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SYNTHESIS OF BIS(BROMOMETHYL) DIMETHYL CROWN ETHERS AND COMPLEXATION PROPERTIES OF THEIR DERIVATIVES HAVING ELECTRON-DONATING SIDEARMS

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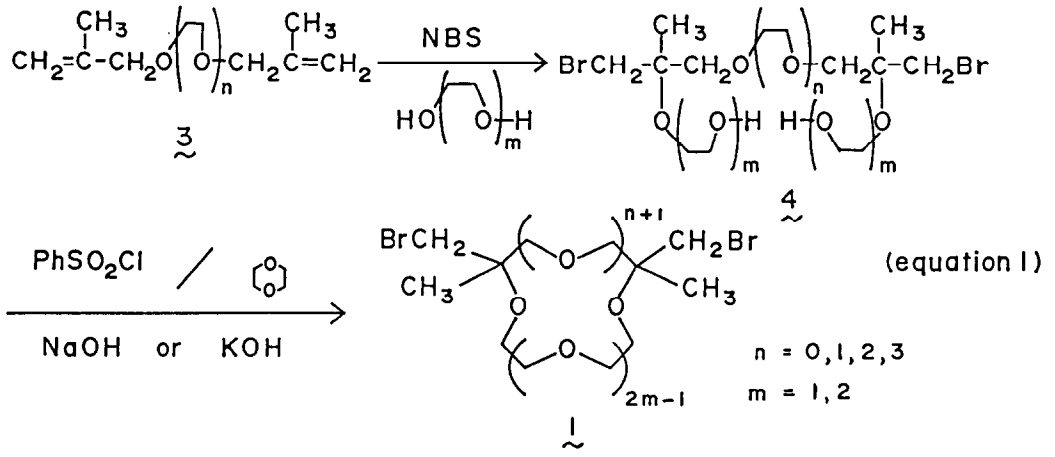
Summary: Several bis(bromomethyl) dimethyl 15-crown-5, 18-crown-6, and 21-crown-7 were prepared according to two methods without protecting reactive bromo substituents. Cis and trans isomers of 1a are separated and the structures are inferred by considering the complexation property of their derivatives having electron-donating sidearms toward sodium and potassium cations.

Reactive crown ethers are potentially important key intermediates of highly functionalized derivatives such as crown polymers,[1,2] bis(crown ether)s,[3,4] lariat ethers,[5,6] and synthetic ionophores.[7-9] As introduction of plural reactive groups to the crown ring is expected to stimulate further applications, we now report convenient synthetic routes for preparing novel crown ethers having two bromomethyl groups.

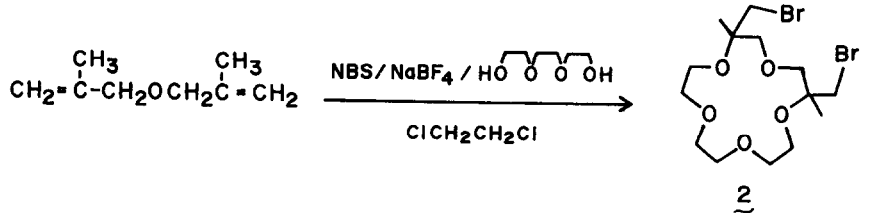


Bis(bromomethyl) dimethyl crown ethers(1) were prepared by the cyclization of the corresponding oligoethylene glycols(4), which were obtained by the bromoalkoxylation reaction[10] of bis(2-methylallyl) ethers(3), in the presence of an appropriate template cation according to the equation 1.

The typical cyclization procedure is as follows. A mixture of 4a (9.04 g, 0.02 mol) and benzene sulfonyl chloride(3.88 g, 0.022 mol) in dioxane(100 ml) was added dropwise to a stirred suspension of NaOH in dioxane(100 ml) over a period of 5 h at 50°C and the mixture was stirred at that temperature for another 5 h. The insoluble matter was removed by filtration and the solvent was evaporated off. Water was added to the residue and extracted with dichloromethane. Further purification was carried out by a silica gel column chromatography(2-5 vol.% acetone in hexane) and a Kugelrohr distillation to afford 2,9-bis(bromomethyl)-2,9-dimethyl-15-crown-5(1a) as a slightly yellow oil. 1a(n=1, m=1): Yield 41%; B.p. 140°C/0.01 Torr(Kugelrohr); n_D^{20} 1.5115; ^{1}H NMR(CCl_4, δ) 1.23(s, 6H) and 3.23-3.61(m, 20H); MS(m/e) 436, 434, 432, 355(2), 353(2), 139(42), 137(49), 115(32), 101(30), 73(62), 71(43), 55(69), 45(96), and 43(100); IR(neat) 2890(s), 1460(m), 1380(m), 1300(m), 1260(m), 1200(m), 1140(s), 970(m), and 680(m) cm^{-1}. Found: C, 38.35%; H, 6.32%; Br, 36.43%. Calcd for $C_{14}H_{26}O_5Br_2$: C, 38.73%, H, 6.04%; Br, 36.81%. 1b(n=0, m=2): Yield 31%; B.p. 150°C/0.01 Torr(Kugelrohr); n_D^{20} 1.5067. 1c(n=2, m=1): Yield 25%; B.p. 150°C/0.01 Torr(Kugelrohr); n_D^{20} 1.5055. 1d(n=1, m=2): Yield 19%; B.p. 160°C/0.01 Torr(Kugelrohr); n_D^{20} 1.5010. 1e(n=3, m=1): Yield 20%; B.p. 170°C/0.01 Torr(Kugelrohr); n_D^{20} 1.5025.

The difference in reactivity as a leaving group between the bromo group and the sulfonate group generated *in situ* under the reaction conditions used for the cyclization makes possible the sythesis of objective compounds.

On the other hand, 2,6-bis(bromomethyl)-2,6-dimethyl-15-crown-5(2), which is a positional isomer of 1a, was prepared by bromoalkoxylation reaction of bis(2-methylallyl) ether with triethylene glycol in the presence of a template ion(Na^+) according to the equation 2. Yield 10%; a colorless liquid; B.p. 130°C/0.01 Torr(Kugelrohr); n_D^{20} 1.5130; ^{1}H NMR($CDCl_3$, δ) 1.25(s, 3H), 1.29(s, 3H), and 3.42-3.80(m, 20H); MS(m/e) 436, 434, 432, 355(14), 353(14), 89(42), 87(47), 73(42), 71(46), 55(69), 45(100), and 43(89). Found: C, 38.53%; H, 6.06%; Br, 37.10%. Calcd for $C_{14}H_{26}O_5Br_2$: C, 38.73%; H, 6.04%, Br, 36.81%.



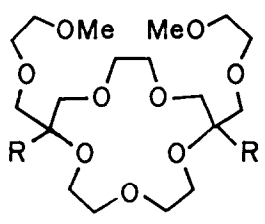
(equation 2)

2

All compounds obtained by these synthetic methods were observed to be mixtures of cis(meso) and trans(±) stereoisomers by ^{1}H NMR (in the case of 1b and 2) or ^{13}C NMR. So, we attempted the separation of two stereoisomers of 1a by a silica gel column chromatography. The success of the separation was determined by ^{13}C NMR examination($CDCl_3$) of the each fraction. A isomer, which was eluted before B isomer, and B isomer showed the methyl signals at 19.675 and 19.944 ppm, respectively.

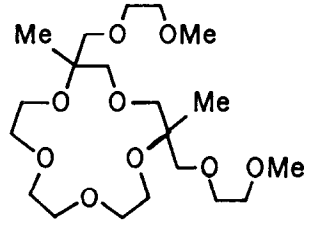
The reaction of 1a or 2 with sodium alkoxide of ethyelene glycol monomethyl ether at 120°C for 24 h almost quantitatively gave 5 or 6, respectively.

Recently, the coordination mode of the electron-donating sidearm of 15-crown-5 was disclosed to display interesting characteristics in response to the size of Na^+ and K^+.[11] In order to assign both isomers of 1a, we examine the complexation properties for their derivatives(5) toward Na^+ and K^+ and summarize them with the data of some reference crown ether derivatives in the Table.



5 : R = Me

7 : R = H



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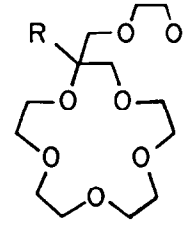

8 : R = Me

9 : R = CH_2O OMe

Table: Binding Data[a] for Crown Ether Derivatives

Compound	log K'(Na^+)	log K'(K^+)	K'(Na^+)/K'(K^+)
1a(Mixture)	2.81	2.38	2.7
2 (Mixture)	2.56	2.13	2.7
5 (from A)	3.89	3.36	3.4
5 (from B)	4.22	3.61	4.1
5 (Mixture)	4.11	3.54	3.7
6 (from A)	4.15	3.37	6.0
6 (Mixture)	4.36	3.58	6.0
7 (Mixture)	3.09	3.13	0.9
8	(3.87)[b]	(3.42)[b]	2.8
9	(3.84)[b]	(3.44)[b]	2.5

a) determined by using ion-selective electrode; in MeOH; 25°C b) ref. 11

Since the size of K^+ is much larger than the cavity size of 15-crown-5 and the cation is considered to be apart from the plane of polyether oxygen, one can expect the effective coordination of only one sidearm in the case of trans isomer. In other words, the stability constant of trans isomer toward K^+ is expected to be similar to that of 8 and 9. In addition, cis isomer may show a higher stability constant toward K^+ than trans isomer because of the effective coordination of two sidearms. According to the consideration mentioned above, the data of stability constants for 5, 8, and 9 (see the Table) strongly suggest that 5 (from A) and 5 (from B) are trans and cis isomers, respectively, although a definate conclusion must wait for further additional informations such as a X-ray analysis. Anyway, 5 and 6 having methyl groups at the pivot positions displayed over ten fold stability constants for Na^+ in comparison with that of the corresponding analog having no methyl groups (7)[12], possibly because of the restriction in the movement of the electron-donating sidearms.[6] Also, a higher Na^+/K^+ selectivity was observed in 5 and 6 in accordance with the case of methyl lariat ethers.[6,11] Consequently, it is clear that plural electron-donating sidearms can coordinate Na^+ and K^+ and this approach is expected to be useful for the molecular design of novel synthetic host molecules for specific cations.

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12. This compound 7 was prepared by the intermolecular condensation reaction of 7,14-dihydroxy-2,5,9,12,16,19-hexaoxaeicosane, which was prepared from ethylene glycol diglycidyl ether and ethylene glycol monomethyl ether, with diethylene glycol ditosylate in *t*-BuOH/*t*-BuONa system. Yield 80%. B.p. 150°C/0.01 Torr(Kugelrohr); ^1H NMR($CDCl_3$, δ) 3.36(s, 6H) and 3.48-3.88(m, 30H).

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