Lipophilic Bis(crown ether) Derivatives of 15-Crown-5 and 18-Crown-6 as Neutral Carriers of Ion-selective Electrodes

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Lipophilic bis(crown ethers) containing 15-crown-5 and 18-crown-6 rings were synthesized so as to obtain excellent neutral carriers for K^+- and Cs^+-selective electrodes, respectively. The K^+-selective electrode based on the dodecylmethylmalonate of bis(15-crown-5), (I) ($n = 1$, R = Me), exhibited eminent electrode properties, proving of great practical use, while the Cs^+-selective electrode of the bis(18-crown-6) derivative (I) ($n = 2$, R = Me) did not give results as good as expected. The electrochemical selectivities of the K^+ electrode based on the dodecylmalonate of bis(15-crown-5), (I) ($n = 1$, R = H), and octadecanoyloxymethyl-15-crown-5 (II) are also discussed.

Crown ethers have enjoyed widespread use in various fields since their introduction. They also have a good future as ionophores (neutral carriers) for ion-selective electrodes, which are convenient analytical tools for determining ionic species in solutions. Crown ether-based ion-selective electrodes, which are attractive particularly for analyses of alkali and alkaline earth metal ions, have been tested so far for their usefulness.[1-5]

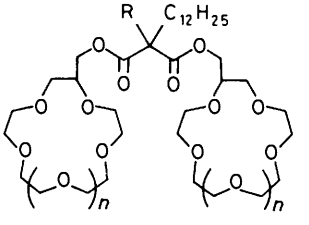
We recently communicated preliminary results[6] of K^+-selective electrodes using lipophilic bis(crown ether) (I) ($n = 1$, R = Me). The main electrodic property is believed to arise predominantly from the macrobicyclic structure, by which the bis(crown ether) is thought to form stable sandwich-type K^+ complexes intramolecularly, and the high lipophilicity of the long aliphatic chain. Very recently, we also synthesized a bis(18-crown-6) derivative with a similar structure, (I) ($n = 2$, R = Me), aimed at producing high-performance Cs^+-selective electrodes.

In this paper, we report in detail the syntheses of the lipophilic bis(crown ether) derivatives and their electrodic properties as K^+- and Cs^+-selective electrodes of the coated-wire type. The K^+-selective electrodes based on the 2-monosubstituted malonate of bis(15-crown-5), (I) ($n = 1$, R = H), and a monocyclic analogue (II) are also described for comparison.

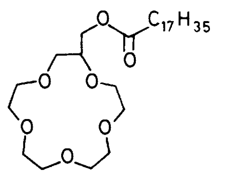
Experimental

Hydroxymethyl-15-crown-5 or 2-Hydroxymethyl-1,4,7,10,13-pentaoxapentadecane.—The crown ether was obtained by condensation of 1,2-dihydroxy-3-benzyloxypropane with 1,11-dichloro-3,6,9-trioxaundecane in t-butyl alcohol in the presence of lithium t-butoxide and lithium bromide, followed by hydrogenolysis on palladium carbon, in a modification of the published method for the 12-crown-4 cycle.[7] Vacuum distillation gave a colourless viscous liquid, b.p. 120—134 °C (0.02 Torr); $\nu_{max.}$(neat) 3 320 (OH) and 1 120 cm^{-1} (C–O–C); δ_H (100 MHz; $CDCl_3$) 3.20 (1 H, s, OH) and 3.5—3.9 (21 H, m, CH_2 and CH); *m/z* 250 (M^+, 0.2%) and 45 (100). Hydroxymethyl-18-crown-6 or 2-hydroxymethyl-1,4,7,10,13,16-hexaoxaoctadecane had b.p. 140—153 °C (0.015 Torr); δ_H (100 MHz; $CDCl_3$) 3.20 (1 H, s, OH) and 3.5—3.9 (25 H, m, CH_2 and CH); *m/z* 294 (M^+, 0.2%) and 45 (100).

Lipophilic Bis(crown ether)s (I) (n = 1, 2; R = Me, H).—The bis(crown ether)s were synthesized by the reaction of the hydroxymethylcrown ethers with the corresponding malonic chloride derivatives with the aid of silver cyanide.[8]



(I) (n=1,2; R =Me,H)



(II)

In a typical procedure, dry silver cyanide (2.81 g, 20.9 mmol) was suspended in a dry benzene solution (200 ml) of hydroxymethyl-15-crown-5 (3.23 g, 12.9 mmol), and then 2-dodecyl-2-methylmalonic chloride (1.74 g, 5.38 mmol) dissolved in benzene (10 ml) was added to the suspension. The mixture was allowed to reflux with vigorous stirring for about a week. After being cooled to room temperature, the reaction mixture was passed through a short Celite column and most of the product was eluted out with benzene. Preparative scale gel permeation chromatography and/or reversed-phase chromatography yielded a pure product of the *dodecylmethylmalonate of bis*(15-*crown*-5), (I) (n = 1, R = Me), or 2,2-*bis*[(1′,4′,7′,10′,13′-*pentaoxacyclopentadecyl*)*methoxycarbonyl*]*tetradecane* (1.6 g, 40%), colourless oil (Found: C, 60.76; H, 9.41. $C_{38}H_{70}O_{14}$ requires C, 60.78; H, 9.40%); $\nu_{max.}$(neat) 1 730 (C=O) and 1 250 cm^{-1} (C–O–C); δ_H (100 MHz, $CDCl_3$) 0.88 (3 H, t, CH_2CH_3), 1.24 (20 H, m, $CH_2CH_2CH_2$), 1.40 (3 H, s, CMe), 1.84 (2 H, t, CCH_2CH_2), 3.4—3.9 (38 H, m, CH_2OCH_2 and CH), and 4.1—4.3 (4 H, m, CO_2CH_2); *m/z* 750 (M^+, 2%) and 45 (100). This bis(15-crown-5) derivative can also be prepared by the ester-exchange reaction[9] of diethyl 2-dodecyl-2-methylmalonate with hydroxymethyl-15-crown-5, but the proposed method using silver cyanide gave a better result.

Dodecylmethylmalonate of *bis*(18-*crown*-6), (I) (n = 2, R = Me), or 2,2-*bis*[(1′,4′,7′,10′,13′,16′-*hexaoxacyclo-octadecyl*)-*methoxycarbonyl*]*tetradecane* was also a colourless oil (Found: C, 60.06; H, 9.54. $C_{42}H_{78}O_{16}$ requires C, 60.12; H, 9.37%); $\nu_{max.}$(neat) 1 730 (C=O) and 1 250 cm^{-1} (C–O–C); δ_H (100 MHz; $CDCl_3$) 0.88 (3 H, t, CH_2CH_3), 1.24 (20 H, m, $CH_2CH_2CH_2$), 1.40 (3 H, s, CMe), 1.84 (2 H, t, CCH_2CH_2), 3.5—3.9 (46 H, m, CH_2OCH_2 and CH), and 4.1—4.3 (4 H, m, CO_2CH_2); *m/z* 839 (M^+, 0.4%) and 45 (100).

Similarly, the reaction using 2-dodecylmalonic chloride afforded the *dodecylmalonate of bis*(15-*crown*-5), (I) (n = 1, R = H), or 1,1-*bis*[(1′,4′,7′,10′,13′-*pentaoxacyclopentadecyl*)-*methoxycarbonyl*]*tridecane* as a colourless oil (Found: C, 60.72; H, 9.44. $C_{37}H_{68}O_{14}$ requires C, 60.30; H, 9.30%); $\nu_{max.}$(neat) 1 730 (C=O) and 1 140 cm^{-1} (C–O–C); δ_H (100

MHz; $CDCl_3$) 0.85 (3 H, t, Me), 1.20 (20 H, m, $CH_2CH_2CH_2$), 1.8—2.0 (3 H, m, $CHCCH_2$), 3.4—3.9 (38 H, m, CH_2OCH_2 and OCH), 4.1—4.3 (4 H, m, CO_2CH_2); m/z 736 (M^+, 1%) and 45 (100).

Octadecanoyloxymethyl-15-*crown*-5 (II) *or* 2-*Octadecanoyloxymethyl*-1,4,7,10,13-*pentaoxacyclopentadecane*.—Hydroxymethyl-15-crown-5 (2.0 g, 8 mmol) and triethylamine (1.21 g, 12 mmol) were dissolved in dry benzene (100 ml), and octadecanoyl chloride (3.03 g, 10 mmol) in dry benzene (30 ml) was added dropwise to the solution which was being stirred with cooling in an ice-bath. After the careful addition the reaction mixture was then refluxed for 40 h. The benzene solution was washed with water, and the solvent was evaporated off. Silica gel column chromatography with ethyl acetate–acetone (3 : 1) as eluant gave a pure product of *octadecanoyloxymethyl*-15-*crown*-5 (2.7 g, 65%), m.p. 35—35.5 °C (Found: C, 67.80; H, 11.10. $C_{29}H_{56}O_7$ requires C, 67.40; H, 10.92%); $\nu_{max.}$(neat) 1 730 (C=O) and 1 120 cm^{-1} (C–O–C); δ_H (100 MHz; $CDCl_3$) 0.88 (3 H, t, Me), 1.24 (30 H, m, $CH_2CH_2CH_2$), 2.30 (2 H, t, CH_2CO), 3.5—3.9 (19 H, m, CH_2OCH_2 and CH), and 4.16 (2 H, t, CO_2CH_2); m/z 516 (M^+, 3%) and 45 (100).

Other Chemicals.—The plasticizer of the polymeric membrane, *o*-nitrophenyl octyl ether (NPOE), was prepared using a procedure in the literature.[10] Poly(vinyl chloride) (PVC) with an average polymerization degree of about 1 100 was purchased from Wako, Japan, and purified by reprecipitation from tetrahydrofuran (THF) in methanol. Analytical-reagent grade metal salts were utilized without further purification. Water was demineralized and distilled.

Electrodes and Potentiometry.—The coated-wire ion-selective electrodes (CWISEs) based on the crown ethers were constructed according to the procedure reported previously.[5,11] The coating solution contained 10—12 mg (3.2—3.8% w/w) of crown ether [except in the case of (II)], 200 mg of NPOE, 100 mg of PVC, and 3 ml of THF, unless otherwise stated. The K^+- and Cs^+-electrodes were conditioned by soaking in 0.05M-KCl and -CsCl aqueous solutions, respectively. The reference electrode was a calomel electrode combined with a 0.1M-NH_4NO_3 agar bridge. The e.m.f. measurements were made at 25 ± 0.1 °C using a Corning 130 type pH–mV meter. On the e.m.f. reading, the sample solution was stirred at a rate of about 500 rev min^{-1}, although the stirring rate did not seem crucial. Selectivity coefficients (k_{MN}) were determined by a mixed solution method, by taking a constant background of an interfering ion and varying primary ion concentrations.

Results and Discussion

Highly lipophilic bis(crown ethers) (I) (n = 1, 2; R = Me, H) were synthesized, with the aim of producing high-performance ion-selective electrodes. Ion-selective electrodes of the coated-wire type,[12] where a silver wire was coated with PVC membrane including a crown ether and a plasticizer, were selected, their construction being simple.

Lipophilic Bis(15-*crown*-5) *Derivatives for* K^+-*selective Electrodes*.—The bis(15-crown-5) derivatives (I) (n = 1) were expected to be suitable for neutral carriers of K^+-selective electrodes. The calibration plots and selectivity curves for the K^+-selective electrode of the dodecylmethylmalonate of bis(15-crown-5), (I) (n = 1, R = Me), are depicted in Figure 1. The K^+-electrode showed a linear response to the K^+ activity in the range 1 × 10^{-4}—1 × 10^{-1}M-KCl, the slope being near-Nernstian (55 mV per decade of activity range).

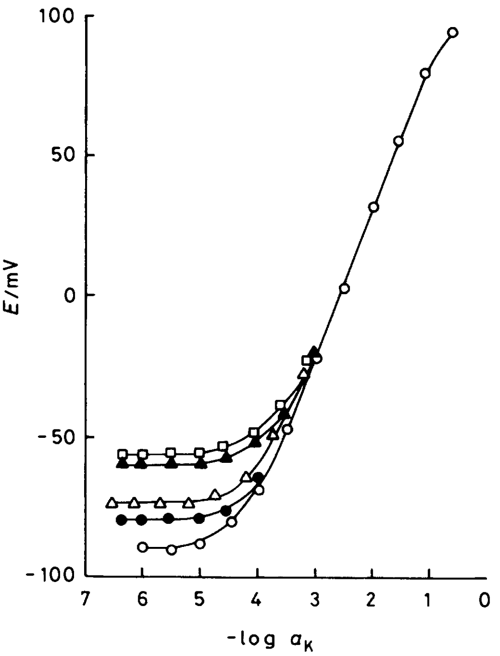


Figure 1. Calibration plots and selectivity curves for K^+-selective electrode based on the dodecylmethylmalonate of bis(15-crown-5), (I) (n = 1, R = Me). Calibration plots (○); selectivity curves in the presence of 1 × 10^{-2}M-NH_4Cl (□), 1 × 10^{-3}M-RbCl (▲), 1M-NaCl (△), and 1 × 10^{-3}M-CsCl (●)

Selectivity coefficients (k_{KM}) of the K^+ electrode based on (I) (n = 1, R = Me), which were calculated from the selectivity curves, are given in Table 1. The value decreases in the order $Rb^+ > NH_4^+ > Cs^+ > Na^+$ (the smaller the k_{KM} value, the higher the preference for K^+ over M^+ in the electrode), which may also be anticipated from the cation-binding abilities of the previous bis(benzo-15-crown-5) derivatives.[3,13] The most striking is the extremely high preference for K^+ over Na^+ in the electrode, which seems almost comparable to that of the K^+-selective electrode based on valinomycin, a highly efficient, naturally occurring K^+ ionophore.

The dodecylmalonate of bis(15-crown-5), (I) (n = 1, R = H), which does not carry a 2-methyl group unlike the bis(crown ether) (I) (n = 1, R = Me), was also tested for its usefulness as a neutral carrier of K^+-selective electrodes. The K^+ electrode based on (I) (n = 1, R = H) afforded similar calibration plots and maximum slopes to those of the (I) (n = 1, R = Me) -based electrode, but some difference in the selectivity coefficient was observed between two of the bis(15-crown-5) derivatives. The dodecylmalonate of bis(15-crown-5) electrode is slightly worse in its preference for K^+ over Na^+ and Rb^+ than the dodecylmethylmalonate derivative, as can be seen in Table 1. Also, on removing the 2-methyl substituent from the dodecylmethylmalonate of bis(15-crown-5), there is a remarkable drop in the preference for K^+ over Cs^+ in the K^+ electrodes. This selectivity change may be attributed to the rigidity difference between the bis(crown ethers), *i.e.*, CPK molecular model considerations suggested that the dodecylmalonate of bis(15-crown-5), (I) (n = 1, R = H), is more flexible than the dodecylmethylmalonate derivative, (I) (n = 1, R = Me).

For comparison with the bis(15-crown-5) derivatives, a lipophilic monocyclic analogue, octadecanoyloxymethyl-15-crown-5 (II), was also used as a neutral carrier of K^+-selective electrodes. The selectivity coefficients of K^+ over Na^+ (k_{KNa}) for the K^+ electrode based on (II) varied remark-

Table 1. Electrode properties of K^+-selective electrodes based on bis(15-crown-5) (I) (n = 1, R = Me, H) and monocyclic 15-crown-5 derivative (II)

Crown ether	Maximum slope (mV per decade)	pK range[b]	Selectivity coefficient (k_{KM})			
			Na^+	Rb^+	Cs^+	NH_4^+
(I) (n = 1, R = Me)	55	4—1	2×10^{-4}	2×10^{-1}	1×10^{-2}	4×10^{-2}
(I) (n = 1, R = H)	55	4—1	4×10^{-4}	3×10^{-1}	2×10^{-1}	3×10^{-2}
(II)[a]	53	3.5—1	2×10^{-3}	4×10^{-1}	3×10^{-1}	5×10^{-2}

[a] The content of (II) in the PVC membrane of the electrode was 5% w/w. [b] pK = $-\log [K^+]$.

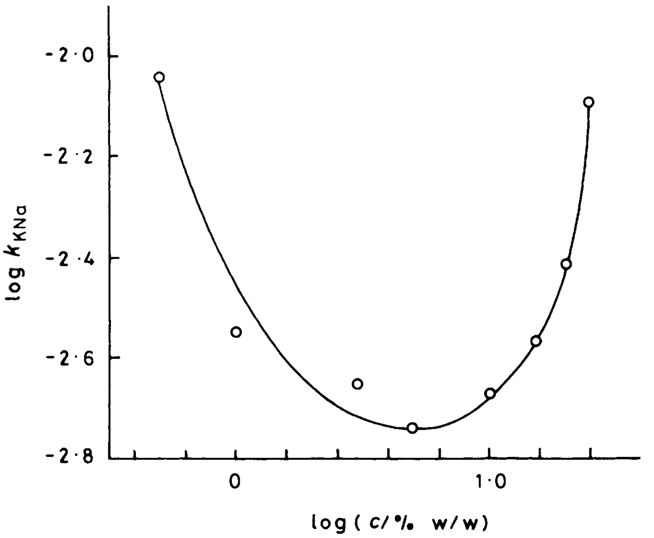


Figure 2. Dependence of neutral carrier concentration (c) in PVC membrane upon selectivity coefficient for a K^+-selective electrode based on octadecanoyloxymethyl-15-crown-5 (II)

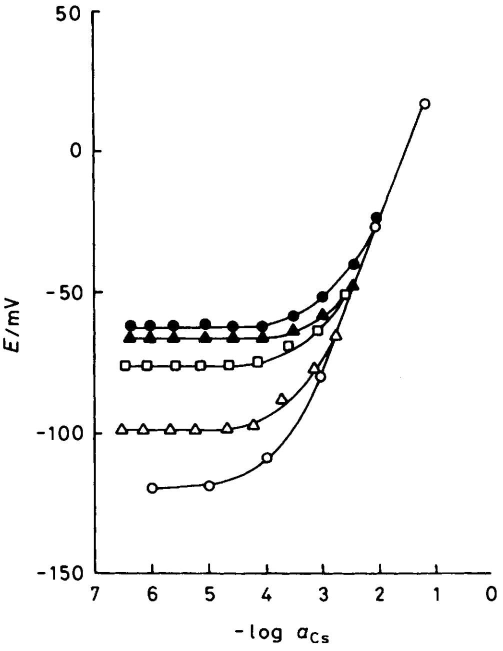


Figure 3. Calibration plots and selectivity curves for a Cs^+-selective electrode based on the dodecylmethylmalonate of bis(18-crown-6), (I) (n = 2, R = Me). Calibration plots (○); selectivity curves in the presence of 1×10^{-2}M-KCl (●), 1M-NaCl (△), 1×10^{-2}M-RbCl (▲), and 1×10^{-1}M NH_4Cl (□)

ably with the crown ether concentration in the PVC membrane, as illustrated in Figure 2, although the values for both of the K^+-selective electrodes based on bis(crown ether)s (I) (n = 1, R = Me and H) were essentially independent of the crown ether concentration. The k_{KNa} value for the electrode based on (II) decreased with a rise in the crown ether concentration in the PVC membrane up to about 5% w/w. However, the value increased with concentrations over 5% w/w. This dependence of ion selectivity on neutral carrier concentration in the K^+-selective electrode of the monocyclic 15-crown-5 derivative implies that various metal ion species such as 2 : 1 and 1 : 1 crown ether-to-ion complexes are formed with the monocyclic crown ether in the PVC membrane.[14] Thus, the highest preference for K^+ over Na^+ for the K^+ electrode based on octadecanoyloxymethyl-15-crown-5 was attained at *ca.* 5% w/w of the crown ether concentration, the k_{KNa} value being 2×10^{-3}. However, the monocyclic crown ether is worse in its preference for K^+ over Na^+ in the electrode than the dodecylmethylmalonate of bis(15-crown-5) by about one order of magnitude. This finding strongly supports the view that the macrobicyclic structure of the bis(15-crown-5) derivatives contributes intrinsically to the excellent K^+ selectivity. Furthermore, the monocyclic crown ether, (II), was inferior to the bis(crown ethers), (I), in the linearity of calibration plots and in the sensitivity of the K^+-selective electrodes.

Lipophilic Bis(18-*crown*-6) *Derivative for* Cs^+-*selective Electrodes*.—The dodecylmethylmalonate of bis(18-crown-6), (I) (n = 2, R = Me), was tried as a neutral carrier of Cs^+-selective electrodes, because bis(18-crown-6) derivatives are likely to complex Cs^+ rather strongly, in a manner similar to the bis(15-crown-5) derivative–K^+ systems. The calibration plots and the selectivity curves for the Cs^+ electrode are shown in Figure 3, the electrode properties being summarized in Table 2, together with those of a bis(benzo-18-crown-6) derivative reported previously.[4] It seems that the lipophilic bis(18-crown-6) derivative (I) (n = 2, R = Me) is not as good as the previous bis(benzo-18-crown-6) derivative in its electrode properties. In particular the former bis(crown ether) is distinctly inferior to the latter in the maximum slope of the calibration plots, which is indicative of the electrode sensitivity. One of the reasons may be that in bis(crown ether) (I) (n = 2, R = Me) two crown ether rings are a little too close to each other for the formation of stable intramolecular sandwich-type Cs^+ complexes, as has been suggested elsewhere.[3,4,15]

Table 2. Electrode properties of Cs^+-selective electrode based on bis(18-crown-6) (I) ($n = 2$, R = Me) and a bis(benzo-18-crown-6) derivative

Crown ether	Maximum slope (mV per decade	pCs range [b]	Selectivity coefficient (k_{CsM})			
			Na^+	K^+	Rb^+	NH_4^+
(I) ($n = 2$, R = Me)	51	3—1	1×10^{-3}	1×10^{-1}	1×10^{-1}	1×10^{-2}
bis(benzo-18-crown-6) [a]	59	6—2	9×10^{-4}	8×10^{-2}	8×10^{-2}	9×10^{-3}

[a] 1,5-Bis[3′,4′-(1″,4″,7″,10″,13″,16″-hexaoxacyclo-octadec-2″-enyl)benzyloxycarbonyl]pentane; these values were determined for a conventional PVC membrane electrode as described in ref. 4. [b] pCs = $-\log [Cs^+]$.

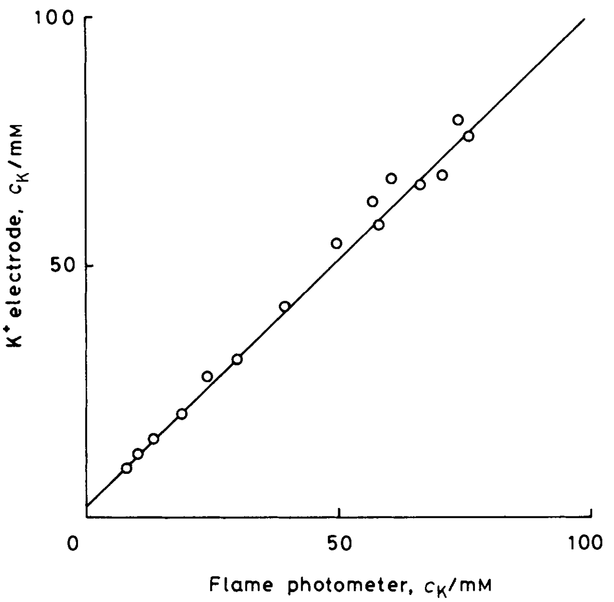


Figure 4. Correlation of results of K^+ determination in human urine samples obtained by flame photometry and potentiometry using a K^+-selective electrode of bis(crown ether) (I) ($n = 1$, R = Me). The human urine samples were diluted 100-fold. The procedures were identical with those in ref. 11. Slope 0.994, r 0.994, intercept 2.85

Practical Use of a K^+-selective Electrode based on Bis(crown Ether) (I) ($n = 1$, R = Me).—The K^+-selective electrode based on the dodecylmethylmalonate of bis(15-crown-5) was tested for its practical use. Determination of K^+ in human urine samples was carried out using 16 samples, and the results were compared with those obtained by flame photometry. Figure 4 demonstrates the linear correlation between the potentiometric and flame-photometric data. The slope (0.994) and the relative coefficient (0.994) of the straight line are very close to unity, although the intercept (2.85) showed a slight positive value, which is possibly due to an error in calculation using the least-square methods. Therefore the K^+-selective electrode can offer reliable data in practical applications. Thus, the dodecylmethylmalonate of bis(15-crown-5), (I) ($n = 1$, R = Me), proved a promising neutral carrier for K^+-selective electrodes.

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