Synthesis and Selectivity for Lithium of Lipophilic 14-Crown-4 Derivatives bearing Bulky Substituents or an Additional Binding Site in the Side Arm

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Two types of 6,6-disubstituted 14-crown-4 (1,4,8,11-tetraoxacyclotetradecane) derivatives have been synthesized in the hope of improving on the selectivity of the parent macrocycle for Li^+, especially against Na^+ and K^+. Selectivity enhancement was expected to result from incorporation of bulky substituents which suppress the formation of stable sandwich-type complexes with Na^+ and K^+, and from the attachment of an additional binding site possessing affinity for Li^+. Studies of the electrochemical selectivity of membranes containing the crown ethers showed that selectivities for Li^+ with respect to Na^+ and K^+ are augmented in 6,6-dibenzyl- and 6-diethylcarbamoylmethyl-6-dodecyl-14-crown-4, (**6**) and (**18**), as compared with the 6-dodecyl-6-methyl derivative (**2**).

In analytical and biological applications of Li^+ ionophores, such as crown ethers, high selectivities for Li^+ with respect to Na^+ and K^+ are often required. Although many crown ethers exhibit poor complexing abilities for Li^+, crown ethers with relatively small cavities possess Li^+ affinity.[1-8] We have already reported that 14-crown-4 (1,4,8,11-tetraoxacyclotetradecane) cycle shows remarkable selectivity for Li^+.[6] This macrocycle is the most selective for Li^+ of crown-4 derivatives (crown ethers containing four ring oxygen atoms) with 12—16-membered rings. This high selectivity was explained in terms of goodness of fit of Li^+ in the macrocycle cavity. Some 14-crown-4 derivatives have been applied successfully as neutral carriers in Li^+-selective electrodes, which are expected to be convenient tools for Li^+ assay in environmental and biological systems.[7] Czech *et al.*[8] have also observed marked selectivities for Li^+ of similar 14-crown-4 derivatives in cation extraction.

However, the selectivities of 14-crown-4 derivatives synthesized so far are not ideal for practical application to systems containing Na^+ and K^+ as well, at high concentrations. Still higher selectivities are desirable to alleviate the unfavourable effects of the coexistent ions. We have therefore tried to improve the selectivity of the 14-crown-4 derivatives by modifying the macrocycle with substituents which affect its cation-complexing ability. This paper is concerned with the synthesis of 6,6-disubstituted 14-crown-4 derivatives (**3**)—(**19**), and a study of their selectivities for Li^+ as neutral carriers of membrane electrodes. A bis-(14-crown-4) derivative (**20**) is also described, for comparison with the monocyclic derivatives.

Experimental

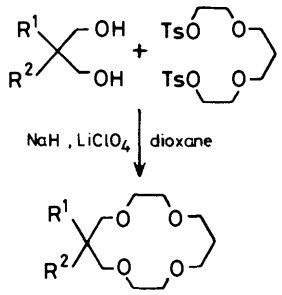
Synthesis.—Several 14-crown-4 derivatives carrying two octyl, dodecyl, or benzyl groups at the centre of the trimethylene moiety [(**3**)—(**6**)] were synthesized by cyclization of an appropriate 2,2-disubstituted propane-1,3-diol with 3,7-dioxanonane-1,9-diyl ditosylate[6] in the presence of NaH and $LiClO_4$ (Scheme 1). The Li^+ salt is a template for the cyclization. Similar reactions afforded the dodecyl-methoxyethyl- (**7**), dioxaheptyl-dodecyl- (**8**), benzyloxyethyl-dodecyl- (**9**), diethoxyethyl-dodecyl- (**10**), and ethyl-hydroxymethyl- (**12**) derivatives, and a spiro-14-crown-4 derivative (**11**). The 2,2-disubstituted propane-1,3-diols were prepared by one-step or stepwise alkylation of diethyl malonate in refluxing ethanol, followed by reduction with $LiAlH_4$ in diethyl ether.[9] 5,5-Bis(hydroxyethyl)-2-phenyl-1,3-dioxane is easily accessible from pentaerythritol and benzaldehyde.[10]

Hydrogenolysis of (**9**) over Pd–C gave the dodecyl-hydroxyethyl-14-crown-4 (**13**), which in turn was converted into the corresponding bromoethyl derivative. The acetoxyethyl-dodecyl- (**14**), diethoxyphosphoryloxyethyl-dodecyl- (**15**), and dodecyl-quinolyloxyethyl- (**16**) 14-crown-4 derivatives were then synthesized according to Scheme 2. Acid-catalysed hydrolysis of (**10**) and subsequent oxidation with $KMnO_4$ yielded the carboxymethyl-dodecyl-14-crown-4. The crown ether was converted into the methoxycarbonylmethyl-dodecyl- (**17**) and diethylcarbamoylmethyl-dodecyl- (**18**) derivatives as shown in Scheme 3. The spiro-14-crown-4 (**11**) was hydrolysed to yield the bis(hydroxymethyl)-14-crown-4, which was then converted into the bis(octyloxymethyl) derivative (**19**) (Scheme 4). The bis-(14-crown-4) derivative (**20**) was synthesized by the reaction of 2-dodecyl-2-methylmalonyl chloride with (**12**) in the presence of AgCN[11] (Scheme 5). The yields for the syntheses of the disubstituted 14-crown-4 derivatives and the bis(crown ether) were not optimized.

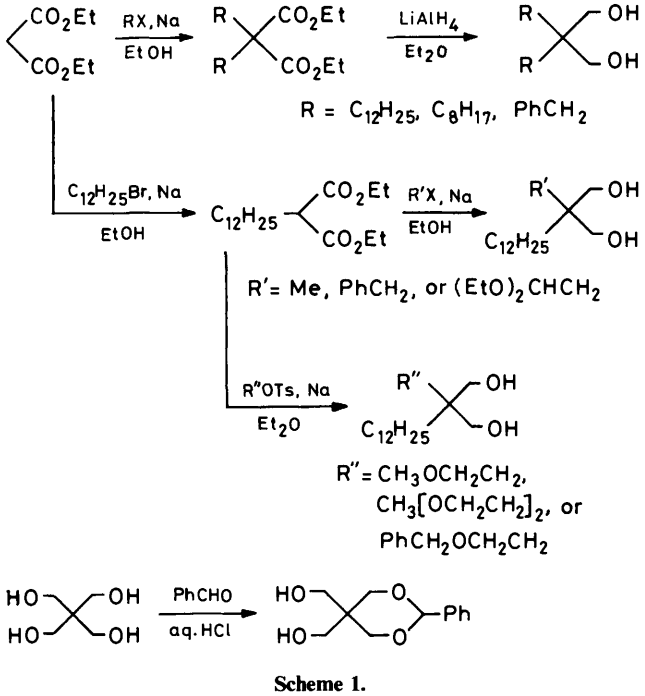
General Procedure for Cyclization to 14-Crown-4 Derivatives.—In a solution of an appropriate 2,2-disubstituted propane-1,3-diol (10 mmol) in dry dioxane (400 ml) was suspended NaH (25 mmol); the mixture was then refluxed for 0.5 h with stirring. To the refluxing suspension was added $LiClO_4$ (25 mmol), and subsequently a solution of 3,7-dioxanonane-1,9-diyl ditosylate (10 mmol) in dioxane (50 ml) was added dropwise. Refluxing was continued for an additional 20 h. The mixture was then filtered and the solvent evaporated off. The residue was stirred with water and $CHCl_3$ (200 ml each) and the $CHCl_3$ layer was separated. The aqueous layer was further extracted with $CHCl_3$ (50 ml × 2). The combined extract was washed with water and dried ($MgSO_4$). Evaporation left a crude product, which was purified by chromatography on silica gel [gradient elution with benzene–methanol except for (**4**), for which heptane–benzene was used], followed by preparative reversed-phase liquid chromatography [octadecylsilanized silica (ODS); MeOH].

Dioctyl-14-crown-4 (**3**) (*6,6-dioctyl-1,4,8,11-tetraoxacyclotetradecane*) was obtained as a colourless oil (25%) (Found: C, 72.9; H, 12.5. $C_{26}H_{52}O_4$ requires C, 72.9; H, 12.2%); $\nu_{max.}$(neat) 1 130 and 1 110 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.88 (6 H, t, *J* 6 Hz, CH_3), 1.00—1.50 (28 H, m, $CH_3[CH_2]_7$), 1.50—1.76 (2 H, m, $OCH_2CH_2CH_2$), 3.21 (4 H, s, OCH_2C), and 3.45—3.67 (12 H, m, OCH_2); *m/z* 428 (M^+, 2.8%) and 103 (100).

Didodecyl-14-crown-4 (**4**) (*6,6-didodecyl-1,4,8,11-tetraoxacyclotetradecane*) was isolated as a colourless oil (18%) (Found: C, 75.4; H, 13.0. $C_{34}H_{68}O_4$ requires C, 75.5; H, 12.7%); $\nu_{max.}$(neat) 1 125 and 1 110 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.87 (6 H, t, *J* 6 Hz, CH_3), 1.00—1.40 (44 H, m, $CH_3[CH_2]_{11}$), 1.50—1.78 (2 H, m, $OCH_2CH_2CH_2O$), 3.19 (4 H, s, OCH_2C),



(1) R^1 = H, R^2 = $C_{12}H_{25}$ (2) R^1 = CH_3, R^2 = $C_{12}H_{25}$
(3) R^1 = R^2 = C_8H_{17} (4) R^1 = R^2 = $C_{12}H_{25}$
(5) R^1 = $PhCH_2$, R^2 = $C_{12}H_{25}$ (6) R^1 = R^2 = $PhCH_2$
(7) R^1 = $CH_3OCH_2CH_2$, R^2 = $C_{12}H_{25}$ (8) R^1 = $CH_3[OCH_2CH_2]_2$, R^2 = $C_{12}H_{25}$
(9) R^1 = $PhCH_2OCH_2CH_2$, R^2 = $C_{12}H_{25}$ (10) R^1 = $(EtO)_2CHCH_2$, R^2 = $C_{12}H_{25}$
(11) R^1R^2 = $(CH_2O)_2CHPh$ (12) R^1 = $HOCH_2$, R^2 = Et



Scheme 1.

and 3.42—3.61 (12 H, m, OCH_2); *m/z* 540 (M^+, 1.7%) and 103 (100).

Benzyl-dodecyl-14-*crown*-4 (**5**) (6-*benzyl*-6-*dodecyl*-1,4,8,11-*tetraoxacyclotetradecane*) was a colourless oil (16%) (Found: C, 75.0; H, 11.2. $C_{29}H_{50}O_4$ requires C, 75.3; H, 10.9%); $\nu_{max.}$(neat) 1 120 and 1 105 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.88 (3 H, t, *J* 6 Hz, CH_3), 1.10—1.46 (22 H, m, $CH_3[CH_2]_{11}$), 1.52—1.78 (2 H, m, $OCH_2CH_2CH_2O$), 2.44 (2 H, s, $PhCH_2$), 3.21 (4 H, s, OCH_2C), 3.43—3.70 (12 H, m, OCH_2), and 7.00—7.20 (5 H, m, aromatic); *m/z* 462 (M^+, 0.8%) and 103 (100).

Dibenzyl-14-*crown*-4 (**6**) (6,6-*dibenzyl*-1,4,8,11-*tetraoxacyclotetradecane*) was isolated as a colourless oil, which solidified (17%); m.p. 102—103 °C (from MeOH) (Found: C, 74.7; H, 8.4. $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%); $\nu_{max.}$(KBr) 1 120 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 1.64—1.88 (2 H, m, $OCH_2CH_2CH_2O$), 2.54 (4 H, s, $PhCH_2$), 3.30 (4 H, s, CCH_2), 3.48—3.74 (12 H, m, OCH_2), and 7.12—7.36 (10 H, m, aromatic); *m/z* 384 (M^+, 0.6%) and 91 (100).

Dodecyl-methoxyethyl-14-*crown*-4 (**7**) [6-*dodecyl*-6-(2-*methoxyethyl*)-1,4,8,11-*tetraoxacyclotetradecane*] was a colourless oil (15%) (Found: C, 69.6; H, 11.9. $C_{25}H_{50}O_5$ requires C, 69.7; H, 11.7%); $\nu_{max.}$(neat) 1 130 and 1 110 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.87 (3 H, t, *J* 6 Hz, CH_3), 1.16—1.54 (24 H, m, $CH_3[CH_2]_{11}$ and CCH_2CH_2O), 1.54—1.76 (2 H, m, $OCH_2CH_2CH_2O$), 3.16—3.38 (9 H, m, CH_2OCH_3 and OCH_2CCH_2O), and 3.44—3.65 (12 H, m, OCH_2); *m/z* 431 (M^+, 3.1%) and 45 (100).

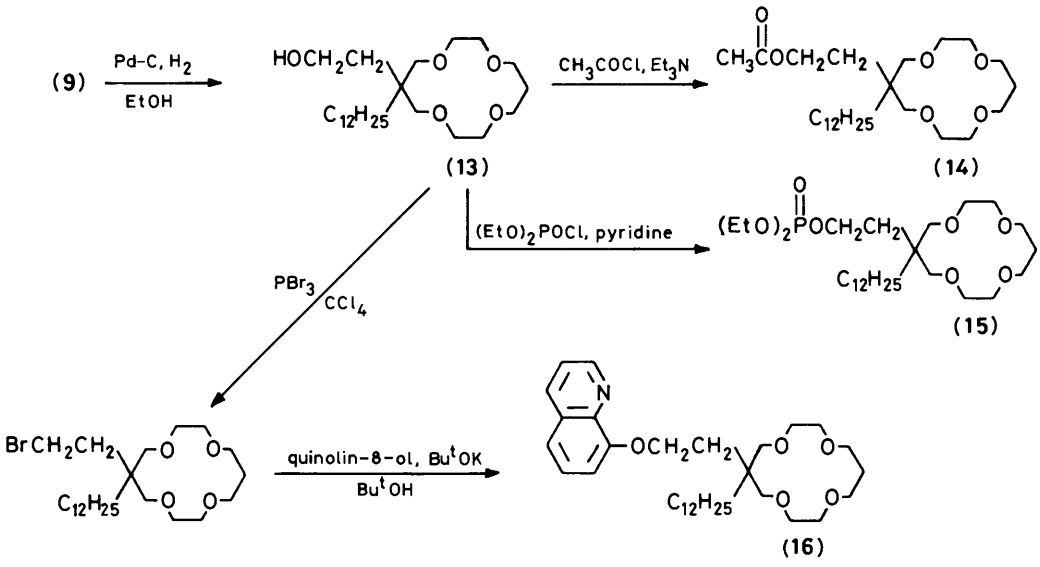
Dioxaheptyl-dodecyl-14-*crown*-4 (**8**) [6-(3,6-*dioxaheptyl*)-6-*dodecyl*-1,4,8,11-*tetraoxacyclotetradecane*] was isolated as a colourless oil (17%) (Found: C, 68.1; H, 11.5. $C_{27}H_{54}O_6$ requires C, 68.3; H, 11.5%); $\nu_{max.}$(neat) 1 120 and 1 110 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.88 (3 H, t, *J* 6 Hz, CH_3), 1.09—1.60 (24 H, m, $CH_3[CH_2]_{11}$ and CCH_2CH_2O), 1.60—1.82 (2 H, m, $OCH_2CH_2CH_2O$), and 3.19—3.72 (25 H, m, OCH_2 and OCH_3); *m/z* 475 (M^+, 1.2%) and 59 (100).

Benzyloxyethyl-dodecyl-14-*crown*-4 (**9**) [6-(2-*benzyloxyethyl*)-6-*dodecyl*-1,4,8,11-*tetraoxacyclotetradecane*] was a colourless oil (43%) (Found: C, 73.6; H, 11.1. $C_{31}H_{54}O_5$ requires C, 73.5; H, 10.7%); $\nu_{max.}$(neat) 1 125 and 1 110 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.88 (3 H, t, *J* 6 Hz, CH_3), 1.05—1.45 (22 H, m, $CH_3[CH_2]_{11}$), 1.45—1.76 (4 H, m, $OCH_2CH_2CH_2O$ and $PhCH_2OCH_2CH_2$), 3.27 (4 H, s, OCH_2C), 3.30—3.70 (14 H, m, OCH_2), 4.42 (2 H, s, $PhCH_2$), and 7.20—7.35 (5 H, m, aromatic); *m/z* 506 (M^+, 0.4%) and 91 (100).

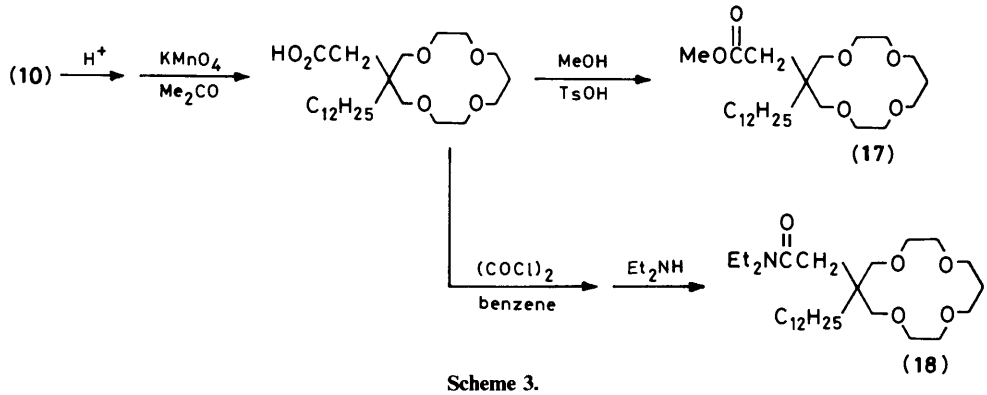
Ethyl-hydroxymethyl-14-*crown*-4 (**12**) (6-*ethyl*-6-*hydroxymethyl*-1,4,8,11-*tetraoxacyclotetradecane*) was also isolated as a colourless oil (17%) (Found: C, 59.3; H, 10.3. $C_{13}H_{26}O_5$ requires C, 59.5; H, 10.0%); $\nu_{max.}$(neat) 3 400 (OH) and 1 125 and 1 110 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.82 (3 H, t, *J* 7 Hz, CH_3), 1.20 (2 H, q, *J* 7 Hz, CH_3CH_2), 1.66 (2 H, q, *J* 5 Hz, $OCH_2CH_2CH_2O$), 2.88 (1 H, s, OH), and 3.25—3.68 (18 H, m, OCH_2 and CH_2OH); *m/z* 262 (M^+).

Dodecyl-hydroxyethyl-14-*crown*-4 (**13**) [6-*Dodecyl*-6-(2-*hydroxyethyl*)-1,4,8,11-*tetraoxacyclotetradecane*].—Compound (**9**) (6.3 mmol) dissolved in ethanol (120 ml), Pd–C (5%, 0.5 g), and a grain of toluene-*p*-sulphonic acid were placed in a glass autoclave. Hydrogenolysis was performed under a hydrogen pressure of 3 atm at 30 °C overnight. After filtration, the solvent was removed by rotary evaporation. Chromatography on silica gel (gradient elution with $CHCl_3$–MeOH) yielded a colourless *oil* (98%) (Found: C, 68.9; H, 11.8. $C_{24}H_{48}O_5$ requires C, 69.2; H, 11.6%); $\nu_{max.}$(neat) 3 400 (OH) and 1 130 and 1 110 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.88 (3 H, t, *J* 6 Hz, CH_3), 1.04—1.53 (24 H, m, $CH_3[CH_2]_{11}$ and CH_2CH_2OH), 1.59—1.81 (2 H, m, $OCH_2CH_2CH_2O$), 2.95 (1 H, s, OH), 3.35 (4 H, s, CH_2CCH_2), and 3.41—3.73 (12 H, m, CH_2O); *m/z* 416 (M^+, 1.1%) and 103 (100).

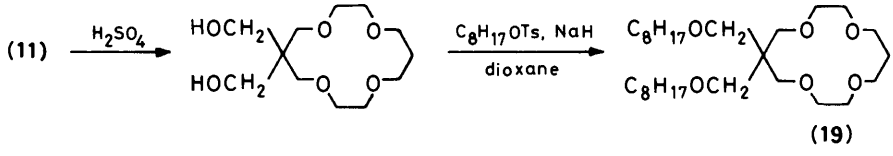
Acetoxyethyl-dodecyl-14-*crown*-4 (**14**) [6-(2-*Acetoxyethyl*)-6-*dodecyl*-1,4,8,11-*tetraoxacyclotetradecane*].—Compound (**13**) (0.75 mmol) and triethylamine (0.9 mmol) were dissolved in dry benzene (20 ml) and then cooled in an ice-bath. To the mixture was added dropwise acetyl chloride (0.9 mmol) with stirring. The reaction was continued for 6 h at room temperature. The mixture was filtered, and the filtrate was washed successively with aqueous 5% $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated. The crude product was purified by reversed-phase chromatography to yield a colourless *oil* (56%) (Found: C, 67.9; C, 11.2. $C_{26}H_{50}O_6$ requires C, 68.1; H, 11.0%); $\nu_{max.}$(neat) 1 730 (C=O) and 1 130 and 1 110 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.88 (3 H, t, *J* 6 Hz, CH_3CH_2), 1.16—1.32 (24 H, m, CH_3-



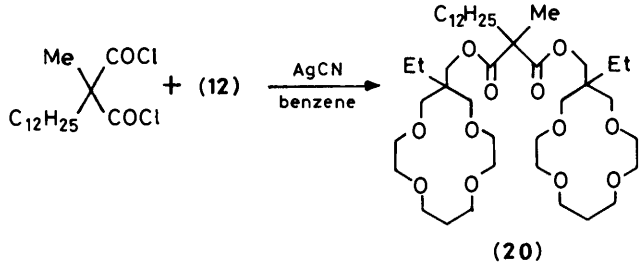
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

$[CH_2]_{11}$ and CH_2CH_2OCO), 1.40—1.70 (2 H, m, OCH_2CH_2-CH_2O), 1.92 (3 H, s, CH_3CO), 3.28 (4 H, s, CCH_2), 3.50—3.64 (12 H, m, OCH_2), and 4.01 (2 H, t, *J* 7 Hz, CH_2OCO); *m/z* 458 (M^+, 0.5%) and 103 (100).

Diethoxyphosphoryloxyethyl-dodecyl-14-*crown*-4 (**15**) {6-[2-(*Diethoxyphosphoryloxy*)*ethyl*]-6-*dodecyl*-1,4,8,11-*tetraoxacyclotetradecane*}.—Compound (**13**) (0.95 mmol) was dissolved in benzene–pyridine (50:50; 20 ml) and the mixture was cooled in an ice-bath. Diethyl chlorophosphate (1.4 mmol) was added dropwise with stirring. The reaction was continued for 1 h at room temperature and then for 2 h at reflux temperature. Water and benzene (50 ml each) were then poured into the mixture with stirring. The benzene layer was separated, washed with

water, dried ($MgSO_4$), and evaporated. Reversed-phase chromatography of the crude product (ODS; MeOH) yielded a colourless *oil* (16%) (Found: C, 60.6; H, 10.5. $C_{28}H_{57}O_8P$ requires C, 60.8; H, 10.4%); $\nu_{max.}$(neat) 1 270 (P=O), 1 120 and 1 110 (C–O–C), and 1 030 cm^{-1} (P–O–C); δ_H(100 MHz; CCl_4) 0.88 (3 H, t, *J* 6 Hz, CH_3), 1.12—1.52 {28 H, m, $CH_3[CH_2]_{11}$ and $P(OCH_2CH_3)_2$}, 1.52—1.78 (4 H, m, $OCH_2CH_2CH_2O$ and CCH_2CH_2OPO), 3.32 (4 H, s, OCH_2C), 3.47—3.69 (12 H, m, OCH_2), and 3.84—4.20 (6 H, m, $POCH_2$); *m/z* 553 (M^+, 0.9%) and 155 (100).

Dodecyl-quinolyloxyethyl-14-crown-4 (**16**) {6-*Dodecyl*-6-[2-(8-*quinolyloxy*)*ethyl*]-1,4,8,11-*tetraoxacyclotetradecane*}.—To a solution of compound (**13**) (1.4 mmol) in CCl_4 (30 ml) was added dropwise PBr_3 (1.4 mmol) dissolved in CCl_4 (10 ml) with stirring and cooling in an ice-bath. The reaction was continued for an additional 1 h at room temperature. The mixture was washed with water and dried ($MgSO_4$). Evaporation left a crude bromoethyl-dodecyl-14-crown-4. A solution of quinolin-8-ol (1.4 mmol) and Bu^tOK (1.5 mmol) in Bu^tOH (20 ml) was refluxed for 1 h under nitrogen. To the mixture was added dropwise the foregoing crude product dissolved in Bu^tOH (3 ml). Refluxing was allowed to continue for 1 day. After the reaction the solvent was evaporated off. Water and diethyl ether (100 ml each) were added to the residue for extraction. The ether layer was separated and then washed with water. The crude product was subjected to chromatography on alumina (gradient elution; $CHCl_3$–MeOH) and reversed-phase chromatography to yield the pure product as a colourless *oil* (35%) (Found: C, 72.6; H, 10.1; N, 2.5. $C_{33}H_{53}NO_5$ requires C, 72.9; H, 9.8; N, 2.6%); $\nu_{max.}$(neat) 1 120 and 1 105 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.88 (3 H, t, *J* 6 Hz, CH_3), 1.14—1.48 (22 H, m, $CH_3[CH_2]_{11}$), 1.52—1.80 (2 H, m, $OCH_2CH_2CH_2O$), 1.91 (2 H, t, *J* 7 Hz, CCH_2CH_2O), 3.32—3.70 (16 H, m, CH_2O), 4.21 (2 H, t, *J* 7 Hz, CH_2OAr), and 6.8—8.8 (6 H, m, aromatic); *m/z* 543 (M^+, 6.1%) and 399 (100).

Carboxymethyl-dodecyl-14-crown-4 (6-*Carboxymethyl*-6-*dodecyl*-1,4,8,11-*tetraoxacyclotetradecane*).—The cyclization reaction described in the general procedure, using 2-(2,2-diethoxyethyl)-2-dodecylpropane-1,3-diol, gave crude diethoxyethyl-dodecyl-14-crown-4 (**10**), which was hydrolysed by dilute HCl to yield the corresponding formyl derivative. To the crude formyl derivative (*ca.* 10 mmol) dissolved in acetone (100 ml) was added dropwise a solution of $KMnO_4$ (13.3 mmol) in acetone (400 ml) with stirring. The reaction was continued for 12 h at room temperature. The mixture was filtered and the solvent was replaced by $CHCl_3$. The $CHCl_3$ solution was washed with dilute HCl until the purple colour of $KMnO_4$ was not observed. The solution was then dried ($MgSO_4$) and evaporated. Reversed-phase chromatography (ODS; MeOH) afforded the pure product as a colourless oil, slowly converted into a *solid* (35%), m.p. 51—52 °C (from MeOH) (Found: 66.7; H, 10.8. $C_{24}H_{46}O_6$ requires C, 66.9; H, 10.8%); $\nu_{max.}$(KBr) 3 400 (OH), 1 695 (C=O), and 1 130 and 1 110 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.88 (3 H, t, *J* 6 Hz, CH_3), 1.10—1.40 (22 H, m, $CH_3[CH_2]_{11}$), 1.50—1.80 (2 H, m, $OCH_2CH_2CH_2O$), 2.20 (2 H, s, CH_2CO), 3.32—3.70 (16 H, m, CH_2O), and 10.53 (1 H, s, OH); *m/z* 430 (M^+, 1.1%) and 103 (100).

Dodecyl-methoxycarbonylmethyl-14-crown-4 (**17**) (6-*Dodecyl*-6-*methoxycarbonylmethyl*-1,4,8,11-*tetraoxacyclotetradecane*).—Carboxymethyl-dodecyl-14-crown-4 (0.58 mmol) and a catalytic amount of toluene-*p*-sulphonic acid were dissolved in benzene–methanol (50:50; 50 ml) and the solution was refluxed for 4 h. The solvent was then evaporated off and the residue was extracted with diethyl ether. The extract was washed with aqueous 5% $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated. Reversed-phase chromatography yielded the pure product as a colourless *oil* (60%) (Found: C, 67.2; H, 11.1. $C_{25}H_{48}O_6$ requires C, 67.5; H, 10.9%); $\nu_{max.}$(neat) 1 730 (C=O) and 1 130 and 1 110 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.87 (3 H, t, *J* 5 Hz, CH_3), 1.19—1.41 (22 H, m, $CH_3[CH_2]_{11}$), 1.50—1.76 (2 H, m, $OCH_2CH_2CH_2O$), 2.14 (2 H, s, CCH_2CO), 3.48—3.64 (15 H, m, CH_2O and CH_3OCO), and 3.36 (4 H, s, $OCH_2CH_2CH_2O$); *m/z* 444 (M^+, 1%) and 103 (100).

Diethylcarbamoylmethyl-dodecyl-14-crown-4 (**18**) [6-(N,N-*Diethylcarbamoylmethyl*)-6-*dodecyl*-1,4,8,11-*tetraoxacyclotetradecane*].—To a dry solution of carboxymethyl-dodecyl-14-crown-4 (1.16 mmol) and oxalyl chloride (1.73 mmol) in benzene (200 ml) were added several drops of dry pyridine. The solution was then stirred for 1 day at room temperature. The mixture was concentrated to *ca.* 100 ml. The precipitate of oxalic acid was filtered off. To the filtrate was added dropwise diethylamine (3 mmol) with stirring and cooling in an ice-bath. The mixture was refluxed for 2 days, the solvent was evaporated off, and the residue was extracted with diethyl ether. The extract was washed successively with dilute HCl and water. Evaporation left the crude product, purified to give a colourless oil by reversed-phase chromatography (56%) (Found: C, 69.5; H, 11.5; N, 2.8. $C_{28}H_{55}NO_5$ requires C, 69.2; H, 11.4; N, 2.9%); $\nu_{max.}$(neat) 1 630 (C=O) and 1 120 and 1 105 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.88 (3 H, t, *J* 6 Hz, $CH_3[CH_2]_{11}$), 1.12 (6 H, t, *J* 7 Hz, CH_3CH_2N), 1.18—1.32 (22 H, m, $CH_3[CH_2]_{11}$), 1.56—1.78 (2 H, m, $OCH_2CH_2CH_2O$), 2.11 (2 H, s, CCH_2CO), 3.10—3.50 (8 H, m, $OCH_2CH_2CH_2O$ and NCH_2), and 3.50—3.64 (12 H, m, CH_2O); *m/z* 485 (M^+, 9.3%) and 115 (100).

Bis(octyloxymethyl)-14-crown-4 (**19**) [6,6-*Bis*(*octyloxymethyl*)-1,4,8,11-*tetraoxacyclotetradecane*].—Compound (**11**) was prepared from 5,5-bis(hydroxymethyl)-2-phenyl-1,3-dioxane[10] according to the general procedure. The spiro-14-crown-4 was hydrolysed by refluxing in 0.1M-H_2SO_4 to yield the corresponding bis(hydroxymethyl) derivative. In a solution of bis(hydroxymethyl)-14-crown-4 (*ca.* 3.3 mmol) in dioxane (50 ml), NaH (7.6 mmol) was suspended and the mixture was refluxed with stirring for 0.5 h. To the refluxing suspension was added dropwise a solution of octyl tosylate (7.6 mmol) in dioxane (10 ml). Refluxing was continued for 20 h. The mixture was then filtered and the solvent was replaced by $CHCl_3$. The $CHCl_3$ solution was washed with dilute HCl and water. Chromatography on silica gel (gradient elution; benzene–methanol) and reversed-phase chromatography (ODS; MeOH) yielded the pure product as a colourless *oil* (12%) (Found: C, 68.6; H, 11.6. $C_{28}H_{56}O_6$ requires C, 68.8; H, 11.6%); $\nu_{max.}$(neat) 1 130 and 1 110 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.91 (6 H, t, *J* 5 Hz, CH_3), 1.15—1.80 (26 H, m, $CH_3[CH_2]_6$ and $OCH_2CH_2CH_2O$), and 3.28—3.70 (24 H, m, CH_2O); *m/z* 488 (M^+, 2.7%) and 185 (100).

Bis(ethyl-14-crown-4-methyl) Dodecyl(methyl)malonate (**20**) {*Bis*-(1-*ethyl*-3,6,10,13-*tetraoxacyclotetradecanylmethyl*) *Dodecyl*(*methyl*)*malonate*}.—In a solution of compound (**12**) (1.9 mmol) in dry benzene (30 ml) was suspended AgCN (3 mmol), and the mixture was stirred for 1 h at room temperature. To the suspension was added a solution of dodecyl(methyl)malonyl chloride (0.7 mmol) in benzene (10 ml); the mixture was refluxed for a week, then filtered and evaporated. Compound (**20**) was purified by reversed-phase chromatography (ODS; MeOH) and isolated as a colourless *oil* (32%) (Found: C, 65.1; H, 10.2. $C_{42}H_{78}O_{12}$ requires C, 65.1; H, 10.1%); $\nu_{max.}$(neat) 1 725 (C=O) and 1 130 and 1 110 cm^{-1} (C–O–C); δ_H(100 MHz; CCl_4) 0.74—1.02 (9 H, m, $CH_3[CH_2]_{11}$ and CH_3CH_2C), 1.06—1.52 (27 H, m, $CH_3[CH_2]_{10}$, CH_3C, and CH_3CH_2C), 1.52—1.90 (6 H, m, $OCH_2CH_2CH_2O$ and $CH_3[CH_2]_{10}CH_2$), 3.32 (8 H, s,

OCH_2CCH_2O), 3.42—3.72 (24 H, m, CH_2O), and 3.88 (4 H, s, CCH_2OCO); *m/z* 775 (M^+, 0.6%) and 103 (100).

Other Chemicals.—Unless otherwise stated all reagents were of the highest grade. The synthesis of dodecyl- and dodecylmethyl-14-crown-4 [(**1**) and (**2**)] has been reported previously.[6] *o*-Nitrophenyl octyl ether was prepared by a modification of the procedure in the literature.[12] Poly(vinyl chloride) (average polymerization degree 1 100) was purified by reprecipitation from tetrahydrofuran in methanol. Potassium tetrakis-(*p*-chlorophenyl)borate was obtained in the usual manner.[13] Water was deionized and distilled.

Measurements of Selectivity Coefficient.—The polymeric membranes containing the crown ethers were prepared according to the procedure reported previously.[6] A disc of 5 mm diameter was cut from each membrane and then incorporated into the electrode body of a Philips IS-561 instrument. The internal filling solution was aqueous 1M-LiCl. The external reference electrode was a double-junction type Ag/AgCl electrode. The electrochemical cell for the e.m.f. measurements was Ag, AgCl/1M-LiCl/PVC membrane/sample solution/0.1M-NH_4NO_3/4M-KCl/AgCl, Ag. The e.m.f. measurements were conducted at 25 °C, by using a pH/mV meter with high input impedance. The selectivity coefficient, as defined in the Nicolsky–Eisenman equation,[14] was determined by the fixed interference method according to the IUPAC recommendation.[15] The e.m.f.–Li^+ activity plots were extrapolated so that the linear portion of the curve possessed a Nernstian slope of 59—60 mV per decade. The background concentrations for the second ions (interfering ions) were 5×10^{-2}M for alkali metal ions and H^+ and 5×10^{-1}M for alkaline-earth metal ions and NH_4^+.

Results and Discussion

Strategy.—The 14-crown-4 ring forms a stable 1:1 complex with Li^+, probably because the cation fits into the ring cavity. The 1:1 stoicheiometry has been confirmed conductometrically for Li^+ complexation of other 14-crown-4 derivatives.[6] On the other hand, Na^+ and K^+, the sizes of which exceed that of the cavity, are likely to form 2:1 (crown ether–cation) sandwich-type complexes, especially at high crown ether concentrations. The 2:1 stoicheiometry of the cation complexes with some 14-crown-4 derivatives [such as (**1**)] is supported by the finding that the selectivities for Li^+ as opposed to Na^+ and K^+ in membranes containing the crown ethers are diminished with increasing crown ether concentrations in the membrane. In other words, when the 14-crown-4 derivatives complex easily with Na^+ and K^+, with 2:1 stoicheiometry, the selectivities of the macrocycles for Li^+ are lowered [as also evidenced by the selectivity of a bis-(14-crown-4) derivative; see later].

Our strategy for enhancing the selectivities of the 14-crown-4 ring for Li^+ as opposed to Na^+ and K^+ was to incorporate bulky groups into the macrocycle at the centre of a trimethylene unit, and thereby to prevent 2:1 complex formation with Na^+ and K^+. Substituents used were octyl, dodecyl, and benzyl. The alternative strategy was to introduce additional binding sites which might interact favourably with Li^+. Incorporation of a potential binding site geminal to another substituent at the 6-position of the crown ring would be advantageous for axial interaction with Li^+; we chose ether, ester, phosphate, quinoline, and amide groups for study.

Lithium Selectivity of Disubstituted 14-*Crown*-4 *Derivatives.*—Lithium selectivities of the 14-crown-4 derivatives synthesized here were evaluated in terms of the potentiometric selectivity coefficients of polymeric membranes containing them. The membranes consisted of a poly(vinyl chloride) (PVC) support, *o*-nitrophenyl octyl ether as membrane solvent, and the crown ethers. A small quantity of potassium tetrakis-(*p*-chlorophenyl)-borote was also contained in the membranes, to reduce electrical resistance. The addition of the lipophilic salt scarcely affected the ion selectivities of the membranes. The selectivity coefficients of Li^+ with respect to alkali and alkaline-earth

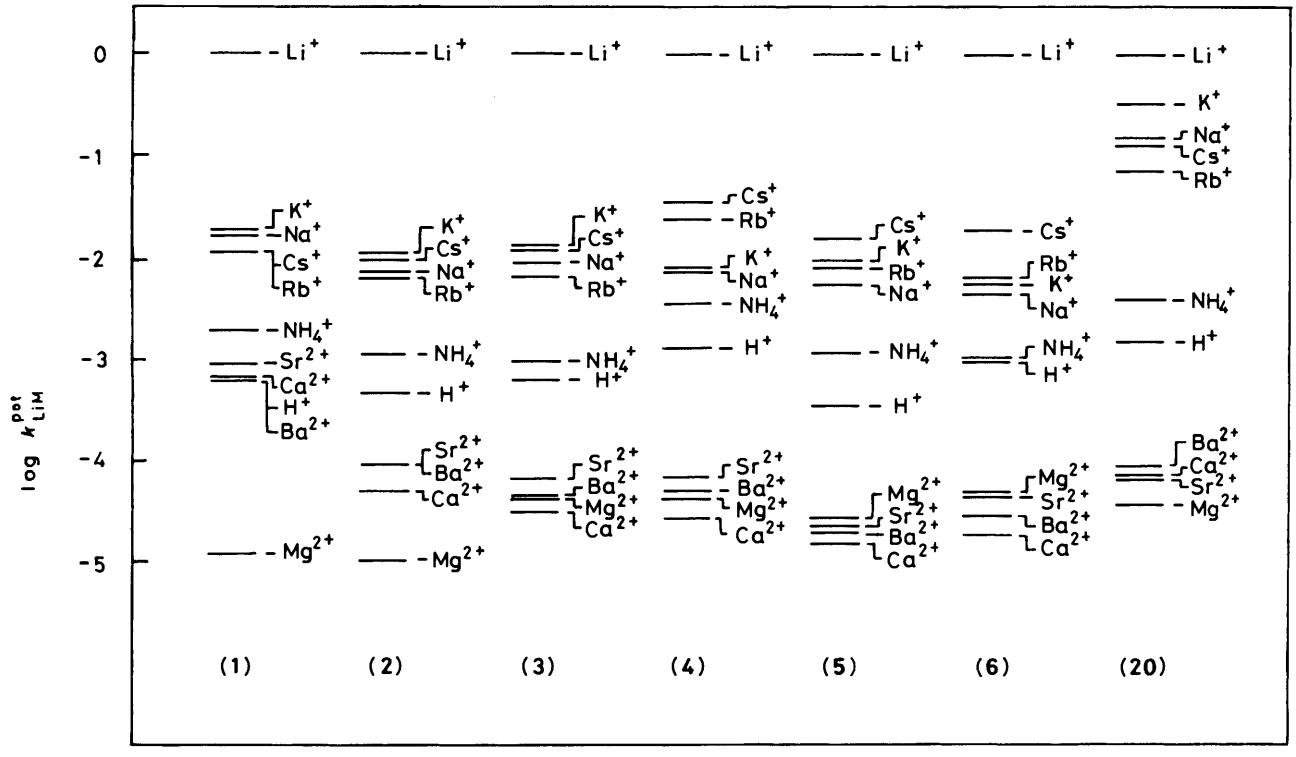


Figure 1. Selectivity coefficients for membranes of 14-crown-4 derivatives bearing bulky substituents and a bis-(14-crown-4) derivative

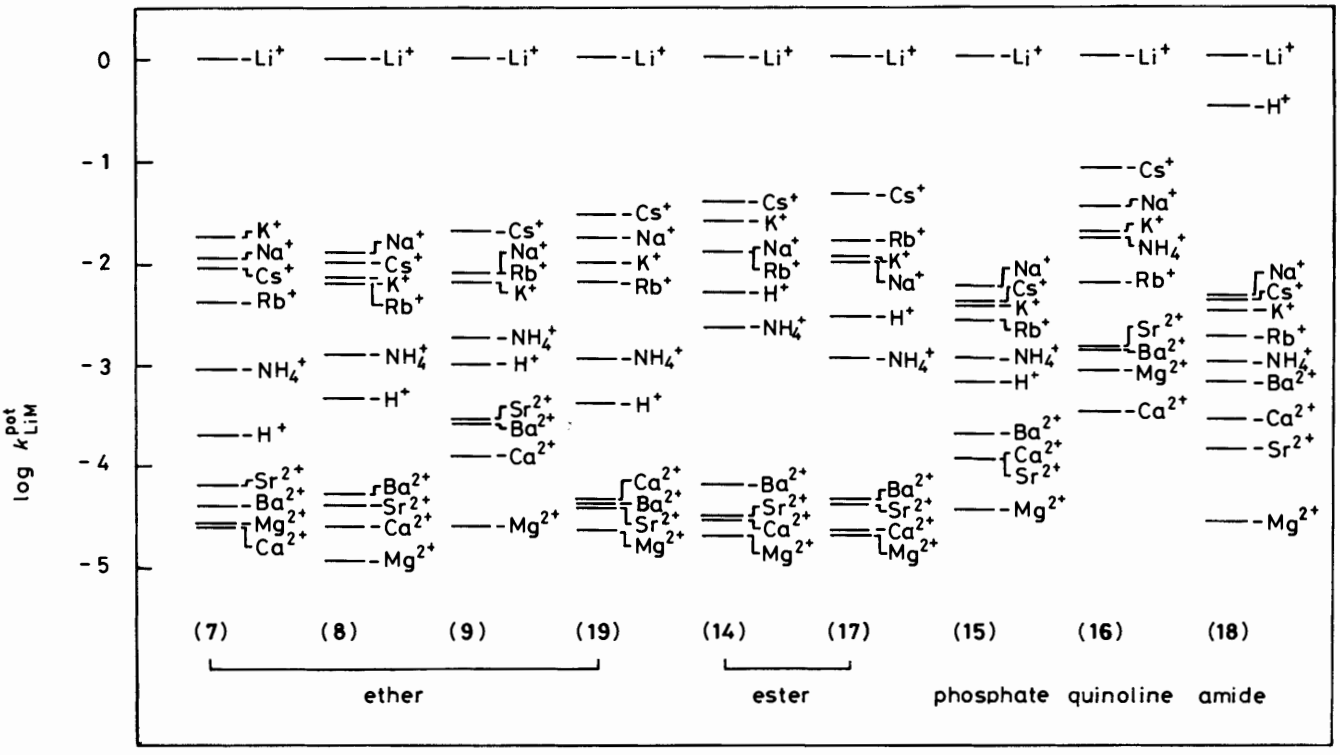


Figure 2. Selectivity coefficients for membranes of 14-crown-4 derivatives bearing potential binding sites in the side-chain

Table. Values of selectivity coefficients for Li^+ with respect to Na^+ and K^+ for membranes containing 14-crown-4 derivatives

	k^{pot}_{LiM}		$1/k^{pot}_{LiM}$	
Compound	Na^+	K^+	Na^+	K^+
(1)	1.6×10^{-2}	1.9×10^{-2}	62	54
(2)	6.9×10^{-3}	1.1×10^{-2}	145	91
(3)	8.7×10^{-3}	1.4×10^{-2}	115	72
(4)	7.4×10^{-3}	7.8×10^{-3}	135	129
(5)	5.4×10^{-3}	9.3×10^{-3}	186	107
(6)	4.4×10^{-3}	5.5×10^{-3}	229	182
(7)	1.1×10^{-2}	1.9×10^{-2}	91	54
(8)	1.3×10^{-2}	7.4×10^{-3}	78	135
(9)	7.8×10^{-3}	6.2×10^{-3}	129	162
(14)	1.4×10^{-2}	2.6×10^{-2}	72	38
(15)	5.5×10^{-3}	3.5×10^{-3}	182	288
(16)	3.4×10^{-2}	1.9×10^{-2}	30	54
(17)	9.5×10^{-3}	1.1×10^{-2}	105	93
(18)	4.4×10^{-3}	3.2×10^{-3}	229	316
(19)	1.7×10^{-2}	1.0×10^{-2}	58	98
(20)	5.0×10^{-2}	3.5×10^{-1}	20	3

metal ions, H^+, and NH_4^+ are illustrated in Figures 1 and 2. The values of the selectivity coefficient of Li^+ with respect to Na^+ and K^+, which should be compared in discussing the relationship between selectivity and the structure of the crown ether, are listed in the Table. For comparison, the values for the 14-crown-4 derivatives (**1**) and (**2**) and a bis-(14-crown-4) derivative (**20**) are also given. The selectivity coefficient, k^{pot}_{LiM}, is defined as the preference of the membrane for Li^+ over the other metal ions (M). The smaller the k^{pot}_{LiM} value, the higher the selectivity of the crown ether membrane for Li^+. The reciprocal, $1/k^{pot}_{LiM}$, is termed the selectivity ratio of Li^+ over M^+.

Perusal of the selectivity coefficient values shows that of the monocyclic 14-crown-4 derivatives are quite selective for Li^+. Selectivities for Li^+ as opposed to Na^+ and K^+ are much less for the bis-(14-crown-4) derivative, which tends to form sandwich-type complexes with Na^+ and K^+ easily by co-operative action of two adjacent crown rings. In the opposite sense, this finding supports strongly the possibility that incorporation of bulky substituents into the 14-crown-4 ring interferes with the proximity of two crown ether rings required for 2:1 complex formation and, therefore improves the selectivity of the macrocycle for Li^+ with respect to Na^+ and K^+. Obviously, 14-crown-4 derivatives bearing two alkyl and/or benzyl groups [(**2**)—(**6**)] are superior to the crown ether (**1**) with only one such group. Employment of a benzyl group as the bulky substituent [in (**5**) and (**6**)] enhanced the selectivities. The selectivity ratio of Li^+ over Na^+ ($1/k^{pot}_{LiM}$) is increased by a factor of 1.5 in (**6**) as compared with (**2**). Furthermore, when a mixture of *o*-nitrophenyl phenyl ether and tris-(2-ethylhexyl) phosphate (90:10) was used as the membrane solvent instead of *o*-nitrophenyl phenyl ether alone, the PVC membrane containing (**6**) exhibited an excellent k^{pot}_{LiM} value of 1.7×10^{-3}, the best value for neutral carrier-based Li^+-selective electrodes obtained so far.

There is a distinct effect of additional binding sites on selectivity. However, in comparison with the 14-crown-4 (**2**), significant enhancement in selectivities for Li^+ with respect to Na^+ and K^+ was not observed for the 14-crown-4 derivatives bearing the potential binding sites except in the case of the amide group. The incorporation of the ether and ester groups decreases rather than increases the selectivities for Li^+ as against Na^+ and K^+. This observation may be explained by the so-called 'lariat-ether' effect.[16] That is to say, crown ethers carrying oligo-oxyethylene side-chains are likely to show increased affinity for cations which are larger than the crown cavities.[17,18] In the 14-crown-4 derivatives with ethereal side-chains, Na^+ and K^+ complexation is promoted and Li^+ selectivities against the cations are in the opposite sense diminished. In contrast crown ethers incorporating a phosphate or an amide group [(**15**) and (**18**)] exhibit improved selectivities

for Li^+ with respect to Na^+ and K^+. This is probably due to the co-ordinating property of the additional binding sites, which favours cations with high charge density like Li^+. In particular (**18**) is similar to the dibenzyl derivative (**6**) in the selectivity for Li^+ against Na^+, and (**18**) exceeds (**6**) in selectivity against K^+. Naturally, selectivities for Li^+ against alkaline-earth metal ions and H^+ are lower for (**15**) and (**18**). The employment of a quinoline group also possessing co-ordinating properties, as in (**16**), however, did not afford any appreciable enhancement in selectivities for Li^+.

Thus, this work has proved that the incorporation of bulky substituents or additional binding sites for Li^+ into the 14-crown-4 ring can enhance the selectivities of the parent macrocycle for Li^+ with respect to Na^+ and K^+.

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