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New Application of Crown Ethers. III.[1] Synthesis of 4′-Hydroxybenzocrown Ethers and Their Bis(benzocrown ether)s Linked by Poly(oxyethylene) Chain

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Baeyer-Villiger oxidation of 4′-acetylbenzocrown ethers followed by alkaline hydrolysis was proved to be a convenient route to 4′-hydroxybenzo-15-crown-5 and -18-crown-6, which formed air-stable hydrated crystals containing three and one mole of water, respectively, on crystallization from the solvent containing a small amount of water. New bis(benzocrown ether)s, connected by poly(oxyethylene) chain, were obtained in good yields by the reaction of the sodium salts with the ditosylates of di-, tri-, tetra-, and pentaethylene glycol.

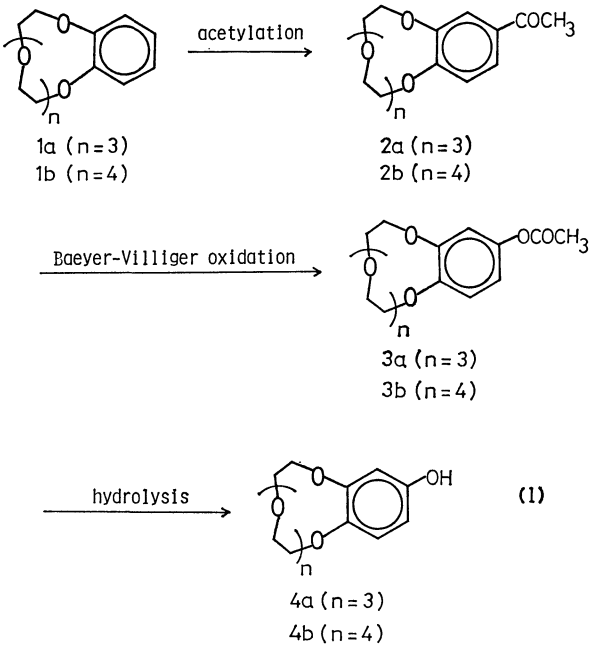
Various substituted benzocrown ethers have been synthesized by either electrophilic substitution to benzocrown ethers or crown ring forming cyclization of substituted catechols. The substituents of the compounds not only serve to modify the nature of complexation with cations, but also have been successfully utilized for preparing other functionalized benzocrown ethers, such as 4′-vinylbenzocrown ethers[2] and several bis(benzocrown ether)s.[3,4] Hydroxybenzocrown ethers are thought to be interesting starting materials for the latter purpose because of the reactive aromatic ring and of the utility of the phenolic hydroxyl group. Thus, various bis(benzocrown ether)s and long-chain substitued benzocrown ethers could be obtained by the reaction of the sodium salts with α,ω-di-, and monotosylates of polymethylene or poly(oxyethylene) chain, respectively. This paper describes the synthesis of 4′-hydroxybenzocrown ethers and the bis(benzocrown ether)s being linked with tri-, tetra-, penta-, and hexa-(oxyethylene) chain.

Results and Discussion

4′-Hydroxybenzocrown Ethers. Successful preparation of 4′-hydroxybenzo-15-crown-5 (**4a**) and -18-crown-6 (**4b**) were achieved by the following route (Eq. 1). Hydrolysis of the diazonium salts of 4′-aminobenzocrown ethers in aqueous acid or in the presence of copper catalyst[5] afforded the mixture being too complex to allow isolation, and oxidation of benzocrown ethers with $Tl(OCOCF_3)$[6] led to decomposition of the starting materials.

4′-Acetylbenzocrown ethers (**2**) were prepared by acetylation of the corresponding benzocrown ethers (**1a** and **1b**) with acetic anhydride–polyphosphoric acid in acetic acid at 45 °C for 3 h. Yields of **2a** and **2b** under the optimized reaction conditions were 83% and 80%, respectively.[7] Use of aluminium chloride as the catalyst was proved to be unpractical because of deactivation of the catalyst, and in the reaction of **1a**, **1a**–aluminium chloride (1:1) complex, stable in protic solvent, could be isolated.[7]

Baeyer-Villiger oxidation[8] of **2** with peracetic acid at 30—32 °C for 5 h affords 4′-acetoxybenzocrown ethers (**3**) in high yields. The crude products were purified by either extraction with hot heptane or chromatography on a short alumina-silica gel column (THF or $CHCl_3$) to give white crystals.



(1)

Hydrolysis of **3** to 4′-hydroxybenzocrown ethers (**4**) was carried out with aqueous sodium hydroxide at 40—50 °C for 3 h under nitrogen atmosphere. The crude product (**4a**) from **3a** was immediately precipitated as fine needles when the reaction mixture was acidified. In cases where the precipitation did not occur due to inadequate concentration of the product in the acidified solution, the product could be collected by extraction with chloroform. The crude product was further purified by recrystallization from a mixed solvent (THF–$CHCl_3$) containing a small amount of water to give white needles. The crystals were shown to contain three moles of water by measurement of loss of weight under vacuum at 110 °C for 3 h, and also by elemental analysis. Since **4b** did not separate as precipitate under the similar treatment, the product was taken up with chloroform and recrystallized from wet diethyl ether to give flat plates containing one mole of water. The monohydrated crystals showed a single melting point, 52.3—52.6 °C, without any visual transition of the crystal form,

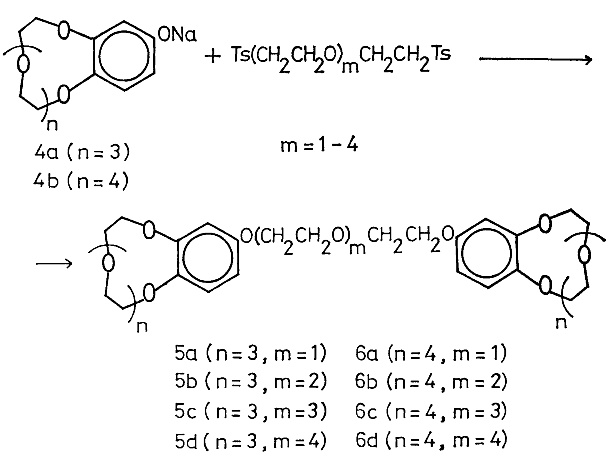
TABLE 1. PREPARATION OF α,ω-BIS(4′-BENZOCROWN ETHER)POLYETHYLENEOXYETHERS

Crown	*n*	*m*	Yield/%	Mp/°C	Found		Calcd (%)		
					C	H	C	H	
5a	3	1	67	73.0—74.5	60.01	7.27	60.18	7.26	($C_{32}H_{46}O_{13}$)
5b	3	2	83	88.9—92.2	59.64	7.49	59.81	7.38	($C_{34}H_{50}O_{14}$)
5c	3	3	21[a)]	73.0—74.0	59.42	7.51	59.49	7.49	($C_{36}H_{54}O_{15}$)
5d	3	4	63	liquid	58.93	7.60	59.21	7.58	($C_{38}H_{58}O_{16}$)
6a	4	1	52	74.6—77.5	58.97	7.48	59.49	7.49	($C_{36}H_{54}O_{15}$)
6b	4	2	78	69.5—72.0	58.82	7.56	59.21	7.58	($C_{38}H_{58}O_{16}$)
6c	4	3	50	52.0—54.5	58.67	7.65	58.96	7.67	($C_{40}H_{62}O_{17}$)
6d	4	4	58	liquid	58.34	7.64	58.73	7.74	($C_{42}H_{66}O_{18}$)

a) 1,8-Dichloro-3,6-dioxaoctane (triethylene glycol dichloride) was used in 1-butanol. The bis(benzocrown ether) was separated by HPLC since the recation product contained butyl ether of 4′-(9-hydroxy-1,4,7-trioxanonyl)-benzo-15-crown-5.

and were easily dehydrated under vacuum at room temperature for a few hours to afford a white solid. On the other hand, the hydrated crystals of **4a** showed two stage of transition of the crystal form at 43—47 °C and 75—78 °C, and completely melted at 100—103.0 °C (mp of the dehydrated crystals). Since, when being dehydrated, both **4a** and **4b** are liable to oxidized by air and readily impart a brown color, it is preferable to store in their hydrated forms and under nitrogen atmosphere. Although Cram and his coworkers[9)] recently described a monohydrated crown ether (a complex), such a trihydrated crown ether has not been reported.

Bis(benzocrown ether)s. Bis(benzocrown ether)s containing crown ether moieties at the two ends of a polymethylene or poly(oxyethylene) chain are known to have increased tendency of loose ion pair formation, and thus are expected to be effective in enhancing the reactivity of anionic species.[3)] Bis(benzocrown ether)s linked by ether linkages with poly(oxyethylene) chain are expected to be more resistant to the action of base (or acid)[4b)] than the known bis(benzocrown ether)s bridged by ester linkages,[3,4a)] and could be favorably utilized to various crown ether assisted reactions. Preparation of the bis(benzocrown ether)s were readily performed by the reaction of *in-situ* prepared sodium salts of **4a** or **4b** (from their dehydrated forms) with two molar equivalents of ditosylates of di-, tri-, tetra-, and pentaethylene glycol in THF (or dioxane–DMSO (10%)) (Eq. 2).



The crude products were chromatographed through an alumina column ($CHCl_3$), and recrystallized from ether–methanol (40:1). The purity and the structures of the products were confirmed by HPLC, IR, NMR, and elemental analysis. The results are summarized in Table 1, but the optimization of the yields has not been carried out.

Features of complex formation with cations and in S_N2 type reactions of these compounds are being investigated.

Experimental

Materials. Benzocrown ethers[10)] (**1a** and **1b**) and the ditosylate[11)] of di-, tri-, tetra-, and pentaethylene glycol were prepared according to the published procedures, respectively. Peracetic acid (9%) in acetic acid was prepared according to the published procedure.[12)]

*4′-Acetoxybenzocrown Ethers (**3a** and **3b**).* Typical procedure was as follows. To the acetic acid solution of **2** (4.8 mmol), 8.0 g (9.5 mmol) of 9% peracetic acid was added dropwise over a 30 min period at 30—32 °C, and further stirred for 5 h. Longer reaction time caused a decrease of product yield. After aq sodium thiosulfate was added to the reaction mixture to decompose the excess peracetic acid, the solution was neutralized to pH 6 by the addition of Na_2CO_3, and extracted with chloroform. The chloroform layer was dried ($MgSO_4$), and the solvent was removed under vacuum. The residue was purified as mentioned above. 4′-Acetoxybenzo-15-crown-5 (**3a**): 82%; mp 57.0—58.2 °C; M^+: 326; ^{1}H-NMR (δ, $CDCl_3$): 2.25 (CH_3, 3H, singlet), 3.10—4.20 ($-OCH_2CH_2O-$, 16H, multiplet), 6.30—6.95 (aromatic protons, 3H, multiplet); Found: C, 58.60; H, 6.78%. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.78%. 4′-Acetoxybenzo-18-crown-6 (**3b**): 65%; mp 48.5—50.0 °C; ^{1}H-NMR (δ, $CDCl_3$): 2.25 (CH_3, 3H, singlet), 3.30—4.30 ($-OCH_2CH_2O-$, 20H, multiplet); Found: C, 58.16; H 7.08%. Calcd for $C_{18}H_{26}O_8$: C, 58.37; H 7.07%.

*4′-Hydroxybenzocrown Ethers (**4a** and **4b**).* To a suspension of 4′-acetoxybenzo-15-crown-5 (**3a**) (40 mmol) in water was added aq NaOH at 40—50 °C and the reaction mixture was stirred for 3 h under nitrogen atmosphere. Acidification of the reaction mixture to pH 2 with concd H_2SO_4 gave **4a** (trihydrated form) as fine needles. The precipitate was purified by recrystallization from THF–$CHCl_3$ (1:5) containing a small amount of water. Since **4b** did not formed from the mixture as precipitate under the similar treatment, the product was extracted with chloroform and the chloroform layer was dried ($MgSO_4$). After evaporation of solvent, the residual oily product was purified by chromatography (alumina, $CHCl_3$) and following recrystallization from wet diethyl ether. 4′-Hydroxybenzocrown ether (**4a**); 93% mp 100.9—103.0 °C (dehydrated crystal); ^{1}H-NMR (δ, CD_3CN): 2.39 (H_2O, 6H, singlet), 3.55—4.30 ($-OCH_2CH_2O-$, 16H, multiplet), 6.10—6.82 (aromatic protons, 3H, multiplet), 6.93 (–OH, 1H, broad singlet); Found: C, 49.62; H, 7.62%. Calcd for $C_{14}H_{20}O_6 \cdot 3H_2O$: C, 49.70; H, 7.74%. 4′-Hydroxybenzocrown ether (**4b**): 82%; mp 52.3—52.6 °C; ^{1}H-NMR (δ, CD_3CN): 2.27 (H_2O, 2H, singlet), 3.52—4.34 ($-OCH_2CH_2O-$, 20H, multiplet), 6.06—7.04 (aromatic protons and –OH, 4H, multiplet and broad singlet were overlapped); Found: C, 55.58; H 7.63%. Calcd for $C_{16}H_{24}O_7 \cdot H_2O$: C, 55.48; H, 7.54%.

*Bis(benzocrown ether)s (**5** and **6**).* General procedure. Triethylene glycol ditosylate or dihalide (1.5 mmol) in THF (or dioxane) was added dropwise to the mixture of 4′-hydroxybenzocrown ether (**3a**) (3 mmol) and sodium hydroxide (5.5 mmol) in THF (or dioxane–DMSO (10%)) under nitrogen atmosphere over a period of 2—3 h and then refluxed for 16—20 h. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residual oily product was chromatographed through an alumina column ($CHCl_3$) and purified by recrystallization from ether-methanol (40:1). The purity and structures of the product was confirmed by IR, NMR, HPLC, and EA. ^{1}H-NMR (δ, $CDCl_3$); **5a**: 3.46—4.35 ($-OCH_2CH_2O-$, 40H, multiplet), 6.15—6.94 (aromatic protons, 6H, multiplet). ^{1}H-NMR of other bis(benzocrown ether)s were closely resemble to that of **5a**.

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