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Synthesis and Alkali-cation Complexing Properties of 12-Crown-4 Derivatives[†]

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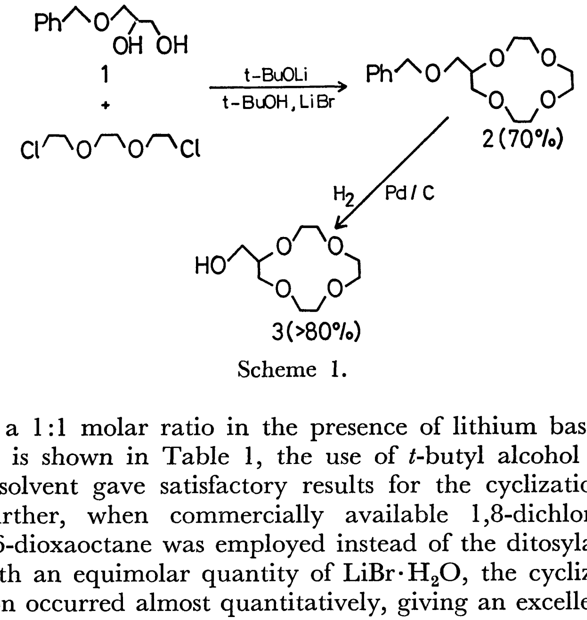
Benzyloxymethyl-12-crown-4, a precursor of hydroxymethyl-12-crown-4, is prepared in an excellent yield by the reaction of 3-benzyloxy-1,2-propanediol with 1,8-dichloro-3,6-dioxaoctane in the heterogeneous *t*-BuOLi/*t*-BuOH/LiBr·2H_2O reaction system. The hydrogenolysis in the presence of *p*-toluenesulfonic acid leads to a good yield of hydroxymethyl-12-crown-4. The sandwich-type 2:1 complexation with Na^+ of 12-crown-4 and hydroxymethyl-12-crown-4 derivatives was discussed on the basis of the stability constants and the solvent extraction in the CH_2Cl_2–water system.

Among a series of macrocyclic ethers, twelve-membered macrocycles, 12-crown-4 and its derivatives, long drew little attention because of their weak complexation due to their small cavity size and because of the difficulty in their preparation. Steiner and his group first reported that 12-crown-4 forms crystalline complexes with alkali and alkaline-earth metal salts and clarified some of their crystalline structure by means of X-ray crystallography.[1,2)] We have been interested in their findings that the 2:1 sandwich-type complexes of 12-crown-4 are formed with NaCl and NaOH and have square-antiprismatic coordination structures. In our previous ^1H NMR studies of polyethers,[3)] we found that, in methanol, 12-crown-4 showed an unusual downfield shift of protons in the presence of Na^+, and that the 2:1 complex with NaSCN including water of crystallization is formed in aqueous methanol and can be recrystallized in acetone. With these facts in view, the present work was undertaken in order to clarify the characteristic interaction of 12-crown-4 macrocycles with Na^+. Although we previously reported a method for the preparation of hydroxymethyl crown ethers,[4)] this paper will describe another facile synthesis of hydroxymethyl-12-crown-4 and its derivatives from commercially available starting materials, and will discuss their complexation with alkali metal cations in comparison with those of 15-crown-5 derivatives.

Results and Discussion

*Synthesis of Hydroxymethyl-12-crown-4(**3**).* The cyclization reactions to 12-crown-4 were generally in low yields because of the side reactions producing cyclic or acyclic oligomers.[5)] As a route to hydroxymethyl-12-crown-4(**3**), we investigated the reactions shown in Scheme 1, and tried to determine whether a high yield of cyclization to benzyloxymethyl-12-crown-4(**2**) could be achieved under the influence of high dilution and the template effect of Li^+.[6)]

3-Benzyloxymethyl-1,2-propanediol(**1**) can be prepared by the benzylation of commercially available 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane, followed by the hydrolysis of the dioxolane ring. The diol(**1**) was allowed to react with triethylene glycol ditosylate in a 1:1 molar ratio in the presence of lithium bases. As is shown in Table 1, the use of *t*-butyl alcohol as a solvent gave satisfactory results for the cyclization. Further, when commercially available 1,8-dichloro-3,6-dioxaoctane was employed instead of the ditosylate with an equimolar quantity of LiBr·H_2O, the cyclization occurred almost quantitatively, giving an excellent yield of the 12-crown-4(**2**), although a long reaction time was required (see Run Nos. 7 and 8). Without LiBr·H_2O, however, no cyclization was observed after a 9-day reaction, indicating that the halogen-exchange reaction to the bromide and its moderate reactivity are possibly favorable for the cyclization. The employment of lithium iodide, however, was accompanied by an unidentified by-product having a smaller retention volume in GLPC analysis, leading to a low yield (*ca.* 15% GLPC yield).



Scheme 1.

It is worth noting that a drop-by-drop addition of the diol(**1**) to a *t*-butyl alcohol solution of *t*-BuOLi immediately causes the turbidity of the finely dispersed lithium salt of the diol(**1**); thus, the reaction system is heterogeneous through the reaction. The heterogeneous intermolecular cyclization was extended to the synthesis of benzyloxymethyl-15-crown-5 from the diol(**1**) and 1,11-dichloro-3,6,9-trioxaundecane. An excellent yield(74%) was confirmed in the *t*-BuOLi/*t*-BuOH/LiBr·H_2O reaction system rather than in the *t*-BuONa/*t*-BuOH system(65%). Recently Czech[7)] and Gokel *et al.*[8)] have independently reported the same cyclization. Lower yields, 35% and 62%, were noted in the reaction systems with dichloride/NaOH/dioxane and with ditosylate or bis(methanesulfonate)/NaH/THF, respectively. Benzyloxymethyl-18-crown-6 could be isolated in a 46% yield according to the

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TABLE 1. SYNTHESIS OF BENZYLOXYMETHYL-12-CROWN-4(**2**)

Run No.		Reaction conditions a)				Yield b)
		Base	Solvent	Temp/°C	Time/d	%
1	X=OTs	LiH	Xylene	Reflux	1	14c)
2	X=OTs	*t*-BuOLi	Xylene	Reflux	1	15c)
3	X=OTs	*t*-BuOLi	Xylene	Reflux	3	17c)
4	X=OTs	*t*-BuOLi	Xylene/*t*-BuOH(1:1)	85—95	2	58c)
5	X=OTs	*t*-BuOLi	*t*-BuOH	Reflux	1	54(64)
6	X=Cl	*t*-BuOLi	*t*-BuOH	Reflux	9	0
7	X=Cl	*t*-BuOLi/LiBr·H_2O	*t*-BuOH	Reflux	10	70(92)
8	X=Cl	*t*-BuOLi/LiBr·H_2O	*t*-BuOH	Reflux	12	70(92) d)

a) Under high dilution conditions: the diol (**1**) (2 g) and the dichloride (2 g) were allowed to react using 150 ml of the solvent. b) The values in parentheses are the GLPC yields. c) The product was extracted by hot hexane to remove the unreacted ditosylated and then distilled by means of a Kugelrohr apparatus. The formation of oligomers was confirmed by means of GLPC. d) Less diluted conditions (see the procedure in the Experimental section).

TABLE 2. STABILITY CONSTANTS IN METHANOL AT 25 °C a)

Macrocyclic polyethers	NaCl			KCl		
	log K_1'	log K_2'	K_2'/K_1'	log K_1'	log K_2'	K_2'/K_1'
12-Crown-4	1.41	2.20	6.15	1.58	0.15	0.08
Benzyloxymethyl-12-crown-4(**2**)	1.35	1.98	4.30	1.42	1.29	0.74
Hydroxymethyl-12-crown-4(**3**)	1.37	1.79	2.61	1.43	<0	0
Octyloxymethyl-12-crown-4	1.32	1.97	4.52	1.36	<0	0
15-Crown-5	3.30	1.44	0.01	3.34	2.21	0.07
Benzyloxymethyl-15-crown-5	3.07	1.94	0.07	3.16	1.27	0.01

a) K_1' and K_2' in L/mol; 99% confidence limits ±0.01.

present method, using 1,14-dichloro-3,6,9,12-tetraoxatetradecane.

The *t*-BuOLi/LiBr/*t*-BuOH reaction system was extended to the synthesis of unsubstituted 12-crown-4 from ethylene glycol and 1,8-dichloro-3,6-dioxaoctane. However, the quantitative cyclization was not confirmed by GLPC analysis; *i.e.*, the dichloride was left unreacted even after a 10-day reaction, and some by-products with a longer retention volume were formed with 12-crown-4. This was also true for the reaction of triethylene glycol and 1,8-dichloro-3,6-dioxaoctane under the same conditions. The yield of 18-crown-6(4 h, <10%) was quite inferior to those of such homogeneous reactions at *t*-BuOK/KBr/*t*-BuOH reactions system(20 h, 51%). In view of these facts, the quantitative cyclization to the benzyloxymethyl-12-crown-4 may be attributed to the heterogeneous reaction on the dispersed Li salt of the diol(**1**), in which the coupling by the attack of the primary alkoxide of the diol(**1**) and the subsequent intramolecular attack of the secondary alkoxide, must occur advantageously under the influence of the template effect of Li^+. A similar heterogeneous metal template synthesis has already been disclosed for the synthesis of 18-crown-6.9,10)

The benzyl group of the benzyloxymethyl-12-crown-4 can be readily removed by hydrogenolysis on the Pd-carbon catalyst in the presence of a catalytic amount of *p*-toluenesulfonic acid, giving more than an 80% yield of hydroxymethyl-12-crown-4. The hydrogenolysis is very slow in the absence of *p*-toluenesulfonic acid. The co-catalysis of *p*-toluenesulfonic acid was discovered by the observation of the smooth debenzylation of the crude benzyloxymethyl-12-crown-4 obtained using the ditosylate. Matsui and Koga11) previously reported the debenzylation of the 18-crown-6 derivatives by means of hydrogenolysis in acetic acid. It seems likely that protic acids catalyze the hydrogenolysis of benzyloxy macrocyclic ethers.

Hydroxymethyl-12-crown-4 can be alkylated in good yields by a reaction using alkyl bromide, potassium *t*-butoxide as the base, and *t*-butyl alcohol as the solvent.

Stability Constants of 12-Crown-4 Complexes with Na^+ and K^+ in Methanol. Employing potentiometry using ion-selective electrodes, the stability constants, *i.e.*, the equilibrium constants for complexation, of 12-crown-4 and its derivatives have been determined in methanol. According to the Frensdorff equations,12) the stability constants, K_1' for 1:1 complexation and K_2' for 2:1 complexation, and K_2'/K_1' were precisely determined. For purposes of comparison, those of 15-crown-5 and benzyloxymethyl-15-crown-5 have also been determined (Table 2). The results show that, as for all Na^+ complexes with 12-crown-4 derivatives, the K_2' values are from 2 to 6 times larger than K_1', indicating the stronger tendency of the 2:1 complexation of 12-crown-4 in methanol as well as in the crystalline complexes with Na^+ salts. The proportions of 2:1 complexation have been calculated; they are

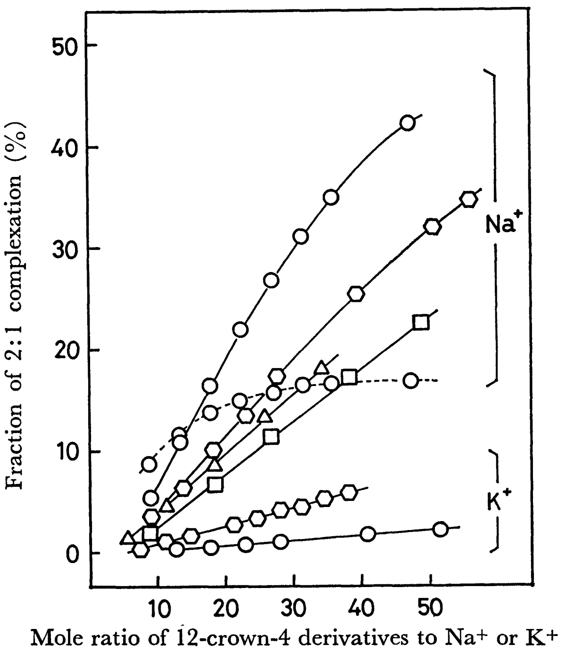

Fig. 1. Fraction of 2:1 complexation *vs.* mole ratio of 12-crown-4 derivatives to Na^+ or K^+.
—○—: 12-Crown-4, —⬡—: benzyloxymethyl-12-crown-4, —□—: hydroxymethyl-12-crown-4, —△—: octyloxymethyl-12-crown-4, ···○···: fraction of the 1:1 complexation of 12-crown-4 with Na^+.

shown graphically in Fig. 1, along with that of the 1:1 complexation of 12-crown-4(see the dotted line in Fig. 1). The sandwich-type complexation increases with an increase in the ratio of the 12-crown-4 to Na^+. These findings, then, demonstrate that the sandwich-type complexation of 12-crown-4 derivatives gradually overcomes the solvation of methanol to Na^+, even if the large-side group causes steric interference in the 2:1 complexation.13) Much the same, but a more remarkable, tendency has recently been observed for 12-crown-4 in propylene carbonate.14)

In contrast, the stability constants for K^+ and the small or negligible proportion of the 2:1 complexation for K^+ (Fig. 1) suggest that 12-crown-4 derivatives are rather inclined to form 1:1 complexes with K^+ in methanol, contrary to the formation of the solid 2:1 complex of 12-crown-4 with KCl.1) This is also true for the complexation of 15-crown-5 derivatives with Na^+ and K^+ in methanol. Thus, the characteristic complexation of 12-crown-4 with Na^+ is apparently due to the contribution of their sandwich-type complexation.

It is interesting to note that, although the $\log K_1'$ values of 15-crown-5 are almost the same for both Na^+ and K^+, the $\log K_2'$ value for K^+ is larger than that for Na^+. The selective complexation of 15-crown-5 with K^+ is also related to a sandwich-type complexation, just as in the case of 12-crown-4 for Na^+.

The effect of a benzyloxymethyl group on complexation with K^+ is worth noting. The stability constant, K_2', for K^+ of benzyloxymethyl-12-crown-4 is about ten times larger than that of 12-crown-4, while benzyloxymethyl-15-crown-5 has a smaller K_2' than 15-crown-5. In other words, the benzyloxymethyl group bound to 12-crown-4 strengthens the 2:1 complexing of K^+. The same effect of a benzyloxymethyl group has also been confirmed in the following solvent extraction.

Extraction of Alkali Picrates. The sandwich-type complexation of 12-crown-4 derivatives with Na^+ has also been derived from solvent extraction using dichloromethane as the solvent. 12-Crown-4 is lipophilic enough for it to be used as an extractant, because 95% of the crown in water can be removed by one extraction with chloroform(see Experimental section). However, because of the low stability constants, 12-crown-4 derivatives were used in a large excess against the picrates. The degree of extraction and the distribution ratio have been determined for alkai picrates; they are summarized in Table 3.

Compared with the extraction of 15-crown-5, 12-crown-4 derivatives all show weak extraction abilities, as expected. However, their selective extraction for Na^+ has now been confirmed. 12-Crown-4 and dodecyloxymethyl-12-crown-4 are the most selective. Benzyloxymethyl-12-crown-4(**2**) also extracts potassium picrate to a comparable extent, which is consistent with its large stability constant, K_2', for K^+ in methanol. It seems likely that the benzyloxymethyl group serves as a π donor for the 2:1 sandwich-type complexation especially with K^+.15)

Extraction with 12-crown-4 was recently reported in a benzene–water system.16) The stoichiometry of the extracted Na^+ species was determined to be 1:1. To ascertain the stoichiometry in the present extraction, the logarithm of the distribution ratios was plotted against the logarithm of the ratio of the 12-crown-4 to the picrate (Fig. 2). The coordination number of the crown in the extracted species can be determined from the slope of the line. A curved line is obtained, indicating that the coordination number changes ap-

Table 3. Solvent extration of alkali picrates with 12-crown-4 derivatives[a]

	12-Crown-4		Benzyloxymethyl-12-crown-4(**2**)		Dodecyloxymethyl-12-crown-4		15-Crown-5	
	EX(%)	D	EX(%)	D	EX(%)	D	EX(%)	D
Li^+	1.7	0.017	2.6	0.027	1.8	0.018	9.0	0.10
Na^+	19.9	0.249	15.2	0.179	15.4	0.181	33.2	0.50
K^+	5.3	0.056	14.1	0.164	4.2	0.044	93.2	13.75
Rb^+	3.5	0.036	13.0	0.149	3.1	0.032	85.4	5.85
Cs^+	2.6	0.027	12.6	0.144	2.6	0.027	43.4	0.76

a) EX(%): Degree of extraction, D: distribution ratio.

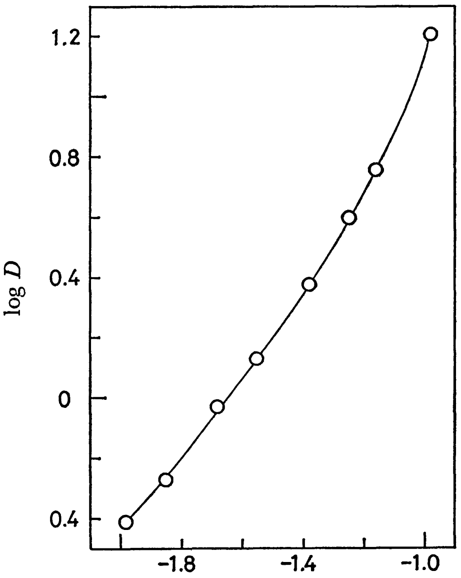

Fig. 2. Distribution ratio of sodium picrate *vs.* concentration of 12-crown-4.

proximately from 1 to 2 as the concentration of the crown increases. This is probably due to the increasing sandwich-type complexation.

The selective complexation of 12-crown-4 derivatives for Na^+ has now been confirmed due to the 2:1 sandwich-type complexation. The specific complexation for Na^+ might be related to the fulfillment of the Na^+ coordination geometry.2)

In view of the facile synthesis and the sandwich-type interaction of 12-crown-4 macrocycle, hydroxymethyl-12-crown-4 may be utilized as a new functional substituent causing a Na^+-promoted bimolecular interaction.

Experimental

Materials. 3-Benzyloxymethyl-1,2-propanediol (**1**) was prepared according to Howe and Malkin.17) The 1,11-dichloro-3,6,9-trioxaundecane, 1,14-dichloro-3,6,9,12-tetraoxatetradecane, and triethylene glycol ditosylate were prepared by the chlorination of tetraethylene glycol and pentaethylene glycol with $SOCl_2$, and by the reaction with tosyl chloride, respectively. The 12-crown-4 (Bokusui Brown Co., Ltd.) and 15-crown-5 (Nakarai Chemical Ltd.,) were purified by distillation. All the other reagents and solvent were obtained commercially and were used without further purification.

Measurement of Spectra. The ^1H NMR, IR, and mass spectra were obtained using JEOL LMN-PS-100, Hitachi 260-10, and Hitachi RMU-6E spectrometers respectively. GLPC analyses were carried out on a Shimadzu GC-4BPT apparatus using Silicone SE-30 on a Diasolid L (60—80 mesh) (4 mm × 1 m).

Preparation of Benzyloxymethyl-12-crown-4 (2). A 3—l three-necked flask equipped with a reflux condenser, an addition funnel, and a magnetic stirrer was charged with *t*-butyl alcohol (1500 ml) and metal lithium (5.7 g, 0.82 mol). After an hour's reflux under stirring, 3-benzyloxy-1,2-propanediol (50 g, 0.27 mol) was added drop by drop, causing the solution to become cloudy because of the precipitation of the lithium salts of 3-benzyloxy-1,2-propanediol (**1**). To the above heterogeneous solution we added 1,8-dichloro-3,6-dioxaoctane (51.4 g, 0.27 mol) and $LiBr\cdot H_2O$ (28.8 g, 0.27 mol) successively. The heterogeneous reaction mixture was refluxed and stirred until the dichloride almost disappeared upon GLPC analysis (12 d). After the bulk of *t*-butyl alcohol had been evaporated under reduced pressure, a 100-ml portion of water was added to the residue. After neutralization, the product was extracted three times with a 100-ml portion of diethyl ether. The extract was dried and condensed under reduced pressure. The resulting liquid was distilled under reduced pressure, giving 56.9 g of benzyloxymethyl-12-crown-4 (**2**) (70% yield): bp 120—130 °C/0.03 Torr (1 Torr = 133.322 Pa); IR (neat, NaCl plates), 3035 (w), 2930 (s), 2870 (s), 1500 (w), 1460 (m), 1135 (s), 1100 (s), 740 (m) cm^{-1}. ^1H NMR ($CDCl_3$), δ 3.48—3.90 (m, 17H), 4.55 (s, 2H), 7.25 (s, 5H); mass spectrum (*m/e* rel intensity) 296 (M^+), 205 (6), 175 (28), 146 (17) 133 (11), 91 (100), 87 (81), 73 (19), 59 (26), 45 (90). Found: C, 64.73; H, 8.16%. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16%. Under comparable conditions, benzyloxymethyl-15-crown-5 and 18-crown-6 were prepared by the reaction of 3-benzyloxymethyl-1,2-propanediol with 1,11-dichloro-3,6,9-trioxaundecane and 1,14-dichloro-3,6,9,12-tetraoxatetradecane respectively: Benzyloxymethyl-15-crown-5 (74% yield); bp 160—180 °C/0.01 Torr (Kugelrohr); IR (neat, NaCl plates) 3035 (w), 2870 (s), 1500 (w), 1460 (w), 1125 (s), 740 (m), 700 (m) cm^{-1}: ^1H NMR ($CDCl_3$) δ 3.48—3.90 (m, 21H), 4.55 (s, 2H), 7.25 (s, 5H); mass spectrum (*m/e*, rel intensity) 340 (M^+, 6), 249 (10), 219 (11), 177 (3), 146 (18), 133 (14), 91 (100), 87 (98), 73 (18). Found: C, 63.49; H, 8.55%. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.21%. Benzyloxymethyl-18-crown-6 (46% yield), bp 190—195 °C/0.03 Torr (Kugelrohr); IR (neat, NaCl plates) 3040 (w), 2860 (s), 1455 (m), 1355 (m), 1300 (w), 1250 (m), 1105 (s), 955 (m), 840 (m), 740 (m), 700 (m). ^1H NMR ($CDCl_3$) δ 3.48—3.90 (m, 25H), 4.52 (s, 2H), 7.30 (s, 5H). Mass spectrum (*m/e*, rel intensity), 384 (M^+), 293 (13), 263 (7), 175 (10), 146 (10), 133 (20), 91 (94), 87 (100), 73 (28), 59 (28). Found: C, 62.20; H, 8.48%. Calcd for $C_{20}H_{32}O_7$: C, 62.47; H, 8.38%.

Preparation of Hydroxytmethyl-12-crown-4 (3). Benzyloxymethyl-12-crown-4 (**2**) (4.5 g, 0.022 mol) and 10 ml of 1,4-dioxane were placed in a 20-ml test tube equipped with a hydrogen inlet. To the solution we then added 0.1 g of Pd–carbon (5%) (Mitsuwa Pure Chemicals) and 50 mg of *p*-toluenesulfonic acid. Hydrogen gas was passed through the solution at 50 °C for 5 h. After the filtration and removal of 1,4-dioxane by means of a rotary evaporator, the residue was distilled under reduced pressure to yield 2.6 g of hydroxymethyl-12-crown-4 (81%): bp 112—113 °C/0.02 Torr [lit,4) 115 °C/0.04 Torr] IR (neat, NaCl plates), 3250 (s), 2930 (s), 2870 (s), 1135 (s), 1100 (s) cm^{-1}: ^1H NMR ($CDCl_3$) δ 3.05 (s, 1H), 3.45—3.90 (m, 17H); mass spectrum (*m/e*, rel intesity), 206 (M^+), 188 (3), 175 (21), 133 (6), 103 (5), 87 (51), 45 (100). Found: C, 52.14; H, 9.09%. Calcd for $C_9H_{18}O_5$: C, 52.41; H, 8.80%.

Preparation of Dodecyloxymethyl-12-crown-4. Hydroxymethyl-12-crown-4 (1.0 g, 4.9 mmol) was allowed to react with dodecyl bromide (1.57 g, 6.4 mmol) at 70 °C for 10 h, using lithium *t*-butoxide (0.71 g, 6.3 mmol) as the base and *t*-butyl alcohol (15 ml) as the solvent. After the subsequent removal of the solvent, water was added and the mixture was neutralized and extracted with diethyl ether. After the usual work-up, dodecyloxymethyl-12-crown-4 (1.4 g, 78% yield) was obtained: bp 150 °C/0.03 Torr, ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.27 (bs, 20H), 3.35—3.50 (m, 19H); mass spectrum, 374 (M+). Found: C, 67.15; H, 11.37%. Calcd for $C_{21}H_{42}O_5$: C, 67.34; H, 11.30%. Octyloxymethyl-12-crown-4 was similarly prepared (85% yield): bp 125 °C/0.04 Torr, ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.27 (bs 12H), 3.33—3.90 (m, 19H); mass spectrum, 318 (M+). Found: C, 64.26; H, 10.64%. Calcd for $C_{17}H_{34}O_5$: C, 64.12; H, 10.76%.

Measurement of Stability Constant. According to Frensdorff's method based on potentiometry with cation-selective electrodes, the stability constants for 1:1 and 2:1 complexes of the crown ethers were determined for Na^+ and K^+. The solvent was absolute methanol (less than 0.1% water) (Wako Pure Chemicals Industry, Ltd.) The following Tohkoh Chemical measuring electrodes were used after step-by-step conditioning: the sodium-ion electrode (Na1100) and a reference electrode (MR-501C) for Na^+, and the potassium-ion electrode (K1200) and a reference electrode (CR-501C) for K^+. The emf was measured with a Beckman 4500 digital pH meter. The *R* values[10] were computed by minimizing the deviation of average K_1' values within 1% using an NEC PC-8001 computer. Seven to 9 measurements were included in regression analysis.

Solvent Extraction. In a stoppered, 30-ml glass tube we placed 10 ml of a dichloromethane solution containing an extractant (1.05×10^{-2} M or more), 5 ml of an alkali hydroxide solution (0.02 M), and 5 ml of a picric acid solution (1.4×10^{-4} M). The solution was shaken for 10 min at 25 °C and then left standing in a thermostated water bath (at 25 °C±0.5) for 12 h. The picrate concentration in the water phase was determined at 354 nm by means of a Shimadzu UV 200 spectrophotometer ($\varepsilon=1.414\times10^4$ cm^{-1} M^{-1}).

Table 4. The extraction of sodium picrate by means of 12-crown-4

Concentration of 12-crown-4	Extraction (%)	Distribution ratio (D)
1.05×10^{-2}	28.2	0.3929
1.40×10^{-2}	35.2	0.5421
2.10×10^{-2}	48.2	0.9292
2.80×10^{-2}	57.4	1.3471
4.20×10^{-2}	70.5	2.3911
5.60×10^{-2}	79.8	3.9607
7.00×10^{-2}	85.1	5.7155
10.50×10^{-2}	94.2	16.3625

The extraction percentages and the distribution ratios were determined at different concentrations of 12-crown-4 (Table 4).

Determination of Lipophilicity of 12-Crown-4. 12-Crown-4 (0.055 g), dissolved in 0.552 g (*ca.* 0.5 ml) of D_2O, was extracted with 0.727 g (*ca.* 0.5 ml) of $CDCl_3$. The concentration of 12-crown-4 in the aqueous phase was determined by ^{1}H NMR, using nitromethane as the internal reference. Ninety-five percent of the 12-crown-4 was extracted by $CDCl_3$ just as in the case of 15-crown-5.

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References

1) E. C. Steiner, R. A. Newton, and F. Boer, U. S. Patent 4025523.

2) a) F. P. Van Remoortere and F. P. Boer, *Inorg. Chem.*, **13**, 2071 (1971); b) F. P. Boer, M. A. Neuman, F. P. Van Remoortere, and E. C. Steiner, *ibid.*, **13**, 2826 (1974).

3) S. Yanagida, K. Takahashi, and M. Okahara, *Bull. Chem. Soc. Jpn.*, **51**, 3111 (1978).

4) I. Ikeda, S. Yamamura, N. Nakatsuji, and M. Okahara, *J. Org. Chem.*, **45**, 5355 (1980).

5) F. L. Cook, T. C. Caruso, M. P. Byrne, C. W. Bowers, D. H. Speck, and C. L. Liotta, *Tetrahedron Lett.*, **1974**, 4029.

6) P-L. Kuo, N. Kawamura, M. Miki, and M. Okahara, *Bull. Chem. Soc. Jpn.*, **53**, 1689 (1980).

7) B. Czeck, *Tetrahedron Lett.*, **1980**, 533.

8) G. W. Gokel, D. M. Dishong, and C. J. Diamond, *J. Chem. Soc., Chem. Commun.*, **1980**, 1053.

9) P-L. Kuo, M. Miki, and M. Okahara, *J. Chem. Soc., Chem. Commun.*, **1978**, 504.

10) J. Yamawaki and T. Ando, *Chem. Lett.*, **1980**, 533.

11) T. Matsui and K. Koga, *Chem. Pharm, Bull.*, **27**, 2295 (1975).

12) H. K. Frensdorff, *J. Am. Chem. Soc.*, **93**, 600 (1971).

13) D. M. Dishong, C. J. Diamond, and G. W. Gokel, *Tetrahedron Lett.*, **1981**, 1663.

14) J. Massaux, J. F. Desreux, and G. Duyckaerts, *J. Chem. Soc., Dalton Trans.*, **1980**, 865.

15) N. Kawashima, T. Kawashima, T. Otsubo, and S. Misumi, *Tetrahedron Lett.*, **1978**, 5025.

16) Y. Takada, *Bull. Chem. Soc. Jpn.*, **53**, 2393 (1980).

17) R. J. Howe and T. Malkin, *J. Chem. Soc.*, **1951**, 2663.