

POTENTIOMETRIC EVALUATION OF THE ION-SELECTIVE CHARACTERISTICS OF 1,4-BRIDGED CUBYL DIESTER CROWN ETHERS

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Cubane diester crown ethers were tested as ion-selective electrodes in poly(vinyl chloride) (PVC) membranes. The four ionophores studied proved to be good K^+ neutral carriers, showing Nernstian and near-Nernstian responses to this ion, in the range 10^{-4} – 10^{-1} M. The fixed interferences method was used to determine relative selectivity coefficients for all the electrodes. The highest selectivity for potassium relative to sodium, lithium, calcium and magnesium ions using potassium tetrakis(*p*-chlorophenyl)borate (KTpCIPB) as a resistance modifier and NPOE as a plasticizer was obtained with the 1,4-cubyl diester-25-crown-7 ether ionophore. The effects of KTpCIPB on membrane selectivity were assessed; its removal was found to increase the selectivity of the four ionophores for potassium relative to cesium, sodium, calcium and magnesium ions with minimal effects on lithium and ammonium ions. The compounds tested exhibited a fast Nernstian response to changes in K^+ concentration which was stable to within $< 100 \mu V h^{-1}$.

INTRODUCTION

Ionophore-impregnated polymeric membrane-based ion-selective electrodes are now commonly used in a variety of analyses.¹⁻⁴ A huge amount of effort has been expended into the syntheses and characterization of these ionophores in order to improve both selectivity and detection limits. A large number of these compounds utilize a 1,3-xylene or 1,3- or 1,2-catechol unit as a nucleus, such as the macrocyclic polyethers⁵⁻⁷ and polythioethers.^{8,9} The benzene nucleus in such systems increases the hydrophobicity and rigidity of the ionophore, thus altering its partition and conformational properties, and in addition the π -system of the nucleus can act as a binding site especially in systems

where it protrudes into the cavity.⁶ In a continuing effort to identify useful macrocyclic structures for analytical and membrane applications, we have synthesized for the first time a new series of macrocyclic polyether structures in which the benzene nucleus is replaced with an alicyclic 1,4-bridged cubyl species. The cubyl nucleus is an ideal lipophilic component for ionophores because of its concentrated hydrophobicity,¹⁰ symmetry and low molecular weight [the partition coefficient ($\log \rho$) for cubane was determined using the shake-flask method in a water-chloroform system to be 1.57, which is much lower than that expected for an eight-carbon hydrocarbon system, reflecting the compact nature of the cubane structure with its very small solvent accessible surface area. The value for $\log \rho$ in an

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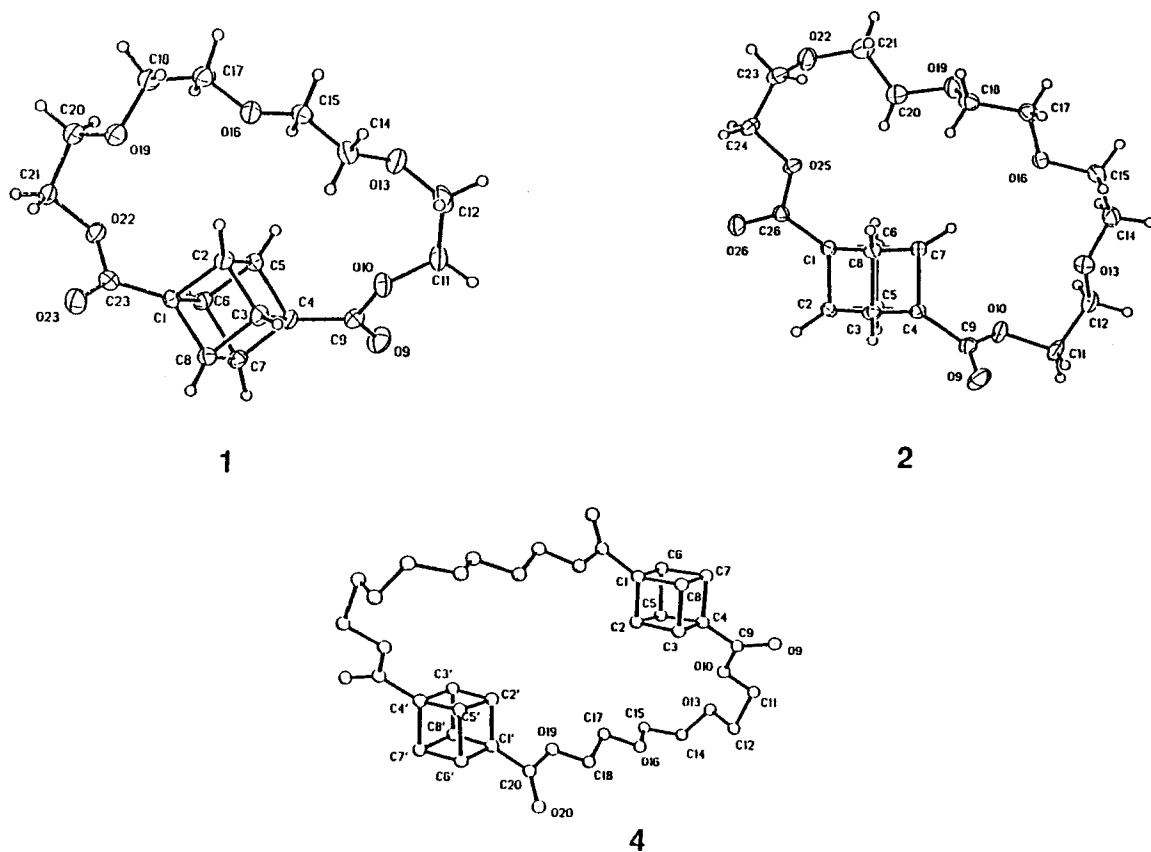


Figure 1. X-ray crystal structures of ionophores 1, 2 and 4

octane-1-ol-water system was computed using the CLOGP program of Hansch and Leo to be 1.26. This is again lower than expected for an eight-carbon system¹⁰].

The x-ray crystallographic structure of cubane diester crown ethers (1, 2 and 4) have been rigorously established¹¹ (see Figure 1). The results show the C—C, C—O and C=O distances have normal values of 1.42–1.55, 1.4–1.42 and 1.18–1.36 Å, respectively. Ionophores 1 and 2 possess no center of symmetry and the addition of the cubyl nucleus probably reduces the flexibility of the ring so that it adopts a typically *gauche* C—C conformation, the *trans*-lactone conformation being a common feature of all examples. Ionophore 4, the dinuclear example, possesses a center of symmetry which persists in solution and its structure is supported by ¹H NMR studies. Its crystal packing structure is centrosymmetric triclinic. ¹H NMR spectra show ionophore 1 to form stable complexes (1:1) with NaSCN, which readily undergoes decomposition on heating in CHCl₃, or washing with water. Ionophore

1 and NaSCN (1:1 or an excess) were heated in methanol over a steam-bath until a clear solution was obtained, then cooled and evaporated. The white solid remaining was dissolved in CDCl₃ and filtered. ¹H NMR spectra (400 MHz) of the above-complexed compound 1 shows a single merged multiplet for all OCH₂ (12H, m) protons at δ 3.55–3.74. Heating the CDCl₃ solution of the complex or washing with water results in decomplexation and recovery of starting material in the pure form which shows three multiplets for OCH₂ protons, at δ 3.57–3.6, 3.62–3.64 and 3.68–3.70.

The cubane diester crown ethers are a group of structurally well characterized ionophores whose physical properties have not been fully characterized. As part of a continuing study to explore the physical properties of these ionophores we have synthesized a series of these compounds in which the macrocyclic ring size has been varied from five to eight oxygen atoms (1–4) (see Figure 1 for structures of 1, 2 and 4) and have studied their potentiometric responses and selectivities in PVC membranes to alkali and alkaline earth metal cations, in the

presence and absence of potassium tetrakis(*p*-chlorophenyl)borate (KTPClPB).

RESULTS AND DISCUSSION

The selectivities reported for a given ionophore vary depending on the membrane composition and the nature of solutions (e.g. ionic strength, pH) to which the membranes are exposed.¹² For comparison purposes, unless stated otherwise, we prepared all ionophores under identical conditions using the same PVC membranes, plasticizer and lipophilic anionic site (e.g. KTPClPB) to obtain relative response due to the ionophores. The typical resistances of the prepared membranes, measured *in situ* using a Keithley 617 electrometer in the ohmmeter mode, ranged from 0.6 to 1.1 M Ω . All compounds used were functionally active as ion-selective electrodes and displayed a wide variation in electrochemical response.

A comparison of the responses obtained due to a sequential series of modifications in which the ring size of the macrocycle was varied from five to eight oxygen atoms was made with ionophores 1–4. All neutral carrier electrodes exhibited a marked selectivity for alkali metal (monovalent) over alkaline earth metal (divalent) cations (see Figure 2). The response curves obtained from plots such as in Figure 2 for the different ionophores 1–4 with different guest ions decreased in the order Cs⁺ > K⁺ > NH₄⁺ > Na⁺ > Ca²⁺ > Li⁺ > Mg²⁺. This pattern appeared to be essentially independent of ring size, indicating that the 'optimal spatial fit concept' (circular recognition)¹³ did not appear to hold for these ionophores when tested under these conditions of measurement. Despite the formation of a stable complex with Na⁺ ions in methanol, ionophore 1 showed no enhanced preference for this ion in these studies. Similar findings have been

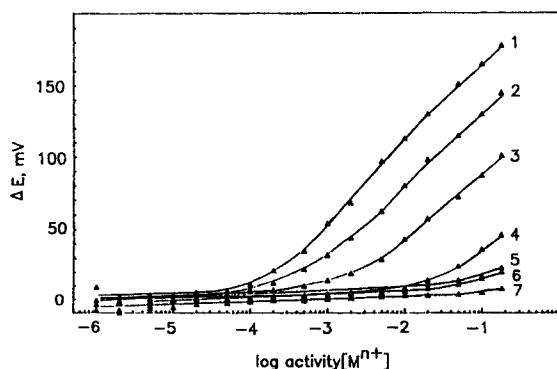


Figure 2. Cation selectivity of an electrode based on ionophore 1 in 0.1 M Tris-HCl (pH 7.5). The electrode was exposed to the salts of cesium (1), potassium (2), ammonium (3), sodium (4), calcium (5), lithium (6) and magnesium (7)

reported in a study of 1,3-xylyl crown ethers,⁴ which, owing to the availability of supporting studies carried out with organic solvents,⁶ was attributed to domination of solvation effects in complexation resulting in the selectivities, reflecting the ease with which the ionophore could substitute water from the inner hydration sphere of ions.

The responses, slopes and detection limits obtained for membranes prepared with KTPClPB and ionophores 1–4 with alkali metal cations determined according to Commission on Analytical Nomenclature rules¹⁴ are shown in Tables 1 and 2. The slopes for the electrodes ranged from 59 to 39 mV per decade with detection limits varying from 2×10^{-5} to 1×10^{-2} M depending on the nature of the cation and ionophore. Nernstian or near-Nernstian responses were observed for K⁺ with ionophores 1–4, Cs⁺ with 1, 2 and 4 and NH₄⁺ with 1 and 2, but not for Na⁺. Selectivity coefficients for K⁺ with respect to other alkaline earth metal cations obtained in the presence of KTPClPB are summarized in Figure 3 and were obtained using the fixed interference method,¹⁴ as this condition is representative of the conditions under which these electrodes could be used. The optimum selectivity for sodium (-1.2), lithium (-2.3), calcium (-2.3) and magnesium (-3.3) was observed with ionophore 3.

Comparison of the selectivities of the cubane diester crown ether membranes containing KTPClPB with membranes prepared without KTPClPB (see Figure 4) showed major differences in selectivity. For all four ionophores improvements in the selectivity of K⁺ relative to Cs⁺, Na⁺, Mg²⁺ and Ca²⁺ were observed in the

Table 1. Performance characteristics of electrodes based on ionophores 1–4

Ionophore	Slope (mV per decade)			
	K ⁺	Na ⁺	Cs ⁺	NH ₄ ⁺
1	57	46	57	56
2	59	46	57	57
3	55	46	39	43
4	59	50	56	49

Table 2. Detection limits of electrodes based on ionophores 1–4

Ionophore	Detection limit (M)			
	K ⁺	Na ⁺	Cs ⁺	NH ₄ ⁺
1	6×10^{-5}	1×10^{-2}	6×10^{-5}	2×10^{-3}
2	2×10^{-4}	1×10^{-2}	4×10^{-5}	1×10^{-3}
3	1×10^{-4}	4×10^{-3}	2×10^{-5}	4×10^{-4}
4	2×10^{-4}	8×10^{-3}	6×10^{-5}	2×10^{-3}

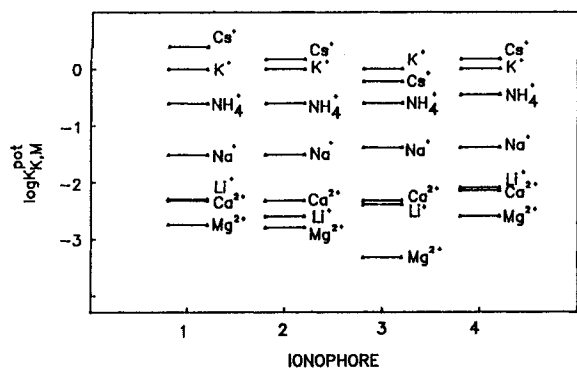


Figure 3. Selectivity coefficient for K^+ in PVC membrane electrodes prepared with ionophores 1-4, KTpCIPB and NPOE

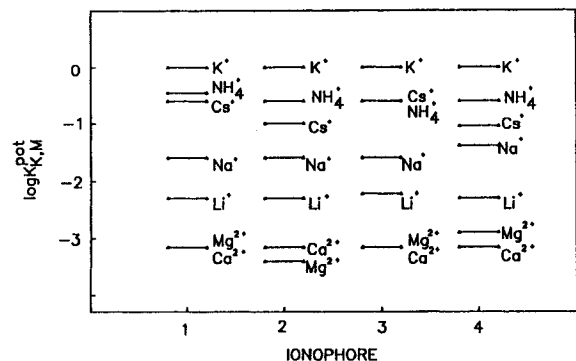


Figure 4. Selectivity coefficient for K^+ in PVC membrane electrodes prepared with ionophores 1-4 and NPOE

absence of KTpCIPB. KTpCIPB is added to membranes to improve the membrane resistance¹⁵ and response characteristics; however, the exchanger can reduce monovalent vs divalent cation selectivity¹⁶ and favour large cations,¹⁷ as observed in this study. In the absence of KTpCIPB the optimum selectivity for sodium (-1.6), ammonium (-0.5), lithium (-2.3), calcium (-3.1) and magnesium (-3.4) ions was observed with ionophore 2. A typical response of a PVC membrane to a stepwise change in K^+ concentration is illustrated in Figure 5 for ionophore 2. The trace shows a fast Nernstian response to a ten-fold increase in K^+ concentration (54 mV) which was essentially complete within a few seconds. Stability measurements in an open, unstirred, thermostated beaker of 10^{-2} M KCl at 25°C showed the electrode to have a stability of $<100 \mu\text{V h}^{-1}$.

In conclusion, it has been shown that cubane diester crown ethers are relatively good potassium-selective ionophores showing good discrimination against alkaline-earth metal cations with a useful detection range

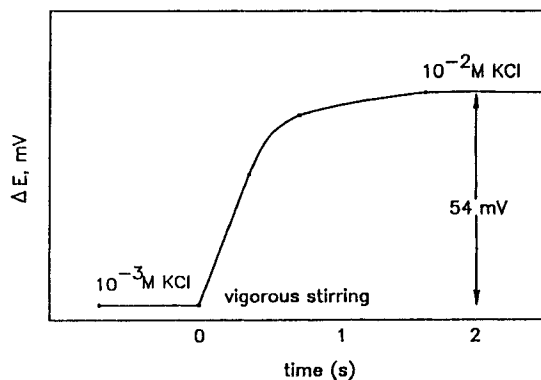


Figure 5. Response curve for a PVC membrane based on ionophore 2 to a change in concentration of KCl from 1×10^{-3} to 1×10^{-2} M

between 10^{-4} and 10^{-1} M. However, given the availability of more selective and sensitive naturally occurring ionophores for potassium (e.g. valinomycin) we predict that these compounds may have greater value if used as modified electrodes in electroanalytical applications. The development of disposable electrodes¹⁸ and a hand-held instrument¹⁹ for environmental monitoring based on anodic stripping voltammetry (ASV), which can determine four heavy metals simultaneously, increases the need for ionophore coatings with a broad selectivity as replacements for the currently used thin mercury films. The broad selectivity of cubane macrocycles, concentrated hydrophobicity, aliphatic nature and numerous options for structural modification make these compounds ideal candidates for development as replacements for mercury films in the determination of heavy metals by ASV.

EXPERIMENTAL

Materials. Lithium chloride (BDH, Speke, Liverpool, UK.) cesium fluoride and sodium chloride (Aldrich Chemical, Gillingham, Dorset, U.K.) were used as received. Cubane 1,4-dicarboxylic acid was purchased from Fluorochem (Azusa, CA, U.S.A.). Di-, tri-, tetra- and pentaethylene glycols were obtained from Aldrich Chemical (Milwaukee, WI, U.S.A.). Potassium tetrakis(*p*-chlorophenyl)borate (KTpCIPB), poly(vinyl chloride) (PVC) and 2-nitrophenyl octyl ether (NPOE) were purchased from Fluka (Glossop, Derbyshire, U.K.). Tetrahydrofuran (THF) was obtained from Rathburn Chemicals (Walkerburn, U.K.) and was dried over sodium. Tris(hydroxymethyl)aminomethane (Tris), potassium chloride, magnesium chloride, ammonium chloride and calcium chloride were purchased from Sigma Chemical (Poole, Dorset, U.K.). All standard solutions and buffers were prepared using water purified

with a Milli-Q system (Millipore). Neutral carriers were prepared as described below.

Syntheses of ionophores. Ionophores 1–4 were prepared by the reaction of cubane-1,4-dicarbonyl chloride with the appropriate polyethylene glycol according to the methods of Moriarty *et al.*¹¹ the general procedure being as follows. In a typical experiment, a solution of polyethylene glycol (5.2 mmol) in dry dichloromethane (100 ml) was added dropwise to a stirred solution of cubane-1,4-dicarbonyl chloride (5.2 mmol) and triethylamine (13.0 mmol) in dry dichloromethane (400 ml) at room temperature under an argon atmosphere. The reaction mixture was stirred for 20 h at room temperature and then poured on to a crushed ice–water mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 100 ml). The combined organic extracts were washed with water (2 × 80 ml) and brine (100 ml), dried (Na₂SO₄), filtered and evaporated *in vacuo* to yield crude cubyl diester polyethers 1–4, which were obtained pure by flash chromatography on silica gel with ethyl acetate eluent.

1,4-Cubyl diester-19-crown-5 ether (1). Yield 25%; m.p. 153–154 °C; IR (KBr), 1727 cm⁻¹; ¹H NMR (400 MHz, CDCl₃), δ 3.57–3.6 (4 H, m, OCH₂), 3.62–3.64 (4 H, m, OCH₂), 3.68–3.70 (4 H, m, OCH₂), 4.29–4.31 (4 H, m, COOCH₂), 4.30 (6 H, s, CH); ¹³C NMR (100.6 MHz, CDCl₃), δ 47.06, 56.69, 64.18, 68.8, 70.34, 71.4, 171.27; chemical ionization (CIMS), (M⁺ + 1) *m/z* 351 (32%); high-resolution electron impact MS, C₁₈H₂₂O₇ requires *m/z* 350.1366, found 350.1369; analysis, calculated for C₁₈H₂₂O₇, C 61.71, H 6.33; found, C 61.84, H 6.37%.

1,4-Cubyl diester-22-crown-6 ether (2). Yield 40%; m.p. 89–90 °C; IR (KBr), 1727 cm⁻¹; ¹H NMR (400 MHz, CDCl₃), δ 3.57–3.59 (8 H, m, OCH₂), 3.62–3.64 (8 H, m, OCH₂), 4.22–4.24 (4 H, m, COOCH₂), 4.25 (6 H, s, CH); ¹³C NMR (100.6 MHz, CDCl₃), δ 46.81, 55.89, 63.54, 68.61, 70.25, 70.56, 70.92, 171.07; CIMS, (M⁺ + 1) *m/z* 395 (28%); analysis, calculated for C₂₀H₂₆O₈, C 60.90, H 6.64; found, C 61.00, H 6.58%.

1,4-Cubyl diester-25-crown-7 ether (3). Yield 20%; m.p. 55–56 °C; IR (neat), 1725 cm⁻¹; ¹H NMR (400 MHz, CDCl₃), δ 3.63–3.68 (20 H, m, OCH₂), 4.24–4.27 (4 H, m, COOCH₂), 4.25 (6 H, s, CH); ¹³C NMR (100.6 MHz, CDCl₃), δ 47.0, 55.85, 63.59, 68.80, 70.38, 70.71, 70.80, 71.15, 171.33; CIMS, (M⁺ + 1) *m/z* 439 (36%); analysis, calculated for C₂₂H₃₀O₉, C 60.26, H 6.90; found, C 60.14, H 6.87%.

1,4-Dibridged-dicubyl diester-32-crown-8 ether (4). Yield 15%; m.p. 122–129 °C; IR (KBr), 1723 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.56 (8 H, s, OCH₂), 3.62–3.64 (8 H, m, OCH₂), 4.14 (12 H, s, CH), 4.16–4.19 (8 H, m, COOCH₂); ¹³C NMR (100.6 MHz, CDCl₃), δ 46.76, 55.5, 63.5, 68.98, 70.63, 171.01; CIMS, (M⁺ + 1) *m/z* 613 (100%); analysis, calculated for C₃₂H₃₆O₁₂, C 62.74, H 5.92; found, C 62.45, H 5.98%.

Membrane and electrode fabrication. The polymeric membranes used were prepared as follows: PVC (31.2 mg), NPOE (66 mg; 263 μM), KTpCIPB (0.4 mg; 0.81 μM) and the appropriate ionophore (8.6 μM) were dissolved in 1 ml of THF. The solution was poured into a flat glass ring (17 mm i.d.), and the solvent evaporated at room temperature overnight²⁰ to yield an elastic, translucent membrane of thickness 0.14–0.18 mm. The resulting polymeric membranes were conditioned for 24 h in 1 × 10⁻² M KCl, then deposited on the end of a glass tube of 5.5 mm i.d. containing an internal reference solution (1 × 10⁻² M) and chloridized silver wire as an internal reference electrode.²¹ The fabricated electrodes were further conditioned for 24 h in 1 × 10⁻² M KCl before use. All potentiometric measurements were performed by the use of the following cell: Hg, Hg₂Cl₂, KCl (sat.) || sample solution | membrane | Tris (0.1 M), KCl (1 × 10⁻² M) AgCl, Ag.

E.m.f. measurements. The response of the electrode was measured with a Thurlby Model 1503 digital multimeter and time-dependent responses were recorded with a Siemens Model X-T C1012 chart recorder. All measurements were performed in a temperature-controlled room at 21 °C relative to a Radiometer porous pin-junction calomel reference electrode. Electrodes were stored in 1 × 10⁻² M KCl when not in use. The electrodes were calibrated by syringing 2 ml aliquots of known concentrations of different electrolyte standard solutions into a stirred beaker containing 20.0 ml of 0.1 M Tris–HCl buffer (pH 7.5).²⁰ To obtain the calibration graphs of the ISEs, the data were plotted as Δ*E* (i.e. the increase in potential with respect to the baseline) vs the logarithm of activities of the cation present in the buffered solution.

Selectivity coefficients (K_{K,M}^{Pot}). Selectivity coefficients were determined by the fixed interference method.²¹ The background concentration of the interfering ions employed were 0.1 M for LiCl, NaCl, KCl, CaCl₂ and MgCl₂ and 0.01 M for CsF and NH₄Cl.

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