Lariat Ethers. Synthesis and Cation Binding of Macrocyclic Polyethers Possessing Axially Disposed Secondary Donor Groups

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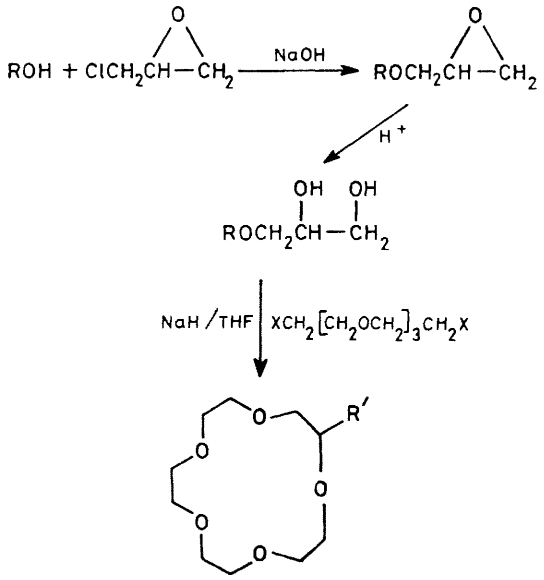
Summary The synthesis and cation binding properties of a series of macrocyclic polyethers which possess ligating arms that enhance cation binding is presented.

Biological processes which involve alkali or alkaline-earth metals often involve organic cation binders.[1] Control of these processes involves (i) cation selectivity, (ii) a critical lipophilic/hydrophilic balance, and (iii) both complexation and release of the active cation. Of the synthetic alkali or alkaline-earth cation-binders that have been reported, the highest stability constants are recorded for Lehn's cryptands,[2] but these molecules are generally difficult to prepare and both complexation and release of the cations tend to be kinetically slow. The acyclic polyethers can be prepared or purchased easily, but these open-chained materials bind cations weakly.[3] For our study of muscle response to cation binders,[4] we have prepared a group of compounds possessing a (crown) macroring and a conformationally mobile arm, capable of offering the complexed cations axially directed binding site(s). By altering the structure of the mobile arm the lipophilic/hydrophilic balance may be adjusted.

Treatment of epichlorohydrin with 2-methoxyphenol (guaiacol) in the presence of NaOH for 16 h at 80 °C afforded 2-methoxyphenyl 2,3-epoxypropyl ether (b.p. 115—116 °C, 0·03 Torr) in 43% yield. Perchloric acid hydrolysis afforded the diol as a white solid (m.p. 66—67 °C) in 81% yield. Treatment of the diol with NaH (2·2 equiv.) and either tetraethylene glycol ditoluene-*p*-sulphonate or tetraethylene glycol dimethanesulphonate in refluxing tetrahydrofuran (THF) (0·5 mol l^{-1}) gave the pure crown (**6**) in 70% yield after column chromatography (alumina, 0—5% Pr^{i}OH–hexanes) (see the Scheme).

Use of the same sequence with 4-methoxyphenol gave the crown (**7**) in only 29% yield (Table). Similarly, the crown (**5**) was obtained (from phenol) in 34% yield but excellent yields were realized when aliphatic arms bearing secondary donor groups were incorporated. For example, a 61% yield of the crown (**10**) (arising from 2-methoxyethanol) was obtained after purification. Slightly lower, but still quite satisfactory, yields were obtained when ligating arms were derived from 2-butoxyethanol (**11**) (55%) or 2-(2-methoxyethoxy)ethanol (3,6-dioxaheptanol) to give the crown (**12**) (48%). We believe that the slightly lower yields observed with the longer aliphatic side chains reflect conformational demands not present in the 2-methoxyphenyl system.



(**1**) R′ = H
(**2**) R′ = CH_2OH
(**3**) R′ = CH_2OMe
(**4**) R′ = CH_2OCOMe
(**5**) R′ = CH_2OPh
(**6**) R′ = $CH_2OC_6H_4OMe$-*o*
(**7**) R′ = $CH_2OC_6H_4OMe$-*p*
(**8**) R′ = CH_2OCH_2Ph
(**9**) R′ = CH_2OCMe_3
(**10**) R′ = $CH_2O[CH_2]_2OMe$
(**11**) R′ = $CH_2O[CH_2]_2O[CH_2]_3Me$
(**12**) R′ = $CH_2O[CH_2]_2O[CH_2]_2OMe$

Scheme.

TABLE Yields and extraction constants for lariat ethers (**2**)—(**12**) obtained *via* the Scheme

Compounds	Yield/%[a]	Extraction constants[b] Na+	K+
(**1**)	29[c]	7 6	5 7
(**2**)	—[d]	2 7	4 4
(**3**)	23	5 1	3 3
(**4**)	—[e]	3 6	5 4
(**5**)	32	4 0	4 3
(**6**)	70	15·7	10 2
(**7**)	29	6 4	10 7
(**8**)	62[f]	7 9	5 8
(**9**)	46	7 3	8 2
(**10**)	61	18 0	13 7
(**11**)	55	11 2	10 9
(**12**)	48	15 7	24 4

[a] Yield is of the material having the expected ^{1}H-n m r and i r spectra and combustion analyses accurate to ±0 3% for C and H [b] Determined in CH_2Cl_2 by the method of Frensdorff and Pedersen (ref 5) [c] Data from F L Cook, L C Caruso, M P Byrne, C W Bowers, D H Speck, and C L Liotta, *Tetrahedron Lett* , 1974, 4029 [d] Yield (50%) is for the hydrogenolysis of (**8**) (10% Pd–C, 60 lb in^{-2}) [e] Yield (90%) is for the acetylation of (**2**) [f] The reaction was conducted under slightly different conditions and may not be directly comparable

An examination of Corey–Pauling–Koltun space-filling molecular models suggested to us that enhanced binding might be observed for compounds which have donor groups correctly aligned for an axial interaction with the complexed metal ions The Na$^+$ extraction constant[5] for (**6**) is more than twice that for the isomer (**7**) and the yields differ by a similar factor The yield difference is no doubt due to differences in the template effect[6] during synthesis

It should be noted that the relative binding abilities of these crowns are reported in CH_2Cl_2 solutions using the extraction method of Pedersen and Frensdorff[5] These numbers will probably be more useful than stability constants when considering applications of these substances in phase transfer catalysis[7] Stability constants in polar solvents will be tabulated in the full report of this work It should also be noted that isolated examples of molecules possessing secondary binding arms have been reported[8] Of these, the most closely related to our own work are the 18-crown-6-molecules prepared by Montanari and Tundo[9] for use as polymer-bound catalysts We believe that using crowns bound to polymer backbones by long ethyleneoxy chains will afford stable, polymer-bound species with enhanced catalytic activity and we are investigating this prospect

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