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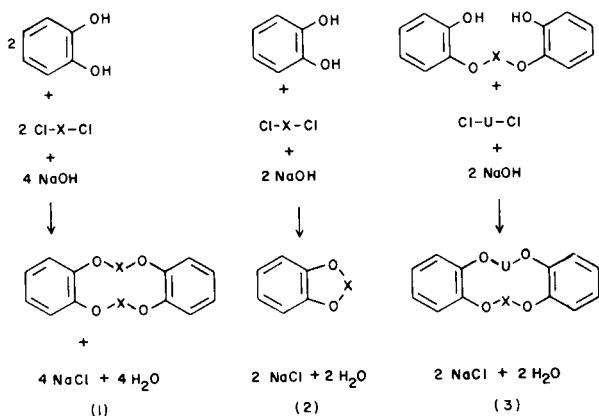
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A new series of 4-substituted derivatives of dibenzo-14-crown-4 including 4-nitro-DB14-crown-4 (**2a**), 4-bromo-DB14-crown-4 (**2b**), 4-chloro-DB14-crown-4 (**2c**) and 4-formyl-DB14-crown-4 (**2d**) has been synthesized with and without a lithium cation template. No matter with or without the template, a satisfactory correlation between the nature of the substituent group on the benzene ring and the reaction yield is observed. The larger  $\sigma$  values for the substituent groups gave lower yields.

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The rapid development in the syntheses of neutral macrocyclic ligands capable of complexing metal ions and organic ions has stimulated a variety of research efforts in many fields of chemistry. The pioneering work of Pedersen (2,3) on the syntheses of macrocyclic polyether (crown ethers) was chiefly concerned with oxygen-containing ring systems which produced a series of powerful complexing agents for alkali and alkaline earth cations. Initially crown ethers were used in extraction analysis (2). The utilization of crown ethers in ion-selective electrode (4,5) in analysis of trace solute removal of radioactive isotopes (6,7) and other applications (8,9) demonstrated their potential for further applications in the future.

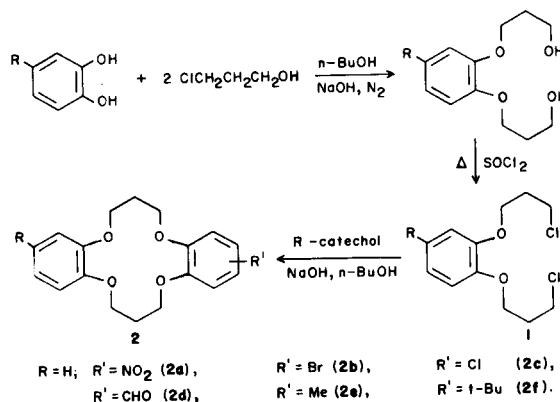
Most crown ethers are made by a straightforward condensation reaction (2,3,10,11), as shown in equations (1) to (3), in which X and U represent divalent organic groups of the types  $-(CH_2CH_2O)_nCH_2CH_2-$ .



More than 60 crown ethers have been synthesized using this method. However, only a few derivatives of dibenzo-14-crown-4 have been reported, such as bis(*t*-butyl)dibenzo-14-crown-4 (3,12), bisaminodibenzo-14-crown-4 (13) and 4-alkyldibenzo-14-crown-4 (14).

An improved synthetic method for preparation of dibenzo-14-crown-4 in high yield and a facile process for the preparation of DB14-crown-4 derivatives, especially

those with two different substituents on two benzo groups have been developed in our laboratory (12,14). The reaction scheme for the preparation of DB14-crown-4 derivatives is given as follows:



This paper deals with not only the synthesis of some new DB14-crown-4 derivatives, including **2a**, **2b**, **2c** and **2d**, but also the variance of template effect of different substituent groups on DB14-crown-4.

### Results and Discussion.

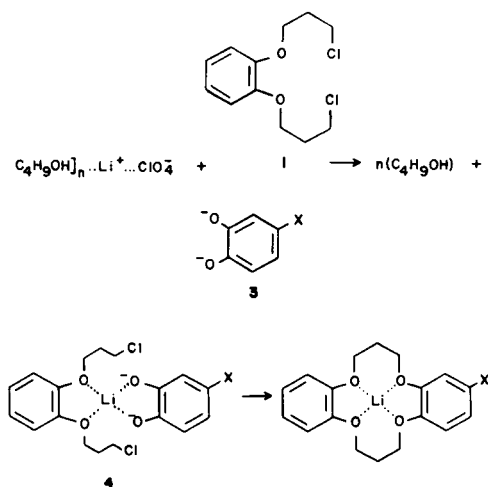
The effect of the substituent groups of the catechol on the synthesis of DB14-crown-4 are shown in the 2nd column of Table II. The substituents on the benzene ring represent somewhat different electronic character, ranging from the strongly electron withdrawing nitro group ( $\sigma = +0.78$ ) to the electron-donating methyl group ( $\sigma = -0.17$ ) (17). We found that the larger the  $\sigma$  value of the substituent on the benzene ring, the lower are the yields of **2** derivatives. Presumably the catechol with electron-withdrawing groups favor the ionization of the proton in the phenolic hydroxyl groups, but the basicity of sodium hydroxide in the reaction medium, we used, is strongly enough to completely ionize all the protons of the phenolic hydroxyl groups. Therefore, we believe that the function of electron-withdrawing substituent is to reduce the basicity of the phenolic oxygen anion, and to weaken its interaction with dichloride **1**, resulting in a decrease of the yield.

Table I

Important Physical Constants of Derivatives of DB14C4

Compound No.	Physical state at room temperature	Mp(°C)	Formula	NMR, $\delta$ (Deuteriochloroform)	Analyses		
					Calcd.	Found	
2a	pale-yellow solid	204-205	C <sub>18</sub> H <sub>19</sub> NO <sub>6</sub>	2.2-4 (4H, q), 4.4-3 (8H, t) 6.7 (7H, s)	C, H, N,	62.61 5.51 4.06	62.50 5.60 4.09
2b	white-solid	154-155	C <sub>18</sub> H <sub>19</sub> BrO <sub>4</sub>	2.2-4 (4H, q), 4.2-4.4 (8H, t) 6.9 (7H, s)	C, H, Br,	56.99 5.01 21.11	57.02 4.98 21.14
2c	pale-yellow solid	146-147	C <sub>18</sub> H <sub>19</sub> ClO <sub>4</sub>	2.16-2.27 (4H, q), 4.16-4.3 (8H, t) 6.9 (7H, s)	C, H, Cl,	64.67 5.69 10.48	64.52 5.69 10.51
2d	buff-solid	170-171	C <sub>18</sub> H <sub>20</sub> O <sub>3</sub>	2.3-2.5 (4H, q), 4.17-4.3 (8H, t) 6.9 (7H, s)	C, H,	69.51 6.10	69.38 6.16

Since the diameter of lithium ion (1.36 Å) fits to the ring size (1.2-1.5 Å) of DB14C4, the lithium perchlorate was chosen as the template. However, the basicity of lithium hydroxide is not strong enough to carry out the Williamson reaction, sodium hydroxide was used for the reaction. The lithium ion plays an important influence on the yield increment by a least 30%, as shown in Table II. The ring closure mechanism of a crown ether in the presence of template ion has been presumed (18) by complexing the open chain precursor, prior to ring formation, and by organizing it a conformation close enough to the ring being formed. In our system, the mechanism could be depicted as follows:



The dichloride **1** and catechol dianion **3** replace most or all of the 1-butanol from the lithium ion, leading to the formation of the so-called "pre-crown ether" intermediate **4**. The driving force, we believe, mainly comes from a favorable (positive) entropy change.

There are two factors which influence the yield in our system, one is the template ion, the other is the substituent groups on catechol. Obviously, the template effect is larger than that of substituent effect, as shown in Table II. By inspecting the last column of Table II, we find that a certain correlation exists between the relative increment of yield and the nature of substituent group on the benzene ring. In the presence of template ion, the relative increment yield in the reaction system involving electron donating groups on the benzene ring is 44% and more than that of involving electron-withdrawing groups (below 40%). A possible reason is that the electron-withdrawing groups disperse the charge density on the oxygen atoms of catechol dianion **3** making a lesser ion-dipole interaction between lithium template ion and oxygen. Consequently, the driving force mainly comes from a favorable (negative) enthalpy change.

#### EXPERIMENTAL

4-Chlorocatechol, 4-nitrocatechol, protocatechualdehyde and dioxane were purchased from Tokyo kasei, Pyrocatechol from Sigma Chemical company, bromine from Kanto (Japan), and 1-butanol, *n*-heptane, methanol, absolute ethanol and lithium perchlorate from Merck. 1,2-Bis-(3-chloropropoxy)benzene (**1**) was prepared as described previously (14). The infrared spectra were recorded by using potassium bromide pellets of the compounds on a JASKA 3A instrument. Proton nmr spectra were recorded in deuteriochloroform with a Bruker Wt 80 DS instrument and TMS was used as an internal standard. Melting points were measured on a Mel-Temp apparatus uncorrected. Mass spectra were taken on Varian MAT 112 gc/ms. Elemental analysis were performed by using Hans Höslí CHA-1 instrument.

The compound 4-bromocatechol was prepared immediately beforehand by the method of Yanoykaya (15). Dioxane dibromide was used as a convenient brominating agent for the bromination of pyrocatechol. The hot dark brown solution of equivalent amounts of dioxane and bromine was poured into a liter of ice with stirring, resulting in an

Table II

## Templated and Untemplated Yields of 4-Substituent DB14C4

Compound	Yield of crude products (a)	Yields of final products	Templated yield of final products	Relative increment of yield (%) (b)
NO <sub>2</sub> -DB14C4	4.5%	3.5%	5%	30
CHO-DB14C4	30%	21%	35%	40
Br-DB14C4	29%	25%	40%	38
Cl-DB14C4	33%	27%	45% (e)	40
DB14C4	35%	28% (c)	—	—
Me-DB14C4	36%	26% (d)	47%	45
<i>t</i> -Bu-DB14C4	38%	30% (d)	53%	43

(a) Based on glc. (b) Column (4th-3rd/4th). (c) Reference (3). (d) Reference (14). (e) Same yield was obtained in DMSO solvent.

orange precipitate. After filtration and drying on plate, dioxane dibromide was obtained with a 86% yield, mp 58-59 (lit 60°) (16). A solution of 25 g (0.1 mole) of dioxane dibromide in 50 ml of ether was added with shaking to 11 g (0.1 mole) of pyrocatechol dissolved in 50 ml of ether. The mixture was washed several times with water, dried over anhydrous magnesium sulfate, and evaporized to remove the solvent to give a gray oil. After prolonged standing on a vacuum line, the silver gray solid of 4-bromocatechol (1.45 g, 76%) was obtained with mp 81° (lit 82°) (15).

Preparation of 4-Nitro-DB14C4 (**2a**), 4-Bromo-DB14C4 (**2b**), 4-Chloro-DB14C4 (**2c**) and 4-Formyl-DB14C4 (**2d**).

According to the Williamson reaction, the 1-butanol solution of 1,2-bis(3-chloropropoxy)benzene (**1**) (5.25 g, 0.02 mole) with sodium hydroxide as base was separately treated with 4-nitrocatechol (1.55 g, 0.01 mole), 4-bromocatechol (1.89 g, 0.01 mole), 4-chlorocatechol (1.45 g, 0.01 mole) and protocatechualdehyde (1.38 g, 0.01 mole). The reactions were carried out by refluxing at 105° for 16 hours under a nitrogen atmosphere. The crude products **2a**, **2b**, **2c** and **2d** were obtained, after removal of 1-butanol by evaporation and were purified by dissolving the solid in chloroform and subsequently washing the reaction mixture with water, 5% sodium hydroxide, and water until buff color appeared. After removing the chloroform by evaporation, the solid residues were separately recrystallized from methanol, *n*-heptane, *n*-heptane and absolute ethanol to give **2a**, **2b**, **2c** and **2d**, respectively. Some important physical constant were summarized in Table I.

Synthesis of **2a-f** via Template Effect.

To a solution of 2.89 g (0.02 mole) of 4-chlorocatechol and 150 ml of 1-butanol which was purged with nitrogen for 0.5 hour, was added 1.6 g of sodium hydroxide in 20 ml of water. After stirring for 10 minutes, 4.26 g (0.04 mole) of anhydrous lithium perchlorate was added in one portion. The resulting mixture was heated to 100° for 10 minutes while stirring, then refluxed at 105° for 18 hours, to which 5.26 g (0.02 mole) of **1** in 50 ml of 1-butanol was added drop by drop. The solution was cooled, filtered, and then evaporated to remove the solvent. The solid residue obtained was dissolved in chloroform and washed successively with water, 5% sodium hydroxide, and water. The chloroform solution was then dried over anhydrous magnesium sulfate. After removing chloroform by evaporation, the crude solid was washed with methanol. The final product, **2c**, was obtained by recrystallization from *n*-heptane.

In order to examine the template effect of lithium perchlorate, similar procedures were carried out with 4-nitrocatechol, 4-bromocatechol, protocatechualdehyde, 4-methylcatechol and 4-(*t*-butyl)catechol. The reaction products were then separately recrystallized from methanol, *n*-heptane, absolute ethanol, *n*-heptane and *n*-heptane to give **2a**, **2b**, **2d**, **2e** and **2f**, respectively. The effect of the template ion on the yield of **2** derivatives were summarized in Table II.

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