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FUNCTIONALIZED LARGE RING CROWN ETHERS

Byungki Son, Bronislaw P. Czech, David A. Babb and Richard A. Bartsch*

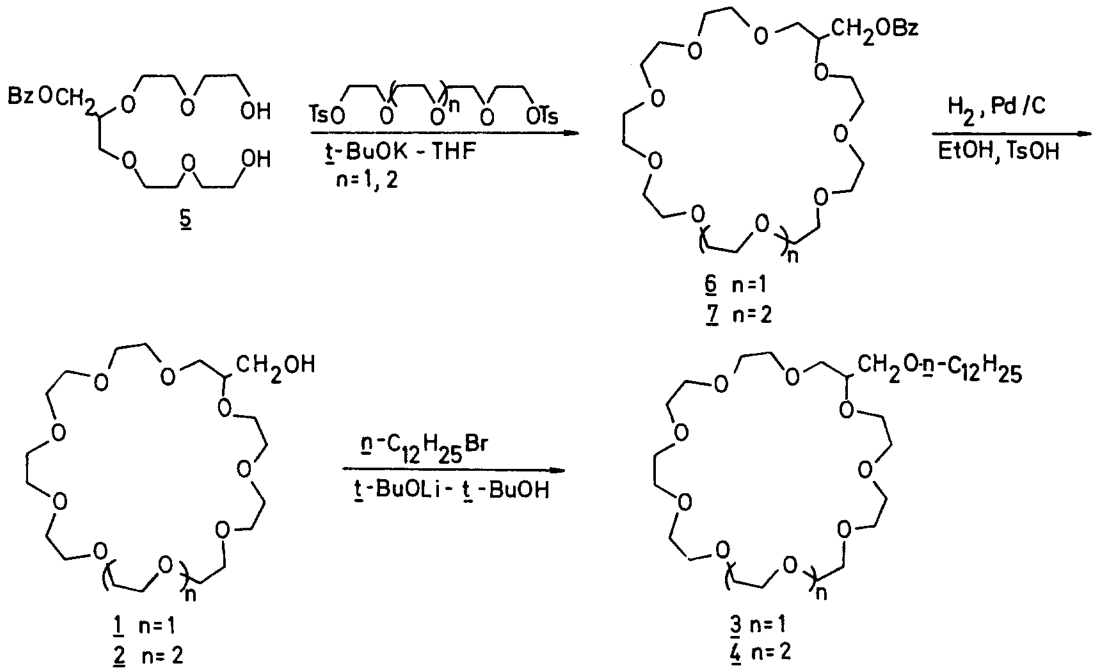
Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

Summary: Reactions of 3,6,9,12-tetraoxa-7-(benzyloxymethyl)-1,14-tetradecanediol with appropriate ditosylates followed by hydrogenolysis produce hydroxymethyl-27-crown-9 and hydroxymethyl-30-crown-10. Alkali metal cation complexation by lipophilic dodecyl ether derivatives of these crowns is examined.

The synthesis of crown ethers with pendant functional groups continues to receive considerable attention. Alternative preparative routes to the versatile hydroxymethyl derivatives of 12-crown-4,[1,2] 15-crown-5,[1-4] and 18-crown-6[1,2,4-8] have been described. The syntheses of hydroxymethyl-21-crown-7 and hydroxymethyl-24-crown-8 have recently been reported.[9] Even larger ring crown ethers are of interest due to their resemblance to naturally-occurring cyclic ionophoric antibiotics. Nevertheless the synthesis of 27-crown-9 itself has not been reported and the preparation of 30-crown-10 appears only in the patent literature.[10] Known functionalized derivatives of 27-crown-9 and 30-crown-10 are limited to a few benzo and dibenzo crown compounds.[11-13] In this paper we describe the syntheses of hydroxymethyl-27-crown-9 (1) and hydroxymethyl-30-crown-10 (2) and their lipophilic dodecyl ether derivatives 3 and 4, respectively.

Reaction of 3,6,9,12-tetraoxa-7-(benzyloxymethyl)-1,14-tetradecanediol(5),[14] a key intermediate in the syntheses of both crowns, with tetraethyleneglycol ditosylate and t-BuOK afforded benzyloxymethyl-27-crown-9 (6)[15] in 38% yield. Hydrogenolysis of 6 over Pd/C in the presence of catalytic p-toluenesulfonic acid gave a 97% yield of hydroxymethyl-27-crown-9 (1).[16] Treatment of the hydroxymethyl crown 1 with n-dodecyl bromide with t-BuOLi as the base[2] provided n-dodecyloxymethyl-27-crown-9 (3)[17] in 36% yield. Similarly, reaction of 5 with pentaethyleneglycol ditosylate and t-BuOK produced benzyloxymethyl-30-crown-10 (7)[18] in 35% yield. Debenzylation of 7 afforded an 86% yield of hydroxymethyl-30-crown-10 (2).[19] Coupling of 2 with n-dodecyl bromide gave dodecyloxymethyl-30-crown-10 (4)[20] in 57% yield. As might be anticipated, the large ring crown ether compounds 1-4, 6, 7 were all found to be extremely hygroscopic.

In a typical experiment, diol 5 (12.0 mmol) was dissolved in 350 ml of dry THF under nitrogen and t-BuOK (24.4 mmol) was added. The resultant mixture was stirred for 1 h and a solution of the appropriate ditosylate (12.0 mmol) in 150 ml of dry THF was added dropwise during a



4 h period. The reaction mixture was stirred at room temperature for 190 h, filtered, and the solvent was evaporated *in vacuo* to give a crude oil which was purified by column chromatography on neutral alumina (Et_2O-EtOH, 95:5). The benzyloxymethyl crown ether (3.5 mmol) was dissolved in EtOH (100 ml) and 10% Pd/C (100 mg/g of crown ether) and 0.05 g of *p*-toluenesulfonic acid were added. The mixture was shaken under 1 atmosphere of hydrogen at room temperature for 19 h, the catalyst was filtered, and the filtrate was evaporated *in vacuo*. The residual oil was chromatographed on neutral alumina using EtOAc-MeOH (96:4) to yield the hydroxymethyl crown ether. After reaction of the hydroxymethyl crown ether (1.5 mmol) with *n*-dodecyl bromide (2.0 mmol) and *t*-BuOLi (2.0 mmol) in *t*-BuOH (5 ml) at 70°C for 84 h, the solvent was removed *in vacuo*. Water (20 ml) was added to the residue and the mixture was neutralized with 5% HCl and extracted with CH_2Cl_2 (5 X 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was evaporated *in vacuo*. The residual oil was purified by column chromatography on neutral alumina (Et_2O-EtOH, 96:4) to produce the dodecyloxymethyl crown ether.

Complexing abilities of the lipophilic dodecyloxymethyl-27-crown-9 (3) and dodecyloxymethyl-30-crown-10 (4) for alkali metal cations were evaluated by the picrate extraction method. An aqueous 0.015 M solution of lithium, sodium, potassium, rubidium or cesium picrate was extracted with an equal volume of a 0.015 M solution of 3 or 4 in $CDCl_3$. The percent of extraction of the alkali metal picrate into the organic phase, extraction constant (K_{ex}), association constant (K_a), and free energy of association ($-\Delta G°$) were calculated from the UV absorbance of the picrate anion in the organic phase according to published methods.[21,22] Data are presented in the Table.

Table. Complexation of Alkali Metal Picrates by 3 and 4 in $CDCl_3$.

Crown Ether	M^+ of M^+Pic^-	% extraction into $CDCl_3$	log K_{ex} [a]	log K_a [a]	$-\Delta G°$ (kcal/mole)
3	Li	1.6	1.88	4.73	6.4
3	Na	11.2	2.85	5.61	7.6
3	K	42.9	4.01	6.60	9.0
3	Rb	33.9	3.72	6.06	8.2
3	Cs [b]	5.6	3.42	5.69	7.7
4	Li	0.6	1.40	4.25	5.8
4	Na	3.3	2.21	4.97	6.7
4	K	45.3	4.09	6.68	9.1
4	Rb	48.0	4.15	6.52	8.9
4	Cs [b]	7.7	3.59	5.86	8.0

[a] The estimated uncertainties in K_{ex} and K_a values are ± 10%. [b] For these extractions 0.005 M cesium picrate and crown ether were used.

Based upon these single ion extraction experiments, alkali metal cation complexation selectivities for dodecyloxymethyl-27-crown-9 (3) and dodecyloxymethyl-30-crown-10 (4) are found to be $K^+ > Rb^+ > Cs^+ \sim Na^+ > Li^+$ and $K^+ > Rb^+ > Cs^+ > Na^+ > Li^+$, respectively. In the x-ray crystal structure of potassium ion complexed by dibenzo-30-crown-10[23] it is found that the polyether ring is folded to provide three dimensional coordination of the cation. The observed preferential complexation of potassium cations by the large ring crown ethers employed in the present study suggests similar wrapping of 3 and 4 around potassium cations.

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15. Data for 6: Colorless oil; ^{1}H NMR ($CDCl_3$, δ) 3.68 (s, 37H), 4.52 (s, 2H), 7.29 (s, 5H); IR (neat, cm^{-1}) 1104 (C-O); MS 516 (M^+). Elem. Anal. Calcd. for $C_{26}H_{44}O_{10}$: C, 60.45; H, 8.58. Found: C, 60.39; H, 8.42.

16. Data for 1: Colorless oil; ^{1}H NMR ($CDCl_3$, δ) 3.69 (s, 38H); IR (neat, cm^{-1}) 3452 (O-H), 1110 (C-O); MS 426 (M^+). Elem. Anal. Calcd. for $C_{19}H_{38}O_{10}$: C, 53.51; H, 8.98. Found: C, 53.34; H, 8.92.

17. Data for 3: Colorless oil; ^{1}H NMR ($CDCl_3$, δ) 0.87 (t, 3H), 1.0-1.7 (m, 20H), 3.2-4.0 (m, 39H); IR (neat, cm^{-1}) 1105 (C-O). Elem. Anal. Calcd. for $C_{31}H_{62}O_{10}$: C, 62.60; H, 10.51. Found: C, 62.93; H, 10.78.

18. Data for 7: Colorless oil; ^{1}H NMR ($CDCl_3$, δ) 3.66 (s, 41H), 4.53 (s, 2H), 7.31 (s, 5H); IR (neat, cm^{-1}) 1100 (C-O); MS 560 (M^+). Elem. Anal. Calcd. for $C_{28}H_{48}O_{11}\cdot 0.75\ H_2O$: C, 58.57; H, 8.69. Found: C, 58.61; H, 8.65.

19. Data for 2: Colorless oil; ^{1}H NMR ($CDCl_3$, δ) 3.67 (s, 42H); IR (neat, cm^{-1}) 3452 (O-H), 1116 (C-O); MS 470 (M^+). Elem. Anal. Calcd. for $C_{21}H_{42}O_{11}$: C, 53.60; H, 9.00. Found: C, 53.42; H, 8.87.

20. Data for 4: Colorless oil; ^{1}H NMR ($CDCl_3$, δ) 0.88 (t, 3H), 1.0-1.7 (m, 20H), 3.2-4.0 (m, 43H); IR (neat, cm^{-1}) 1128 (C-O). Elem. Anal. Calcd. for $C_{33}H_{66}O_{11}$: C, 62.04; H, 10.41. Found: C, 61.79; H, 10.35.

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