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NEW LIPOPHILIC IONIZABLE CROWN ETHERS

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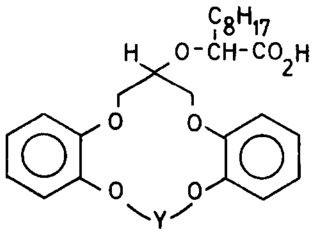
Summary: Two new ionizable crown ethers which bear lipophilic groups are synthesized and found to exhibit selectivity for complexation of K^+ in competitive solvent extractions of alkali metal cations.

For solvent extraction of metal cations from aqueous solutions into organic media, ionizable crown ethers are markedly more efficient than crown ethers without ionizable functional groups. The former have the distinct advantage that transfer of the metal cation to the organic phase does not involve concomitant transport of the aqueous phase anion.[1]

Recently, a number of ionizable crown ethers 1 with two benzene subunits have been prepared[2] and their behavior in solvent extraction of alkali and alkaline earth cations has been extensively studied.[1,3] The presence of a lipophilic group was found to be necessary to confine the complexing agent to the organic phase during contact with a highly alkaline aqueous phase. Measurement of the complexing agent concentration in the organic phase utilized the ultraviolet absorption of the aromatic groups. Although the lipophilic crown ether carboxylic acids 1 may be synthesized from readily-available crown ether alcohols,[4] the three carbon linkage between oxygens in the polyether ring might diminish their cation complexing abilities.[5]

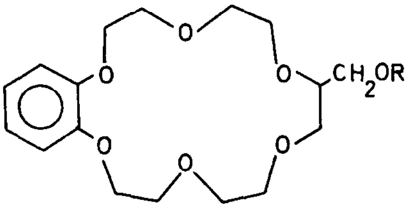


1

Y = CH_2CH_2, $CH_2CH_2CH_2$
$CH_2CH_2OCH_2CH_2$,
$CH_2CH_2OCH_2CH_2OCH_2CH_2$

Therefore, we designed a new family of lipophilic crown ether carboxylic acids which contain a single benzene ring and have bridges of only two carbons between the polyether oxygens. The preparation of two members (5 and 7) of this family is now reported together with preliminary information concerning their selectivity in solvent extractions of alkali metal cations.

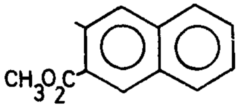
11-Benzyloxymethyl-2,3-benzo-18-crown-6 (2), a key intermediate in the syntheses of 5 and



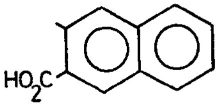
	R
2	$-CH_2C_6H_5$
3	$-H$
4	$-Ts$
5	$-\underset{CO_2H}{CH}(CH_2)_7CH_3$

R

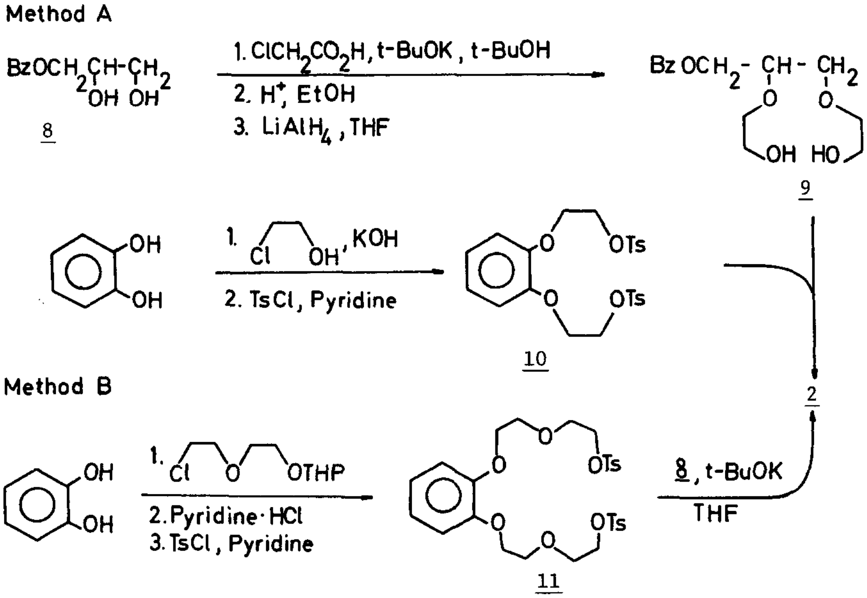
6



7



7 was prepared by two independent routes. Method A.[6] Treatment of catechol with 2-chloroethanol afforded 1,2-bis(2-hydroxyethoxy)benzene,[7] which was subsequently converted to the ditosylate[8] 10. 3,6-Dioxa-4-(benzyloxymethyl)-1,8-octanediol (9), the second component for cyclization, was prepared from 3-O-benzylglycerol[9] (8) by reaction with chloroacetic acid followed by esterification and reduction (Scheme 1). Cyclization of the diol 9 and the ditosylate 10 with KOH in THF-H_2O produced 11-benzyloxymethyl-2,3-benzo-18-crown-6 (2) in 54% yield. Method B. Using the literature procedure,[10] catechol was condensed with 2-(2'-chloroethoxy)ethyl-2"-tetrahydropyranyl ether and subsequently cleaved with pyridine hydrochloride and then treated with p-toluenesulfonyl chloride to afford 1,2-bis(5-hydroxy-3-oxa-1-pentyloxy)benzene ditosylate



Scheme 1

(11). Cyclization of 11 with 3-O-benzylglycerol[9] (8) in THF-t-BuOK gave 2 in 42% yield.[11]

The protecting benzyl group of 2 was removed (H_2, Pd-C) to produce 11-hydroxymethyl-2,3-dibenzo-18-crown-6 (3) in 96% yield.[6]

Reaction of 3 with 2-bromodecanoic acid (NaH, THF) provided the lipophilic crown ether carboxylic acid 5 in 47% yield.[12,13] The hydroxymethyl crown ether 3 was also converted into its tosylate 4 and treated with methyl 3-hydroxy-2-naphthoate[14] and NaH in THF to form the methyl ester 6.[15] Saponification of 6 led to the lipophilic crown ether carboxylic acid 7 in 58% yield[13,15] (based on 3).

The competitive solvent extraction of alkali metal cations from aqueous solutions of alkali metal chlorides into chloroform by crown ether compounds 2, 5 and 7 was examined using the standard technique.[1,3] For all three compounds there was no detectable loss of complexing agent from the chloroform phase to the aqueous phase even when the aqueous phase was highly alkaline (pH = 13). For both ionizable crown ether carboxylic acids 5 and 7, the extraction efficiencies were very high and the selectivities were found to be $K^+ > Rb^+ > Cs^+ > Na^+ \sim Li^+$ with K^+:Na^+ extraction selectivity ratios of 15-20. Total concentrations of alkali metal cations in the organic phase were approximately two orders of magnitude greater for 5 and 7 than in extractions conducted with the unionizable crown ether 2.

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11. A solution of 11 (11.88 g, 20 mmol) in 50 ml of THF was added dropwise to a vigorously stirred and warmed (60°C) solution of 8 (3.64 g, 20 mmol) and t-BuOK (4.93 g, 44 mmol) in 200 ml of THF. The mixture was stirred under nitrogen for 12 h at 60°C and then refluxed for an additional 24 h. After cooling to room temperature, the reaction mixture was filtered, and the filtered solid was washed with CH_2Cl_2. The combined filtrate and washings were evaporated *in vacuo* to afford 10.2 g of a dark-red, viscous oil. Column chromato-

graphy (alumina, petroleum ether-EtOAc, 1:1) gave a yellow oil which was decolorized with Norite A to provide 3.60 g (42%) of 2 as a thiçk, colorless oil. IR (neat) 1120 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$): δ3.40-4.43 (m, 21H), 4.52 (s, 2H), 6.89 (s, 4H), 7.30 (s, 5H).

12. Using a published procedure,[2] the reaction of 3 (4.10 g, 12 mmol), 2-bromodecanoic acid (4.52 g, 18 mmol), and 50% NaH in mineral oil (3.93 g, 82 mmol) was conducted in THF. After workup in which an extraction of unreacted 3 was omitted, 6.7 g of crude product was obtained. This material was dissolved in EtOAc-MeOH (5:1) and filtered through a short column of alumina to remove unreacted 3 (0.35 g recovered from the filtrate). Elution with MeOH and evaporation of the solvent *in vacuo* gave 4.0 g of crude product which was chromtographed on silica gel using EtOAc-MeOH (3:1) and yielded 3.20 g of very viscous, slightly yellow oil. The oil was dissolved in CH_2Cl_2, washed with 6 N HCl and then several times with water. After drying, the solvent was removed *in vacuo* to produce 2.90 g (47%) of 5 as a pale yellow viscous oil.[13] IR (neat) 3600-2400 (COOH), 1735 (C=O), 1130 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$): δ0.65-2.1 (m, 17H), 3.4-4.5 (m, 22H), 6.90 (s, 4H), 8.60 (broad s, 1H).
13. Satisfactory elemental analysis for 5 (as a 0.5 hydrate) and 7 was obtained.
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15. Under nitrogen, NaH (50% in mineral oil, 0.42 g, 8.7 mmol) was washed with pentane and a solution of methyl 3-hydroxy-2-naphthoate[14] (1.54 g, 7.6 mmol) in 20 ml of THF was added. After stirring at room temperature for 1 h, a solution of 4 (3.80 g, 7.65 mmol) in 20 ml of THF was added dropwise and the resulting mixture was refluxed for 3 days. After evaporation of THF and addition of CH_2Cl_2, the mixture was filtered. The solid residue was dissolved in water and extracted with CH_2Cl_2. The filtrate and extracts were combined, washed with water, dried, and evaporated *in vacuo* to give 3.7 g of crude 6.
The crude ester 6 (1.10 g, 1.9 mmol) was dissolved in 10 ml of EtOH and 0.5 g of NaOH dissolved in 2.5 ml of water was added. The mixture was refluxed for 4 h and the solvent was removed *in vacuo*. Water was added and the resulting solution was extracted with CH_2Cl_2. The aqueous layer was acidified with 6 N HCl and extracted three times with CH_2Cl_2. The combined extracts were washed with water, dried, and evaporated *in vacuo* to produce 0.92 g (90%) of 7 as a viscous oil.[13] IR (neat): 3600-2200 (COOH), 1732 (C=O), 1128 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$): δ3.6-4.6 (m, 21H), 6.87 (s, 4H), 7.2-8.1 (m, 6H), 8.70 (s, 1H).

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