ion-selective electrodes.[2-8] However, due to poor selectivities, the electrodes did not arouse any substantial interest. In our previous paper[9] we have reported the results of investigations on the effect of substituents in aromatic macrocyclic polyethers on potassium ion-selective electrode properties. An increase in lipophilicity improved the selectivities of electrodes. This effect was studied using compounds of systematically increasing lipophilicity.

Now, we wish to present the synthetic routes leading to the previously reported compounds. Based on the previous findings we synthesized and studied new compounds in ion-selective electrodes, expecting improved properties. The compounds are shown in Figs. 1 - 4.

The preparation of crown ether derivatives was reviewed by Bradshaw and Stott[10] and later by Gokel and Korzeniowski.[11] Many benzocrown derivatives have been prepared starting from the respective catechol derivatives. The direct derivatisation of crown ethers seems to be very attractive, especially when the parent crown ethers are easily available.

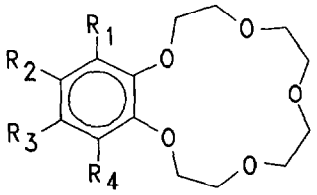

Fig. 1. Derivatives of benzo-15-crown-5

No. of compound	R_1	R_2	R_3	R_4
1	H	H	H	H
2	H	CH_3CO	H	H
3	H	C_2H_5	H	H
4	H	$(CH_3)_3C$	H	H
5	H	$C_9H_{19}CO$	H	H
6	H	$C_{10}H_{21}$	H	H
7	H	$CH_3C(n\text{-}C_4H_9)_2$	H	H
8	H	$(CH_3)_2C(n\text{-}C_{12}H_{25})$	H	H
9	H	$BrCH_2$	$BrCH_2$	H
10	H	CH_3	CH_3	H
11	$BrCH_2$	CH_3	CH_3	H
12	CH_3	CH_3	CH_3	H
13	H	Cl	H	H
14	Cl	Cl	Cl	Cl
15	Cl	Br	Br	Cl
16	H	NO_2	NO_2	H

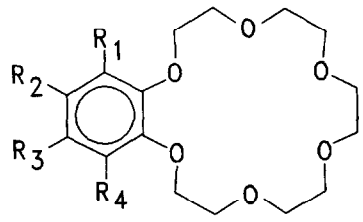

Fig. 2. Derivatives of benzo-18-crown-6

No. of compound	R_1	R_2	R_3	R_4
17	H	H	H	H
18	H	$(CH_3)_3C$	H	H
19	H	$CH_3C(n\text{-}C_4H_9)_2$	H	H
20	H	$BrCH_2$	$BrCH_2$	H
21	H	CH_3	CH_3	H
22	CH_3	CH_3	CH_3	H
23	Cl	Cl	Cl	Cl
24	H	NO_2	NO_2	H

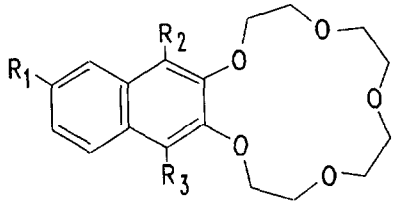

Fig. 3. Derivatives of naphtho-15-crown-5

No. of compound	R_1	R_2	R_3
25	H	H	H
26	$(CH_3)_3C$	H	H
27	$CH_3C(n\text{-}C_4H_9)_2$	H	H
28	$(CH_3)_2C(n\text{-}C_{12}H_{25})$	H	H
29	H	CH_3	CH_3
30	NO_2	H	H
31	H	NO_2	H

The most valuable results are obtained for crown ethers with one benzene ring because, usually, the reaction gives an unambigous product as there is no possibility of isomer formation. Moreover, in the case of synthesis of lipophilic benzocrown ether derivatives, the respective catechol derivatives are not easily or commercially available. Hence, the derivatization of benzocrowns seems to be more effective. 4,5-Dimethylbenzo-15-crown-5, obtained in two steps with the overall yield of 66% by a procedure elaborated in our laboratory, is an example.

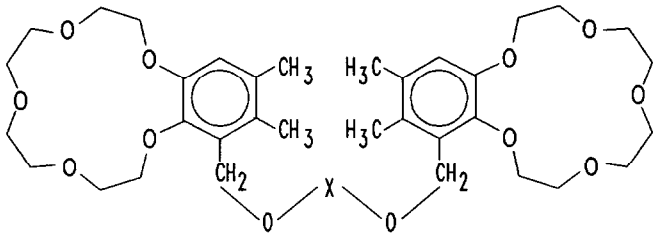

Fig. 4. Bis(crown ether)s

No. of compound

32 X = di-*n*-butylmalonic acid residue

33 X = 1,1-cyclobutanedicarboxylic acid residue

34 X = 1,2-*cis*-cyclohexanedicarboxylic acid residue

RESULTS AND DISCUSSION

Synthesis.

The results of the syntheses have been gathered in Table 1.

We stated previously that benzocrown ethers undergo bromomethylation easily with an excess of formaldehyde in a 40% hydrogen bromide solution in acetic acid. The reaction proceeds at room temperature or at 0°C for 2 days. Practically, two bromomethyl groups are incorporated into one benzene ring. As the previously described procedure[12] is sometimes irreproducible, the reaction has been described again in detail. Bromomethylation was also carried out for benzo-18-crown-6 and naphtho-15-crown-5. In the last case, the 1,4-bis(bromomethyl) derivative was formed mainly but was not isolated in pure form. The reaction mixture was used directly to obtain the dimethyl derivative. The bromomethylation reaction was used subsequently to bromomethylate dimethylbenzo-15-crown-5. This reaction is slower than bromomethylation of benzo-15-crown-5 and results in the formation of 3-bromomethyl-4,5-dimethylbenzo-15-crown-5. The respective

TABLE 1. Properties of crown ether derivatives.

No	Method*	Yield %	M.p. °C	Molecular weight	^{1}H NMR [δ], ppm
4	1a	95	39-41[a]	-	($CDCl_3$): 1.22 (s, 9H); 3.60 - 4.25 (m, 16H); 6.67 - 7.00 (m, 3H)
18	1a	85	35-37[b]	-	($CDCl_3$): 1.20 (s, 9H); 3.60 - 4.27 (m, 20H); 6.76 - 6.96 (m, 3H)
26	1a	43	99-100	374	(d_6-acetone): 1.30 (s, 9H); 3.63 - 4.30 (m, 16H); 7.13 - 7.60 (m, 5H)
7	1b	78	70-71	408	($CDCl_3$): 0.52 - 1.75 (m, 21H); 3,65 - 4.25 (m, 16H); 6.73 (s, 3H)
19	1b	41	oil	452	($CDCl_3$): 0.40 - 1.70 (m, 21H); 3.57 - 4.27 (m, 20H); 6.73 (s, 3H)
27	1b	58	74-76	458	(d_6-acetone): 0.47 - 1.87 (m, 21H); 3.60 - 4.30 (m, 16H); 7.10 - 7.70 (m, 5H)
8	1c	68	oil	478	($CDCl_3$): 0.47 - 1.80 (m, 31H); 3.67 - 4.27 (m, 16H); 6.70(s, 3H)
28	1c	61	43-46	528	(d_6-acetone): 0.43 - 1.80 (m, 31H); 3.60 - 4.20 (m, 16H); 7.00 - 7.67 (m, 5H)
9	2	85	173-176	-	($CDCl_3$): 3.60 - 4.23 (m, 16H); 4.50 (s, 4H), 6.72 (s, 2H)
20	2	95	132-134	-	($CDCl_3$): 3.63 - 4.20 (m, 20H); 4.50 (s, 4H); 6.75 (s, 2H)
10	3	78	64-65	296	($CDCl_3$): 2,07 (s, 6H); 3,50 - 4.17 (m, 16H); 6.18 (s, 2H)
21	3	39	63-64	340	($CDCl_3$): 2.00 (s, 6H); 3.50 - 4.13 (m, 20H); 6.50 (s, 2H)
29	3a	11	oil	346	($CDCl_3$): 2.50 (s, 6H); 3.70 (s, 8H); 3.80 - 4.23 (m, 8H); 7.23 - 7.53 (m, 2H); 7.70 - 8.00 (m, 2 H)
11	4a	98	106-110	-	($CDCl_3$): 2.10 (s, 6H); 3.53 - 4.20 (m, 16H); 4.52 (s,2H); 6.52 (s, 1H)
12	4b	35	91-94	310	(CCl_4): 1.92 (s, 3H); 2.00 - 2.13 (2s, 6H); 3.37 - 4.00 (m, 16H); 6.32 (s, 1H)
22	4c	13	oil	354	($CDCl_3$): 2.00 - 2.23 (2s, 9H); 3.57 - 4.20 (m, 20H); 6.53 (s, 1H)
13	5	55	76-78	302	($CDCl_3$): 3.67 - 4.23 (m, 16H); 6.78 (s, 3H)
14	6	66	103-105	404	($CDCl_3$): 3.70 - 4.33 (m)
23	6	56	88-89	448	($CDCl_3$): 3.60 - 4.37 (m)
15	6	70	118-125[c]	492	($CDCl_3$): 3.63 - 4.33 (m)
16	7a	43	162-165[d]	-	($CDCl_3$): 3.60 - 4.30 (m, 16H); 7.23 (s, 2H)
24	7b	35	89-91	402	($CDCl_3$): 3.55 - 4.40 (m, 20H); 7.28 (s, 2H)
30	8b	38	111-114	363	(d_6-acetone): 3.60 - 4.40 (m, 16H); 7.30 - 7.57 (m, 2H); 7.70 - 8.17 (m, 2H); 8.60 (bs, 1H)
31	8a	14	104-106	363	(d_6-acetone): 3.40 - 4.50 (m, 16H); 7.43 - 7.57 (m, 3H); 7.57 - 8.10 (m, 2H)
32	9	40	oil	832	($CDCl_3$): 0.53 - 1.47 (m, 14H); 1.47 - 2.33 (m, 16H); 3.53 - 4.37 (m, 32H); 5.18 (s, 4H); 6.65 (s, 2H)
33	9	44	oil	760	($CDCl_3$): 1.80 - 2.73 (m, 16H); 3.53 - 4.30 (m, 32H); 5.20 (s, 4H); 6.63 (s, 2H)
34	9	42	oil	788	($CDCl_3$): 1.10 - 1.30 (m, 22H); 3.45 - 4.38 (m, 32H); 5.15 (s, 4H); 6.65 (s, 2H)

* The number of the method corresponds to that in the Experimental Part [a] lit. m.p. 43.5-44.5 °C [14]; [b] lit. m.p. 35-37 °C [14] [c] metastable in the reported range [d] lit. m.p. 168 °C [18]

bromomethyl derivative of dimethylbenzo-18-crown-6 was obtained by a similar procedure. Surprisingly, this reaction is much slower than the reaction with dimethylbenzo-15-crown-5. It runs for two weeks with the final yield of approx. 50%. Bromomethylation of trimethylbenzocrown ethers was unsuccessful.

Bromomethyl and chloromethyl derivatives are very valuable intermediates in the synthesis of many compounds, obtained by nucleophilic substitution of the halogen atom.[13] The dimethyl and trimethyl derivatives of benzocrown ethers, so far undescribed in the literature, have been obtained by reduction of the above compounds with zinc and hydrochloric acid in acetic acid. Dimethylbenzo-15-crown-5 was obtained in a 78% yield and the 18-membered analogue in a 39% yield. Another way of utilising the bromomethyl derivatives is nucleophilic substitution of the bromine atom in the synthesis of bis(crown ether)s.

The *tert*-butylation of benzocrown ethers with *tert*-butanol in phosphoric[12] or polyphosphoric acid is a very facile and effective procedure. *tert*-Butylation of benzo-15-crown-5 afforded *tert*-butylbenzo-15-crown-5 in higher yield than the overall yield in the synthesis of this compound from *tert*-butylcatechol.[14] The *tert*-butylation reaction of naphtho-15-crown-5 is far more complicated. During the reaction performed at 60°C, 6-*tert*-butylnaphtho-15-crown-5 is formed as the main product. It was isolated using column chromatography followed by crystallization. Identification of the position occupied by the *tert*-butyl group in this compound was based on interpretation of NMR spectra.

Introduction of longer alkyl chains by electrophilic substitution using the respective tertiary alcohols and polyphosphoric acid is also easy. Alkyl derivatives 7, 8, 19 have been obtained by this method. Alkylation of naphtho-15-crown-5 proceeds more unequivocally than *tert*-butylation. Products 27 and 28 were obtained in good yields. The lower yield in the case of *tert*-butylation in position 6 of the naphthalene residue as compared with alkylation by higher tertiary alcohols may be interpreted as a consequence of partial *tert*-butylation of the naphthocrown ether, presumably at position 1, followed by splitting of the macrocyclic ring.

The synthesis of bis(crown ether)s was based on a procedure describing the synthesis of benzyl like esters.[15] This procedure is efficient and produces the respective esters in moderate yields. The 3-bromomethyl-4,5-dimethylbenzo-15-crown-5 was also reacted with salts of dicarboxylic acids. The respective diesters were obtained starting from triethylammonium salts of di-*n*-butylmalonic, 1,1-cyclobutane-dicarboxylic and 1,2-*cis*-cyclohexanedicarboxylic acids. A bis(crown ether) with a 2-oxapropylene chain between the monocrowns is formed as a byproduct.

We also synthesized tetrachlorobenzo-15-crown-5 and tetrachlorobenzo-18-crown-6. The reaction was carried out in the absence of light by passing chlorine through a solution of the benzocrown ethers in chloroform. The yields were excellent. The conditions of the reaction were exactly the same as those described for chlorination of dibenzo-18-crown-6.[16] 4,5-Dibromo-3,6-dichlorobenzo-15-crown-5 was obtained in two steps, first by bromination[17]

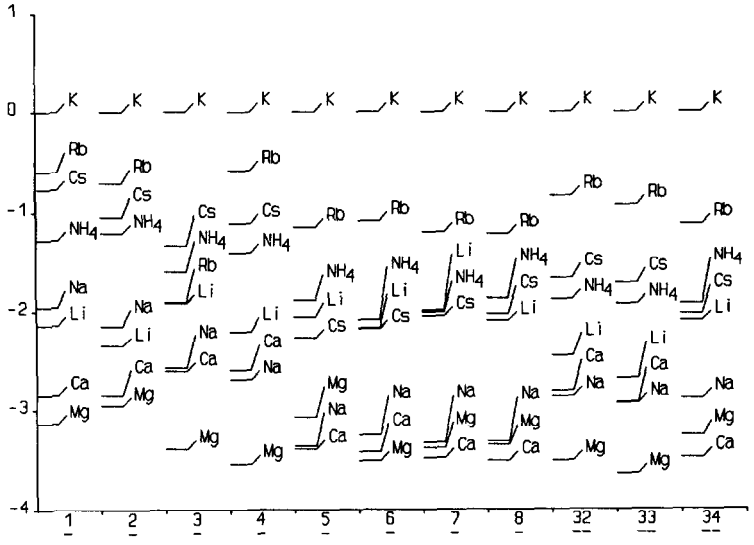

Fig. 5. Log $K_{K,X}$ for benzo-15-crown-5 derivatives

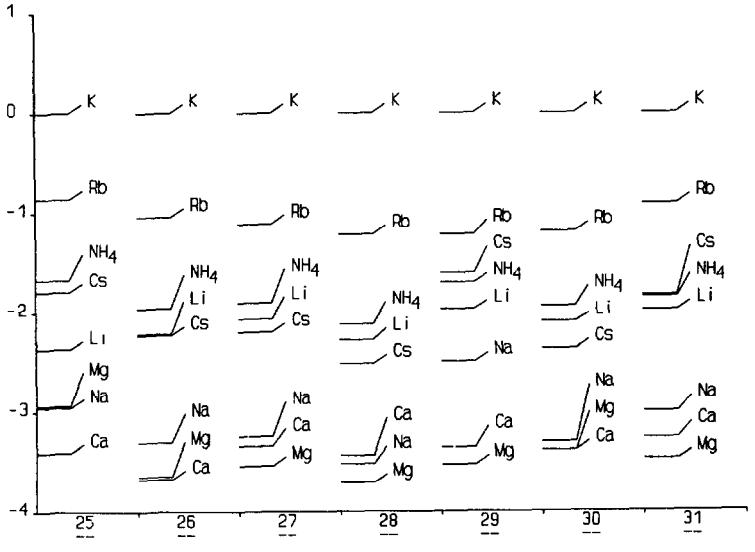

Fig. 6. Log $K_{K,X}$ for naphtho-15-crown-5 derivatives

of benzo-15-crown-5 and then subsequently chlorination. Nitration of benzo-15-crown-5 and benzo-18-crown-6 to obtain dinitro derivatives was effected in fuming nitric acid. The yields of recrystallized products were high. This indicates the stability of the macroring towards fuming nitric acid. Under much milder conditions, the yields were lower.[18] The synthesis of the reported compounds is quite simple and relatively high yields have been obtained.

Ion-Selective Electrode Investigations.

Some novel derivatives, amongst them bis(crown ether)s, have been tested by ion-selective electrodes, confirming our previous findings.[9] The selectivity coefficients, compared with those for some reported compounds, are presented in Figs. 5 and 6.

The electrode properties of the most lipophilic compounds are most promising and confirm the lipophilicity - selectivity relationship. Highly lipophilic substances like 6-(1',1'-dimethyltridecyl)naphtho-15-crown-5 (28, log P = 10.61) are similar in selectivity to many bis(crown ether)s. Such lipophilic compounds may be used in ion-selective electrodes for practical purposes, e.g. in medical applications.

In the case of benzo-18-crown-6 derivatives, no pronounced effect was stated on the K,Na selectivity. However, an effect on the Cs,K selectivity is observed (e.g. log $K_{Cs,K}$ values: 17 1, 18 -1.07, 19 -1,67)

The discovered effect of an increased lipophilicity on the improvement of selectivity of a carrier in an ion-selective membrane is observed, first of all, for the 15-membered macrocyclic compounds suggesting participation of a 2:1 ligand to potassium ion stoichiometry of the species which undergoes distribution between water and the membrane in ion-selective electrodes. On the other hand, it is known that the linkage of two crown ether moieties is connected also with an increase of selectivity. We studied the mutual effect of both phenomena, i.e. linkage and lipophilicity, expecting the best properties for bis(crown ether)s with lipophilic substituents in both subunits shown in Fig. 4.

The selectivity coefficients for these bis(crown ether)s are not as good as expected. They are, in fact, worse than for some of the monocrown ether derivatives. This is probably due to the introduction of polar ester groups (in spite of incorporating lipophilic substituents into the dicarboxylic acid residues and the aromatic rings). The possibility of unfavourable conformation of the bis(crown ether) caused by linkage through the benzene carbon atom in position 3 is not advantageous. A similar problem was also discussed by Kimura.[19]

The lipophilicity - selectivity relation led to the synthesis of compounds with selectivity coefficients similar to those for the best bis(crown ether)s applied in potassium ion-selective electrodes.[20] Introduction of substituents into position 1 and/or 4 of naphtho-15-crown-5 does not increase the selectivity. This may be a result of the stereochemical influence of substituents in position 3 and 6 of the benzocrown[9] and positions 1 and/or 4

of the naphthocrown on conformation of the macrocyclic unit. A positive effect of a nitro group in position 6 of naphtho-15-crown-5 on selectivity is unusual and is similar to that reported by Toke et al.[21] for bis(crown ether)s.

CONCLUSIONS

Lipophilicity is an important factor affecting selectivity. This phenomenon is explained by formation of complexes of different stoichiometry between the crown and potassium (2:1) and sodium (1:1).

Highly lipophilic compounds 5, 6, 7, 8, 26, 27 and 28 exhibit the best selectivities towards potassium with log $K_{K,Na}$ values of approx. -3.3 to -3.5. These values are similar to values for some bis(crown ether)s.

A rise in lipophilicity is also advantageous as it causes an increase of the membrane stability.

Further exploration of the influence of lipophilicity of other compounds on ion-selective electrode properties is in progress.

EXPERIMENTAL

The synthesis of benzo-15-crown-5, benzo-18-crown-6 and naphtho-15-crown-5 was performed according to Pedersen.[14] Benzo-18-crown-6 was additionally purified by synthesis of its complex with acetonitrile. The yields are reported for pure compounds.

Acyl and alkyl derivatives 2, 3, 5 and 6 were obtained acc. to Bradshaw[22] and Tashmukhamedova.[23]

All solutions were dried using anhydrous magnesium sulphate. Column chromatography was performed using silica gel (MN, 50-100 mesh) or alumina (Fluka, type 507C) as indicated in the detailed description of procedures.

NMR spectra were taken on a Varian 60 MHz spectrometer. The mass spectra were recorded on Varian MAT 711 spectrometer using the FD technique.

Electrodes were prepared and tested by procedures described previously.[9] Lithium acetate was used as external electrolyte in the double-junction reference electrode.

1). Synthesis of 4-*tert*-alkylbenzo- and 6-*tert*-alkylnaphthocrown ethers

A mixture of 5 mmoles of benzocrown or naphthocrown ether, 10 mL of polyphosphoric acid and a) 30, b) 20 or c) 12 mmoles of the respective tertiary alcohol was heated for 5 hours at 60°C. After cooling the mixture was diluted with water, the product extracted with chloroform and the organic layer washed with water and dried. The residue, obtained

after removing the solvent, was purified on an alumina column using a) methylene chloride, b) methylene chloride - n-heptane (1:1) or c) n-heptane as eluent. The product was finally crystallized from n-heptane.

2). Synthesis of 4,5-bis(bromomethyl) derivatives of benzocrown ethers

4 Mmoles of benzocrown ether and 0.55 g of paraformaldehyde were dissolved in 6 mL of 40% solution of hydrogen bromide in acetic acid. The reaction mixture was allowed to stand for 1 hour at room temperature and then for 2 days at +5°C. The solvent was then removed under reduced pressure at a temperature not exceeding +50°C. The residue was mixed with a small amount of tetrahydrofuran and crystallized at 0°C for a few hours. The collected crystals were dried under reduced pressure.

3). Synthesis of 4,5-dimethylbenzocrown ethers

A portion of 7 mmoles of bis(bromomethyl)benzocrown ether was suspended in a mixture of 35 mL of glacial acetic acid and 28 mL of concentrated hydrochloric acid. An excess of zinc dust was added during 1 hour. After the vigorous reaction ceased, the reaction mixture with an excess of zinc was allowed to stand at room temperature for 1 day. Finally the reaction mixture was heated at 60°C for 1 hour. The solution was separated, the remaining zinc washed a few times with small portions of water and the combined solutions evaporated under reduced pressure. The residue was diluted with water and the product extracted four times with chloroform. The combined organic solutions were washed with a small amount of water and evaporated under reduced pressure. The residue was extracted with boiling *n*-heptane, preconcentrated by removing the solvent and finally crystallized from cyclohexane.

3a). Synthesis of 1,4-dimethylnaphtho-15-crown-5

A 0.86 g portion of naphtho-15-crown-5 and 0.26 g of paraformaldehyde were dissolved in 7 mL of 40% solution of hydrogen bromide in glacial acetic acid. The reaction was carried out at +5°C for 3 days. The solvent was removed under reduced pressure at a temperature not exceeding +50°C. The residue was dissolved in a mixture of 11 mL of acetic acid and 9 mL of conc. hydrochloric acid and an excess of zinc dust was added during 1 hour. The reaction was carried out for 1 day at room temperature. The mixture was diluted with water after removing an excess of zinc and extracted with chloroform. The residue, obtained after evaporation of the solvent, was passed through a silica gel column. The fraction eluted with chloroform was evaporated and extracted with boiling heptane. 100 mg of an oily product were obtained. It was identified (NMR) as 1,4-dimethylnaphtho-15-crown-5.

4). Synthesis of 3,4,5-trimethylbenzocrown ethers

4a). A mixture of 0.59 g (2 mmol) of dimethylbenzo-15-crown-5 and 0.4 g of paraformaldehyde dissolved in 3 mL of 40% solution of hydrogen bromide in acetic acid was allowed to stand for 5 days at room temperature. The reaction mixture was then diluted with water and left for a few hours at 0°C. The crystalline product was collected, washed with water and dried on air.

4b). To a mixture of 0.76 g of 3-bromomethyl-4,5-dimethylbenzo-15-crown-5 and 3 g of zinc dust in 10 mL of glacial acetic acid was added dropwise during 2 hours 10 mL of conc. hydrochloric acid. On the next day the reaction mixture was diluted with water and the product extracted with chloroform. The residue obtained after removal of the solvent was passed through a column filled with silica gel. The column was washed with cyclohexane and then the product was eluted with benzene. The solvent was evaporated and the residue was crystallized from cyclohexane.

4c). A solution of 4.42 g (13 mmol) of dimethylbenzo-18-crown-6 and 2.4 g of paraformaldehyde in 18 mL of 40% hydrogen bromide solution in glacial acetic acid was left to stand for two weeks at room temperature. The solvent was removed under reduced pressure and the residue diluted with water. The crystalline precipitate consists of approximately a 1:1 mixture of the starting material and 3-bromomethyl-4,5-dimethylbenzo-18-crown-6. This mixture was dissolved in 35 mL of acetic acid and mixed with 10 g of zinc dust. 35 mL of conc. hydrochloric acid were added dropwise during 2 hours and the reaction mixture was left overnight. The separated solution was diluted with water and extracted several times with chloroform. The crude product, obtained after evaporation of the solvent, was chromatographed on silica gel using methylene chloride as eluent. The chromatographic separation on a column was repeated two more times. The product was an oil.

5). Synthesis of 4-chlorobenzo-15-crown-5

This synthesis was carried out similarly to Pedersen.[14] To a mixture of 10 g (70 mmol) of 4-chlorocatechol,[24] 104 mL of *n*-butanol and 5.95 g of sodium hydroxide dissolved in 7 mL of water was added 16 g of 1,11-dichloro-3,6,9-trioxaundecane. The mixture was refluxed for 30 hours, then acidified by addition of 0.55 mL of conc. hydrochloric acid and cooled to 30°C. The solid material which was removed by filtration was washed with methanol. The combined filtrates were evaporated under reduced pressure. The product was extracted from the residue using boiling *n*-heptane.

6). Chlorination of benzocrown ethers

Through an ice-cooled solution of 4 mmoles of the respective crown ether in 10 mL of chloroform a slow stream of chlorine-gas was passed for 4 hours in the absence of light. The mixture was evaporated and the residue was crystallized from a small amount of methanol.

7). Synthesis of 4,5-dinitrobenzocrown ethers

To 2 mL of ice-cooled fuming nitric acid 4 mmoles of the respective crown ether were added. The reaction was carried out a) for 2 hours at room temperature or b) for 24 hours at room temperature. The reaction mixture afforded a crystalline material after dilution with water. The crude products were crystallized from ethanol.

8). Synthesis of nitronaphtho-15-crown-5 ethers

These compounds was obtained under conditions analogous to nitration of benzo-15-crown-5.[12] A mixture of 1 g of naphtho-15-crown-5, 10 mL of chloroform, 9 mL of acetic acid and 2.6 mL of conc. nitric acid was stirred overnight at room temperature. Then the mixture was neutralized with sodium carbonate and the product extracted with chloroform. The solvent was removed and the residue passed through a silica gel column. The products were eluted with a) chloroform and b) with ethyl acetate. The fractions, differentiated by TLC, were separated and crystallized from ethanol. Both compounds were identified as mononitroderivatives of naphtho-15-crown-5.

9). Synthesis of bis(crown ether)s from 3-bromomethyl-4,5-dimethylbenzo-15-crown-5

A mixture of 0.25 mmoles of dicarboxylic acid, 200 mg of 3-bromomethyl-4,5-dimethylbenzo-15-crown-5, 52 mg of triethylamine and 5 mL of ethyl acetate was refluxed for 5 hours. The cooled mixture was washed with water. The aqueous washings were extracted twice with small portions of ethyl acetate. The combined organic extracts were washed with 1 N hydrochloric acid and finally with water. The solvent was removed under reduced pressure and the residue was purified on a column with silica gel. The column was washed with chloroform and the desired product was washed out with ethyl acetate.

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