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Potassium Selective Chromoionophores

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Abstract. The ionisable chromoionophores **5** were synthesised from simple precursors. These chromoionophores extract alkali metal cations from aqueous solutions at pH > 7 into dichloromethane. The ratio of extraction coefficients for the chromoionophore **5c** for K^+ and Na^+ indicate that it has potential for use in optical fibre sensors for K^+ in the presence of Na^+, Mg^{2+}, and Ca^{2+} at extracellular concentrations.

Key words. Chromoionophores, potassium, hemispherand, optical fibre sensors.

1. Introduction

The discovery of crown ethers [1] by the late Charles Pedersen[1] has led to the possibility of designing and synthesising ionophores that are specific for selected alkali metal cations. Thus the crown ether concept has been elegantly enlarged by the development of more rigid and selective systems such as the cryptands [2], hemispherands [3], and spherands [4], and, more recently, suitably bridged and functionalised calixarene derivatives [5]. The availability of these selective synthetic ionophores, which may readily be modified through synthesis has resulted in their exploitation in analytical devices [6] such as ion selective electrodes, selective chromogenic reagents for cations, and ion selective membranes for cation transport. The development [7] of other major areas in supramolecular and host-guest chemistry has also been inspired both directly and indirectly by the crown ethers and the chemistry of the next century will increasingly be based upon this new ability to design and control non-covalent interactions between synthetic compounds and between synthetic compounds and natural macromolecules.

The presence of metal cations in mmolar concentrations in both intracellular and extracellular fluids has led [8] to the development of reagents and analytical procedures for their estimation. Our interests have been in the development of optical fibre sensors and this has required the synthesis of ion selective chromoionophores to use as transducers at the tip of the optical fibre. The ionic concentrations in mammalian blood pose a particular problem for the measurement of potassium ion concentration (*ca* 4 mM) in the presence of a much higher concentration of sodium ions (*ca* 140 mM) and comparable concentrations of calcium (*ca* 1.8 mM) and magnesium (*ca* 1.5 mM) ions.

This paper is dedicated to the memory of the late Dr C. J. Pedersen.
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2. Experimental

2.1. GENERAL

All reactions were performed under a nitrogen atmosphere using reagent grade materials in dried and purified solvents unless otherwise stated. The extraction experiments were carried out with ACS grade alkali and alkaline earth chlorides. Proton NMR spectra were recorded on Perkin Elmer R34 (220 MHz), Bruker WH250 (250 MHz), and Bruker AC200 (200 MHz) spectrometers, and ^{13}C NMR spectra were recorded on an AC200 (50.3 MHz) spectrometer. Visible and UV absorption spectra were recorded on Perkin Elmer Lambda 5 and Hewlett Packard 8452A spectrometers using quartz cells at ambient temperature.

2.2. MEASUREMENT OF EXTRACTION COEFFICIENTS

The hemispherands **5** were dissolved to known concentration (*ca* 6×10^{-5} M) in methylene chloride. A sample of the hemispherand solution (3 mL) was shaken with aqueous buffer (3 mL, pH 8 trishydroxymethylmethylamine hydrochloride (trisHCl) at 5×10^{-2} M) and the spectrum of the organic layer was recorded. A second sample of the hemispherand (3 mL) was shaken with an aqueous solution of MOH (3 mL, 1 M) and the spectrum was recorded. Similarly a third sample of the hemispherand solution was shaken with a buffered aqueous solution of MCl (3 mL, 1 M, pH 8, trisHCl buffer at 5×10^{-2} M) and the spectrum of the organic layer was recorded.

The extraction coefficient for the metal ion M^+ was calculated using the expression:–

$$K_e = [H^+]_{aq} \cdot (A - A_0)/[M^+]_{aq} \cdot (A_{00} - A)$$

where $[H^+]_{aq}$ is the proton concentration in the aqueous layer; $[M^+]_{aq}$ is the metal ion concentration in the aqueous layer; A is the absorbance of **5** at λ with MCl; A_0 is the absorbance of **5** at λ with pH 8 buffer; A_{00} is the absorbance of **5** at λ with MOH.

Due to the affinity of the hemispherands for alkali metal cations it was necessary to conduct extraction experiments using either acid washed pyrex glassware or polythene equipment. All measurements of K_e were carried out at least in duplicate and the value of K_e is independent of pH.

2.3. PREPARATION OF CHROMOIONOPHORES **5**

2-Methoxy-5-methylphenylboronic Acid **6**

A solution of butyl lithium in hexane (248 mmol) was added to TMEDA (37.5 mL, 248 mmol) in ether (30 mL) and left at room temperature for 20 min under an argon atmosphere. The above solution was added dropwise over 30 min to a stirred solution of 4-methylanisole (30 g, 245 mmol) in ether (150 mL) at room temperature. The solution was stirred at room temperature for 6 h then added to a solution of trimethyl borate (90 mL, 786 mmol) in THF (30 mL) at −78°C. The mixture was allowed to warm to room temperature and stirred for 2 h followed by

partitioning between HCl (600 mL, 3 M aqueous solution) and ether (600 mL). The organic layer was washed with water and brine, dried ($MgSO_4$) and evaporated to give a semi-solid residue which gave the *boronic acid* **6** as a white crystalline powder (50–60% yield) which was used without further purification. δ ($CDCl_3$) 2.30 (*s*, 3 H, ArCH_3), 3.90 (*s*, 3 H, ArOCH_3), 6.40 (*s*, 2 H, B(OH)$_2$), ABC system, δ_A7.65, δ_B7.25, δ_C6.82 (J_{AB}2 Hz, J_{BC}8 Hz, 3 aryl-*H*). (*Found*; C, 58.1; H, 6.7%; M^+, 166.0787. $C_8H_{11}BO_3$ *requires* C, 57.9; H, 6.7%; M^+, 166.0801).

2,2″-Dimethoxy-5,5″-dimethyl-2′-hydroxy-1,1′:3,1″-terphenyl **8**

Tetrakis(triphenylphosphine) palladium(0) (2.30 g, 2 mmol) and Na_2CO_3 (25 mL, 2 M aqueous solution) were added to a solution of 2,6-dibromophenol **7** (5.00 g, 19.9 mmol) and 2-methoxyphenylboronic acid **6** (7.90 g, 47.6 mmol) in toluene (50 mL) and ethanol (10 mL). The mixture was refluxed with stirring for 16 h, cooled to room temperature, hydrogen peroxide (10 mL, 30% wt. aqueous solution) added, and the mixture stirred for a further 1 h. The resulting dark mixture was partitioned between water (300 mL) and ether (600 mL) and the organic layer washed with water and brine, dried ($MgSO_4$), and evaporated to give a brown viscous oil. Chromatography (dry flash, eluting solvent CH_2Cl_2) gave a major product (R_f 0.5 in CH_2Cl_2) as a pale yellow oil which crystallised from ethanol to give the *terphenyl derivative* **8** as a white powder, mp 112–114°C (yield 60–80%). δ ($CDCl_3$) 2.35 (*s*, 6 H, ArCH_3), 3.80 (*s*, 6 H, ArOCH_3), 6.45 (*s*, 1 H, OH), AB system, δ_A7.27, δ_B6.91 (J_{AB}10 Hz, 4 aryl-*H*), A_2B system, δ_A7.17, δ_B7.05 (J_{AB}8 Hz, 3 aryl-*H*), 7.19 (*s*, 2 aryl-*H*). (*Found*: C, 78.9; H, 6.5%; M^+, 334.1570. $C_{22}H_{22}O_3$ *requires* C, 79.0; H, 6.6%; M^+, 334.1569).

2,2″-Dimethoxy-5,5″-dimethyl-2′-methoxymethyleneoxy-1,1′:3′,1″-terphenyl **9**

Sodium hydride (80% suspension in oil, 0.54 g, *ca* 18 mmol) was added to a solution of the terphenyl derivative **8** (5.00 g, 15 mmol) in THF (50 mL) and the mixture stirred for 1 h at room temperature. Chloromethyl methyl ether (1.40 mL, 18 mmol) was added dropwise and the mixture stirred for a further 24 h. Water (30 mL) was added, and the product extracted with dichloromethane (100 mL, 2 × 50 mL) and the combined extracts washed with water and brine, dried ($MgSO_4$), and evaporated to give a discoloured semi-solid residue. Chromatopgraphy (dry flash, eluting solvent CH_2Cl_2) gave a major product (R_f 0.40 in CH_2Cl_2) as a pale yellow oil which crystallised from ethanol to give the *product* **9** as a white crystalline powder, m.p. 111–113°C (yield > 90%). δ ($CDCl_3$) 2.40 (*s*, 6 H, ArCH_3), 2.70 (*s*, 3 H, ArOCH$_2$OCH_3), 3.84 (*s*, 6 H, ArOCH_3), 4.45 (*s*, 2 H, ArOCH_2OCH$_3$), 6.94 (*d*, *J* 10 Hz, 2 aryl-*H*), 7.25 (*m*, 7 aryl-*H*). (*Found*: C, 76.3; H, 6.9%; M^+, 378.1835. $C_{24}H_{26}O_4$ *requires* C, 76.2; H, 6.9%; M^+, 378.1831).

3,3″-Diformyl-2,2″-dimethoxy-5,5″-dimethyl-2′methoxymethyleneoxy-1,1′:3′,1″-terphenyl **13**

A solution of butyl lithium in hexanes (19.8 mmol) was added to TMEDA (3.0 mL, 19.8 mmol) in ether (10 mL) and the solution left at room temperature under an

atmosphere of argon for 20 min. The above solution was added over 30 min to a solution of the terphenyl **9** (3.00 g, 7.92 mmol) in ether (130 mL) and the stirred solution left for 6 h at room temperature. DMF (3.30 mL, 39.6 mmol) was added and the mixture stirred for 16 h before the addition of HCl(50 mL, 3M aqueous solution) and the extraction of the product into dichloromethane (3 × 100 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and evaporated to give an off-white residue which was triturated with cold ether, filtered, and washed with light petroleum (bp 40–60°C) to give the *dialdehyde* **13** as a white powder, mp 148–150°C, which was used without further purification (yield 65–70%). δ ($CDCl_3$) 2.47 (*s*, 6 H, $ArCH_3$), 2.63 (*s*, 3 H, OCH_2OCH_3), 3.70 (*s*, 6 H, $ArOCH_3$), 4.48 (*s*, 2 H, OCH_2OCH_3), AB_2 system, δ_A7.40, δ_B7.53 (J_{AB}8 Hz, 3 aryl-*H*), AB system, δ_A7.77, δ_B7.56 (J_{AB}2 Hz, 4 aryl-*H*), 10.52 (*s*, 2 H, ArC*H*O). (*Found*: C, 72.3; H, 6.1%; M^+, 434.1724. $C_{26}H_{26}O_6$ *requires* C, 71.9; H, 6.0%; M^+, 434.1729).

3,3″-Bis(hydroxymethyl)-2,2″-dimethoxy-5,5″-dimethyl-2′-methoxymethyleneoxy-1,1′:3′1″-terphenyl **14**

Sodium borohydride (0.35 g, 9.20 mmol) was added to a solution of the above dialdehyde **13** (2.00 g, 4.60 mmol) in ethanol (25 mL). The solution was refluxed for 2 h, cooled, and evaporated to dryness. The residue was partitioned between HCl (50 mL, 3 M aqueous solution) and dichloromethane (100 mL) and the aqueous layer extracted wtih dichloromethane (2 × 50 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated to give the *diol* **14** (yield *ca* 100%) as a white foam which was used without further purification. δ ($CDCl_3$) 2.30 (*s*, 6 H, $ArCH_3$), 2.35 (*br.s*, 2 H, O*H*), 2.67 (*s*, 3 H, OCH_2OCH_3), 3.55 (*s*, 6 H, $ArOCH_3$), 4.50 (*s*, 2 H, OCH_2OCH_3), 4.82 (*s*, 4 H, 2 × $ArCH_2OH$), 7.25 (*s*, 4 aryl-*H*), AB_2 system, δ_A7.30, δ_B7.45 (J_{AB}8 Hz, 3 aryl-*H*). (*Found*: C, 70.7; H, 6.9%; M^+, 438. $C_{26}H_{30}O_6$ *requires* C, 71.2; H, 6.9%; M^+, 438).

3,3″-Bis(bromomethyl)-2,2″-dimethoxy-5,5″-dimethyl-2′-methoxymethyleneoxy-1,1′:3′,1″-terphenyl **10**

Dimethyl sulphide (1.2 mL, 16.5 mmol) was added dropwise to a suspension of *N*-bromosuccinimide (2.45 g, 13.8 mmol) in dichloromethane (15 mL) at 0°C. The mixture was stirred for 15 min. A solution of the above diol **14** (2.00 g, 4.6 mmol) in dichloromethane (30 mL) was added dropwise at 0°C, the solution was allowed to warm to room temperature and stirred for a further 16 h. Light petroleum (50 mL, bp 40–60°C) was added and the solution washed with ice cold water (3 × 20 mL) and ice cold brine (20 mL), dried ($MgSO_4$), and percolated through a wet flash chromatography column (15 cm long), further product was eluted with dichloromethane. The *dibromide* **10** (R_f0.65 in CH_2Cl_2) was recovered from the eluent as a colourless viscous oil (yield 60–70%). δ ($CDCl_3$) 2.40 (*s*, 6 H, $ArCH_3$), 2.67 (*s*, 3 H, OCH_2OCH_3), 3.62 (*s*, 6 H, $ArOCH_3$), 4.48 (*s*, 2 H, OCH_2OCH_3), 4.70 (*br.s*, 4 H, $ArCH_2Br$), 7.27 (*m*, 5 aryl-*H*), 7.47 (*d*, *J* 6 Hz, 2 aryl-*H*). (*Found*: C, 55.1; H, 5.0%; M^+, 566, 564, 562, $C_{26}H_{28}Br_2O_4$ *requires* C, 55.3; H, 5.0%; M^+, 566, 564, 562).

28,29-Dimethoxy-9,26-dimethyl-30-methoxymethyleneoxy-13,16,19,22-tetraoxatetracyclo [22.3.1^{2,6}.1^{7,11}]triaconta-1(28),2,4,6(30),7,9,11(29),24,26-nonaene **11b**

A solution of the bis(bromomethyl)terphenyl **10** (0.65 g, 1.15 mmol) and triethyleneglycol (0.17 g, 1.15 mmol) in THF was added dropwise over 4 h, using a mechanical syringe, to a stirred suspension of sodium hydride (0.14 g, 80% suspension in oil, 4.6 mmol) and potassium bromide (0.27 g, 2.30 mmol) in refluxing THF (50 mL). Heating was continued for a further 12 h, the mixture was allowed to cool, water (30 mL) was added, and the product was extracted with dichloromethane (3 × 70 mL). The extracts were washed with water and brine, dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed (30 g wet flash silica mixed with 3 g KBr), major impurities were eluted first ($CHCl_3$ and $CHCl_3$–3% EtOH) followed by the required product ($CHCl_3$–15% EtOH) and KBr. The required fractions were combined, washed with HCl (50 mL, 3 M aqueous solution) and water, dried ($MgSO_4$), and evaporated. The residual solid was recrystallised from ethyl acetate to give the *macrocycle* **11b** as a white powder, mp 128–130°C (yield 50–60%). δ ($CDCl_3$) 2.35 (*s*, 6 H, $ArCH_3$), 2.50 (*s*, 3 H, OCH_2OCH_3), 3.55 (*s*, 6 H, $ArOCH_3$), 3.65 (*m*, 12 H, OCH_2), 4.20 (*s*, 2 H, OCH_2OCH_3), AB system, δ_A4.80, δ_B4.25 (J_{AB}11 Hz, 4 H, $ArCH_2O$), 7.10 (*s*, 2 aryl-*H*), 7.25 (*m*, 1 aryl-*H*), 7.35 (*m*, 4 aryl-*H*); ^{13}C NMR ($CDCl_3$) 20.3 ($ArCH_3$, 2C), 55.6 (OCH_2OCH_3), 61.3 ($ArOCH_3$, 2 C), 68.5 (OCH_2, 2 C), 69.1 (OCH_2, 2 C), 69.5 (OCH_2, 2 C), 70.6 (OCH_2, 2 C), 98.1 (OCH_2OCH_3), 123.7 (aryl-*C*), 129.7 (aryl-*C*, 2 C), 129.9 (aryl-*C*, 2 C), 131.6 (aryl-*C*, 2 C), 132.2 (aryl-*C*, 2 C), 132.3 (aryl-*C*, 2 C), 133.3 (aryl-*C* 2 C), 155.8 (aryl-*C*). (*Found*: C, 69.3; H, 7.3%; M^+, 552.2716. $C_{32}H_{40}O_8$ *requires* C, 69.5, H, 7.3%, M^+, 552.2723).

28,29-Dimethoxy-9,26-dimethyl-30-hydroxy-13,16,19,22-tetraoxatetracyclo-[22.3.1.1^{2,6}.1^{7,11}]triaconta-1(28),2,4,6(30),7,9,11(29),24,26-nonaene **15b**

The O-protected macrocycle **11b** (0.34 g, 0.61 mmol) was dissolved in dichloromethane (5 mL) and a trifluoroacetic acid (0.5 mL) water (0.5 mL) mixture was added. The suspension was stirred at room temperature for 16 h, diluted with water (20 mL) and extracted with dichloromethane (3 × 30 mL). The extract was dried ($MgSO_4$) and evporated and the residual solid crystallised from ethyl acetate to give the *phenolic hemispherand* **15b** as an analytically pure sample, m.p. 134–136°C (yield 60–70%). δ ($CDCl_3$) 2.37 (*s*, 6 H, $ArCH_3$), 3.50 (*s*, 6 H, $ArOCH_3$), 3.63 (*m*, 12 H, OCH_2), 4.35 (*br. s*, 2 H, $ArCH_2O$), 4.80 (*br. s*, 2 H, $ArCH_2O$), 7.10 *s* and *t*, *J* 10 Hz, 5 aryl-*H*), 7.40 (*d*, *J* 10 Hz, 2 aryl-*H*); ^{13}C NMR ($CDCL_3$) 20.65 ($ArCH_3$, 2 C), 61.55 ($ArOCH_3$, 2 C), 68.58 (OCH_2, 2 C), 68.82 (OCH_2, 2 C), 69.96 (OCH_2, 2 C), 70.46 (OCH_2, 2 C), 120.6 (aryl-*C*), 128.28 (aryl-*C*), 129.72 (aryl-*C*), 130.09 (aryl-*C*), 131.57 (aryl-*C*), 132.09 (aryl-*C*), 132.85 (aryl-*C*), 133.69 (aryl-*C*), 151.74 (aryl-*C*), 154.87 (aryl-*C*). (*Found*: C, 69.9; H, 7.1%; M^+, 508.2453. $C_{30}H_{36}O_7$ *requires* C, 70.8; H, 7.1%; M^+, 508.2461).

28,29-Dimethoxy-9,26-dimethyl-13,16,19,22-tetraoxatetracyclo-[22.3.1.1^{2,6}.1^{7,11}]triaconta-1(28),2,5,7,9,11(29),24,26-octaene-4,30-dione **12b**

A solution of the phenolic macrocycle **15b** (100 mg, 0.20 mmol) in chloroform (70 mL) was added carefully to a stirred solution of thallium trinitrate (0.27 g, 0.60 mmol) in methanol (80 mL) and ethanol (240 mL). The resulting orange solution was stirred at room temperature for 10 min, water (150 mL) was added and the solution stirred for a further 15 min. The organic layer was separated, washed twice with water, and evaporated to dryness. The residual orange solid was purified by chromatography on silica/KBr (10% w/w) and elution with dichloromethane/ethanol (0–10%). The major fraction was washed with aqueous HCl (100 mL, 3 M) and water and evaporated to given the *quinone* **12b** as orange crystals, m.p. 158–160°C (yield 65%). δ ($CDCl_3$) 2.32 (*s*, 6 H, ArCH_3), 3.52 (*s*, 4 H, OCH_2), 3.62 (*m*, 8 H, OCH_2), 3.80 (*s*, 6 H, ArOCH_3), 4.55 (*br. s*, 4 H, ArCH_2O), 6.80 (*s*, 2 H, =CH—), AB system, δ_A7.22, δ_B7.00 (J_{AB} 2 Hz, 4 aryl-*H*); ^{13}C NMR ($CDCl_3$) 21.0 (ArCH_3), 63.5 (ArOCH_3), 68.5 (OCH_2), 69.0 (OCH_2), 70.3 (OCH_2), 70.7 (OCH_2), 128.7, 130.0, 130.8, 132.8, 133.8, 149.0, 156.2 (12 aryl-*C* and 4 alkenyl-*C*), 187.7 (> C=O), (*Found*: C, 68.7; H, 6.5%; M^+, 522.2257. $C_{30}H_{34}O_8$ *requires* C, 69.0; H, 6.6%; M^+, 522.2254).

28,29-Dimethoxy-9,26-dimethyl-4-(2′,4′-dinitrophenylazo)-30-hydroxy-13,16,19,22-tetraoxatetracyclo[22.3.1.1^{2,6}.1^{7,11}]-triaconta-1(28),2,4,6(30),7,9,11(29),24,26-nonaene **5b**

Two mL of a solution of 2,4-dinitrophenylhydrazine (1.29 g, 6.5 mmol) and sulphuric acid (2.5 mL) in ethanol (20 mL) was added to a solution of the macrocyclic quinone **12b** (50 mg, 0.096 mmol) in chloroform (30 mL) and ethanol (50 mL). The solution was refluxed with stirring for 4 h, cooled, and left overnight. Dichloromethane (50 mL) was added and the solution was washed with water and evaporated to dryness, the residue was chromatographed (tlc, silica) and the major orange band extracted into dichloromethane and ethanol, washed with HCl (3 M, aqueous) and water and the solvent evaporated to give the *macrocyclic azophenol* **5b** which crystallised from ethyl acetate as an orange solid, m.p. 210–212°C (yield 85%). δ ($CDCl_3$) 2.40 (*s*, 6 H, ArCH_3), 3.55 (*s*, 6 H, ArOCH_3), 3.57 (*s*, 4 H, OCH_2), 3.60 (*m*, 8 H, OCH_2), *ca* 4.50 (*br. s*, 4 H, ArCH_2O), 7.21 (*s*, 4 aryl-*H*) 8.08 (*s*, 2 aryl-*H*), ABC system, δ_A8.78, δ_B8.53, δ_C7.90 (J_{AB}2 Hz, J_{BC}9 Hz, 3 aryl-*H*). (*Found*: C, 61.7; H, 5.3; N, 7.8%. $C_{36}H_{38}N_4O_{11}$ *requires* C, 61.5; H, 5.5; N, 8.0%); MS (CI source, carrier gas NH_3)$(M + NH_4)^+$, 720 (32%).

32,33-Dimethoxy-9,30-dimethyl-34-methoxymethyleneoxy-13,16,23,26-tetraoxapenta-cyclo[26.3.1.1^{2,6}.1^{7,11}.0^{17,22}] tetratriaconta-1(32),2,4,6(34),7,9,11(33),17(22),18,20,28,30-dodecaene **11c**

A similar method was used to that described for the preparation of the analogous macrocycle **11b**. The terphenyl derivative **10** (1.38 g, 2.45 mmol) was refluxed in THF with bis(2-hydroxyethyl)catechol (0.49 g, 2.45 mmol), sodium hydride (0.29 g, 80% dispersion in oil, 9.78 mmol), and potassium bromide (0.6 g, 5 mmol). Purifi-

cation of the product gave the required *macrocycle* **11c** as a white foam (yield 35–40%) which crystallised from ethyl acetate as white crystals, m.p. 161–162°C. δ ($CDCl_3$) 2.30 (*s*, 6 H, $ArCH_3$), 2.43 (*s*, 3 H, OCH_2OCH_3), 3.72 (*s*, 6 H, $ArOCH_3$), 4.00 (*m*, 8 H, OCH_2), 4.20 (*s*, 2 H, OCH_2OCH_3), AB system, δ_A4.40, δ_B4.80 (J_{AB}12 Hz, $ArCH_2O$), 6.86 (*s*, 4 aryl-*H*), 7.15 (*s*, 4 aryl-*H*), 7.30 (*m*, 3 aryl-*H*); ^{13}C NMR ($CDCl_3$) 20.5 ($ArCH_3$), 56.0 ($ArCH_2OCH_3$), 62.1 ($ArOCH_3$), 66.7 (OCH_2), 67.2 (OCH_2), 68.5 (OCH_2), 98.2 (OCH_2OCH_3), 111.6, 120.4, 123.9, 129.5, 129.6, 132.0, 132.1, 132.3, 132.6, 133.3, 148.1, 153.3, 156.1, (24 aryl-*C*). (*Found*: C, 71.8; H, 6.8%; M^+, 600.2726. $C_{36}H_{40}O_8$ *requires* C, 72.0; H, 6.7%; M^+, 600.2723).

32,33-Dimethoxy-9,30-dimethyl-34-hydroxy-13,16,23,26-tetraoxapentacyclo[26.3.1.1^{2,6}.1^{7,11}.0^{17,22}]tetratriaconta-1,(32),2,4,6(34),7,9,11(33),17(22),18,20,28,30-dodecaene **15c**

A similar method was used to that described for the preparation of the analogous phenolic macrocycle **15b**. The *phenol* **15c** was obtained as a white foam (*ca* 100% yield) which crystallised from ethyl acetate to give white crystals, m.p. 199–201°C. δ ($CDCl_3$) 2.35 (*s*, 6 H, $ArCH_3$), 3.45 (*s*, 6 H, $ArOCH_3$), 3.80 (*br. s*, 4 H, OCH_2), 4.00 (*br. s*, 4 H, OCH_2), 4.45 (*br. s*, 2 H, $ArCH_2O$), 4.75 (*br. s*, 2 H, $ArCH_2O$), 6.80 (*s*, 4 aryl-*H*), 7.15 (*s*, 4 aryl-*H*), AB_2 system, δ_A7.10, δ_B7.35 (J_{AB}8 Hz, 3 aryl-*H*); ^{13}C NMR ($CDCl_3$) 20.6 ($ArCH_3$), 61.8 ($ArOCH_3$), 66.6 (*br.*, OCH_2CH_2O), 68.0 (*br.*, $ArCH_2O$), 112.0, 120.5, 120.7, 128.2, 129.2, 129.4, 131.8, 132.7, 133.9, 148.0, 154.8 (24 aryl-*C*). (*Found*: M^+, 556.2453. $C_{34}H_{36}O_7$ *requires* M^+, 556.2461); the sodium salt was obtained analytically pure. (*Found*: C, 70.8; H, 6.2%. $C_{34}H_{35}NaO_7$ *requires* C, 70.6; H, 6.1%).

32,33-Dimethoxy-9,30-dimethyl-13,16,23,26-tetraoxapentacyclo[26.3.1.1.1^{2,6}.11^{7,11}.0^{17,27}]-tetratriaconta-1(32),2,5,7,9,11(33),17,(22),18,20,28,30-undecaene-4,34-dione **12c**

A similar method was used to that described for the macrocyclic quinone **12b**. The phenol **15c** (100 mg, 0.18 mmol) was oxidised using thallium trinitrate (0.24 g, 0.54 mmol), the product was purified by chromatography and crystallisation to give the *macrocyclic quinone* **12c** (94% yield) as orange crystals, m.p. 110–112°C. δ ($CDCl_3$) 2.25 (*s*, 6 H, $ArCH_3$), 3.80 (*s*, 6 H, $ArOCH_3$), ca 3.80 (*br.*, 4 H, OCH_2), 3.92 (*br.*, 4 H, OCH_2), 4.48 (*br. s*, $ArCH_2O$), 6.70 (*m*, 4 aryl-*H*), 6.72 (*s*, 2 H, —CH=), AB system, δ_A6.92, δ_B7.18 (J_{AB}2 Hz, 4 aryl-*H*). (*Found*: C, 71.1; H, 6.0%; M^+, 570.2254. $C_{34}H_{34}O_8$ *requires* C, 71.6; H, 6.0%; M^+, 570.2254).

32,33-Dimethoxy-9,30-dimethyl-4-(2′,4′-dinitrophenylazo)-34-hydroxy-13,16,23,26-tetraoxapentacyclo-[26.3.1.1^{2,6}.1^{7,11}.0^{17,22}]tetratriaconta-1(32),2,4,6(34),7,9,11(33),17(22),18,20,28,29-dodecaene **5c**

One mL of a solution of 2,4-dinitrophenylhydrazine (1.29 g, 6.5 mmol) and sulphuric acid (2.5 mL) in ethanol (20 mL) was added to a solution of the macrocyclic quinone **12c** (34 mg, 0.060 mmol) in chloroform (15 mL) and ethanol (25 mL). The

solution was stirred and refluxed for 4 h, cooled to room temperature, and left overnight. Dichloromethane (50 mL) was added, the solution washed with water, and evaporated to dryness. The residue was purified by chromatography (tlc) and the major fraction was extracted with dichloromethane/5% ethanol, washed with HCl (3 M, aqueous solution) and water and evaporated to give the required *macrocyclic azophenol* **5c** which crystallised from ethyl acetate as orange crystals, m.p. 216–217°C (yield 100%). δ ($CDCl_3$) 2.39 (*s*, 6 H, $ArCH_3$), 3.58 (*s*, 6 H, $ArOCH_3$), 3.88 (*m*, 4 H, OCH_2), 4.05 (*m*, 4 H, OCH_2), *ca* 4.60 (*br. s*, 4 H, $ArCH_2O$), 6.83 (*m*, 4 aryl-*H*), AB system, δ_A7.21, δ_B7.24 (J_{AB}2Hz, 4 aryl-*H*), ABC system, δ_A8.79. δ_B8.52, δ_C7.90 (J_{AB}2 Hz, J_{BC} 9 Hz, 3 aryl-*H*), 8.08(*s*, 2 aryl-*H*). (*Found*: C, 64.0; H, 5.0; N, 7.2%. $C_{40}H_{38}N_4O_{11}$ *requires* C, 64.0; H, 5.1; N, 7.5%); MS (CI source, carrier gas NH_3) $(M + NH_4)^+$, 768 (100%).

25,26-Dimethoxy-9,23-dimethyl-27-methoxymethyleneoxy-13,16,19-trioxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene **11a**

A similar method was used to that described for the macrocycle **11b**. The terphenyl derivative **10** (1.36 g, 2.41 mmol) was reacted with 3-oxapentan-1,5-diol (0.26 g, 2.41 mmol) and sodium hydride (0.29 g, 80% dispersion in oil, 9.64 mmol) in refluxing THF. The product **11a** was isolated as before, but using silica/sodium chloride (10% ww) for chromatography, as white crystals, m.p. 143–145°C, from ethyl acetate (yield 60%). δ ($CDCl_3$) 2.35 (*s*, 6 H, $ArCH_3$), 2.40 (*s*, 3 H, OCH_2OCH_3), 3.38 (*s*, 6 H, $ArOCH_3$), 4.00 (*s*, 2 H, OCH_2OCH_3), 4.45 (*d*, *J* 12 Hz, 2 H, $ArCH_2O$), 4.75 (*d*, *J* 12 Hz, 2 H, $ArCH_2O$), 7.06 (*d*, *J* 2 Hz, 2 aryl-*H*), 7.15 (*d*, *J* 2 Hz, 2 aryl-*H*), 7.26 (*t*, *J* 8 Hz, aryl-*H*), 7.44 (*d*, *J* 8 Hz, 2 aryl-*H*). (*Found*: C, 70.7; H, 7.2%; M^+, 508.2458. $C_{30}H_{36}O_7$ *requires* C, 70.8; H, 7.1%; M^+, 508.2461).

25,26-Dimethoxy-9,23-dimethyl-27-hydroxy-13,16.19-trioxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene **15a**

A similar method was used to that described for the phenolic macrocycle **15b**. The *product* **15a** (90–100% yield) was obtained as white crystals, m.p. 159–161°C. δ ($CDCl_3$) 2.38 (*s*, 6 H, $ArCH_3$), 3.45 (*m*, 4 H, OCH_2), 3.57 (*s*, 6 H, $ArOCH_3$), 3.72 (*m*, 4 H, OCH_2), AB system, δ_A4.98, δ_B4.40 (J_{AB}12 Hz, 4 H, $ArCH_2O$), 7.10 (*s*, 2 aryl-*H*), 7.18 (*s*, 2 aryl-*H*), AB_2 system, δ_A7.25, δ_B7.55 (J_{AB}10 Hz, 3 aryl-*H*); ^{13}C NMR ($CDCl_3$) 20.7 ($ArCH_3$), 61.5 ($ArOCH_3$), 67.0 (OCH_2), 69.5 (OCH_2), 70.2 (OCH_2), 121.7, 128.1, 129.8, 130.1, 130.7, 131.9, 133.3, 151.5, 155.8 (18 aryl-*C*). (*Found*: C, 72.4; H, 7.0%; M^+, 464.2193. $C_{28}H_{32}O_6$ *requires* C, 72.4; H, 6.9%; M^+, 464.2199).

25,26-Dimethoxy-9,23-dimethyl-13,16,19-trioxatetracylco-[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,5,7,9,11(26),21,23-octaene-4,27-dione **12a**

A similar method was used to that described for the macrocyclic quinone **12b**. The phenol **15a** (126 mg, 0.27 mmol) was oxidised using thallium trinitrate (0.36 g,

0.81 mmol), the product was purified by chromatography and crystallisation to give the *macrocyclic quinone* **12a** (67% yield) as orange crystals, m.p. 147–149°C. δ ($CDCl_3$) 2.29 (*s*, 6 H, $ArCH_3$), 3.65 (*m*, 8 H, OCH_2) 3.80 (*s*, 6 H, $ArOCH_3$), 4.65 (*br. s*, 4 H, $ArCH_2O$), 6.95 (*s*, 2 H, —CH=), AB system, δ_A7.06, δ_B7.21 (J_{AB}2 Hz, 4 aryl-*H*). (*Found*: C, 69.8: H, 6.3%; M^+, 478.1984. $C_{28}H_{30}O_7$ *requires* C, 70.3; H, 6.3%; M^+, 478.1992).

25,26-Dimethoxy-9,23-dimethyl-4-(2′,4′-dinitrophenylazo)27-hydroxy-13,16,19-trioxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene **5a**

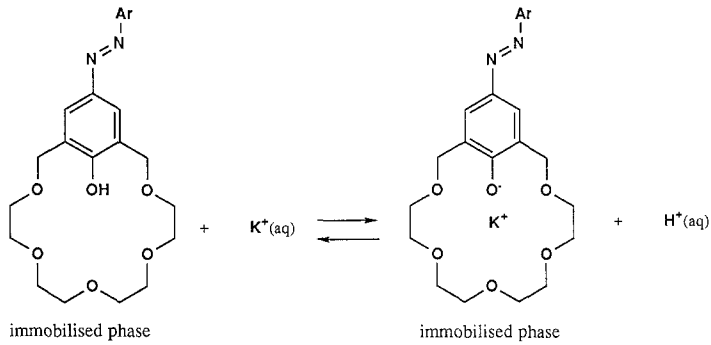
One mL of a solution of 2,4-dinitrophenylhydrazine (1.29 g, 6.50 mmol) and sulphuric acid (2.5 mL) in ethanol (20 mL) was added to a solution of the macrocyclic quinone **12a** (80 g, 0.167 mmol) in chloroform (60 mL) and ethanol (90 mL). The solution was stirred and refluxed for 4 h, cooled, and left overnight. Dichloromethane (100 mL) was added and the solution washed with water and evaporated. The residue was purified by chromatography (tlc), the major band was extracted with dichloromethane/ethanol, the solution washed with HCl (3 M, aqueous solution) and water and evaporated to give the *azophenol* **5a** (*ca* 100% yield) which crystallised as orange crystals, m.p. 226–227°C, from ethyl acetate. δ ($CDCl_3$) 2.36 (*s*, 6 H, $ArCH_3$), 3.44 (*m*, 4 H, OCH_2), 3.60 (*s*, 6 H, $ArOCH_3$), 3.61 (*m*, 4 H, OCH_2), AB system, δ_A4.37, δ_B4.93 (J_{AB}12 Hz, 4 H, OCH_2Ar), AB system, δ_A7.10, δ_B7.18 (J_{AB}2 Hz, 4 aryl-*H*), 7.47 (*s*, O*H*), 8.18 (*s*, 2 aryl-*H*), ABC system, δ_A7.93, δ_B8.55, δ_C8.81 (J_{AB}9 Hz, J_{BC}2 Hz, 3 aryl-*H*). (*Found*: C, 61.3; H, 5.0; N, 7.8%. $C_{34}H_{34}N_4O_{10}$ *requires* C, 62.0; H, 5.2; N, 8.5%), MS (CI source, carrier gas NH_3) $(M + NH_4)^+$, 676 (12%).

3. Results and Discussion

3.1. OPTICAL FIBRE SENSORS FOR CATIONS

In our earlier work [9] it was demonstrated that the the chromoionophore **1** [10] can be immobilised on Amberlite XAD2 resin at the tip of an optical fibre. Such a device responds in the pH range 7–9 to mM concentrations of potassium salts in water but does not show the required selectivity for potassium, as compared with sodium and calcium, for the measurement of potassium ion concentration in extra-cellular fluids.

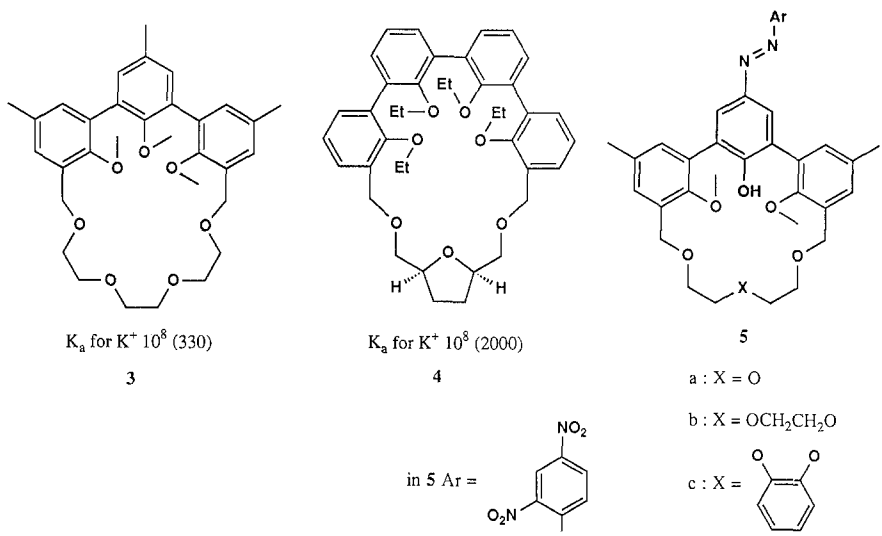
The response of chromoionophores, such as **1**, to ion capture is based upon the process summarised in Scheme 1, which is accompanied by a colour change, yellow to violet, of the azophenol chromophore. It was apparent from this work that a successful sensor for potassium should be based upon an ionophore with a binding energy for potassium ions similar to that of **1** but with a very much higher selectivity for potassium as compared with sodium and calcium. There are a number of reports of ionophores with high potassium selectivity, but for detection using optical fibres a correct value of the extraction coefficient for the concentration range to be detected is essential. Thus there is a possibility of saturation and loss of sensitivity if cation binding is too strong and an obvious loss of sensitivity at low concentrations if cation binding is too weak. The hemispherands **3** [11] and **4** [12]



1 2

Scheme 1. Use of chromoionophores in optical fibre based cation sensors

appeared to be particularly suitable since these have binding constants for potassium in the same range as 18-crown-6 and in both cases the potassium/sodium selectivity is adequate (K_a's, based upon the extraction of potassium picrate from an aqueous solution by a solution of the ionophore in $CDCl_3$, are given below the structures with the ratio of K_a for K^+ and Na^+ given in parentheses). The hemispherand **3** was selected as the ionophore of choice since it is relatively readily synthesised, incorporation of a responding ionisable chromophore into this structure gave the chromoionophore **5b** as a synthetic target.



K_a for K^+ 10^8 (330) K_a for K^+ 10^8 (2000) 5

3 4 a : X = O

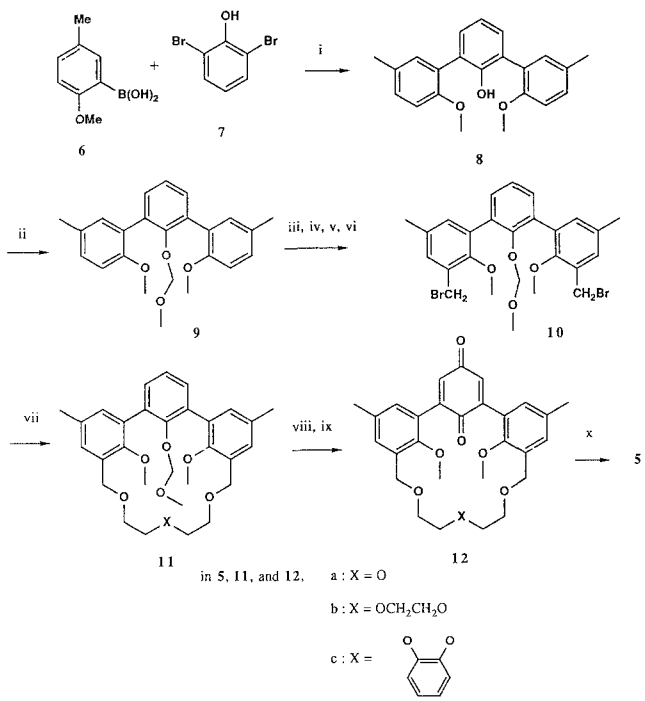
b : X = OCH_2CH_2O

in 5 Ar = NO_2 O_2N c : X =

3.2. THE SYNTHESIS OF CHROMOIONOPHORES 5

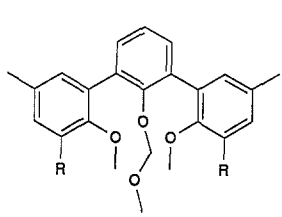
The synthesis of **5b**, and of the closely related chromoionophores **5a** and **5c**, is summarised in Scheme 2, which is largely based upon established methodology but a few points deserve special comment. The synthesis of the terphenyl derivative **8** by Pd(0) catalysed coupling [13] proved to be a very reliable procedure and superior

to a number of alternative methods [14]. The use of the methoxymethyl (MOM) [15] protecting group proved to be better than either protection by allyl or 2-methyoxyethoxymethyl (MEM), in particular it was retained during the formulation of the intermediate **9** so that the dialdehyde intermediate **13** was obtained in good yield. Reduction of the dialdehyde **13** to give the diol **14** was quantitative, but attempted preparation of the dibromide **10** from the diol **14** using PBr_3 in benzene resulted in extensive deprotection. A number of alternative procedures were investigated and eventually it was found that *N*-bromosuccinimide and dimethyl sulphide in CH_2Cl_2 at room temperature [16] gave consistently high yields of the required dibromide **10**.



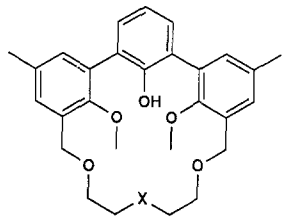
Scheme 2. Synthesis of hemispherand based chromoionophores **5**
Reagents: i, $Pd(PPh_3)_4$, EtOH, C_6H_6, Na_2CO_3/H_2O; ii, $MeOCH_2Cl$, NaH, THF; iii, BuLi, TMEDA, THF; iv, excess DMF; H_3O^+; v, $NaBH_4$; vi, 3 equiv NBS, 3 equiv Me_2S, CH_2Cl_2; vii, H-X-H, NaH, THF; viii, TFA, CH_2Cl_2/H_2O; ix, $Tl(NO_3)_3$; x, $ArNHNH_2$, H^+, EtOH, CH_2Cl_2.

The dibromide **10** reacted with diols under high dilution conditions to give hemispherands **11** in moderate to good yields. Sodium ions probably served as a template for the synthesis of **11a** (65% yield) and addition of potassium bromide to the reaction mixture gave increased yields (*ca* 50%) for the hemispherands **11b** and **11c**. The products **11** were purified by chromatography on silica gel mixed with a suitable metal salt (NaCl for **11a** and KBr for **11b** and **11c** at *ca* 1–2 g per 10 g of silica gel). The cyclic ionophores were eluted as complexes with the added metal salt after non-ionophoric impurities had been eluted by less polar solvents. This procedure has proved to be suitable for the purification of a wide range of



13 R = CHO

14 R = CH_2OH

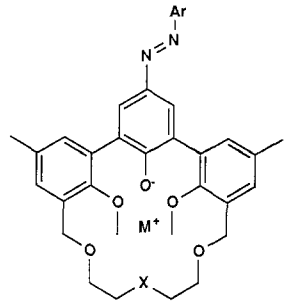


15

in 15 and 16, a : X = O

b : X = OCH_2CH_2O

c : X = 



16

ionophores in other work. The parent ionophore **11** was regenerated from the metal salt complex by washing with water and crystallisation.

The MOM protecting group of **11** was removed quantitatively using TFA and the resulting phenol oxidised with thallium trinitrate [17] to give the quinones **12** in high yield. These reacted with arylhydrazines to give the required azophenols **5**. Alternative, direct coupling of the phenols with diazonium tetrafluoroborates proved to be a less satisfactory procedure. The route outlined in Scheme 2 is generally suitable for the sythesis of phenolic hemispherands **15** and hemispherand quinones **12**, the overall yields from the boronic acid **6** being greater than 10%.

3.3. EXTRACTION BEHAVIOUR OF CHROMOIONOPHORES 5

The azophenols **5** were examined for their selectivity in the extraction of metal cations from water into organic solvents in the pH range 7–9. The resulting values for K_e gave a very useful indication of their potential for use in optical fibre sensors. The results of this examination are given in Table I. Although the azophenols **5** extract all alkali metal ions into CH_2Cl_2 at high pH to form blue solutions of the salts **16**, with the absorption maxima indicated in the table, at lower pH they show

Table I. Extraction coefficients[a] for alkali metal cations and azophenols **5**.

Metal ion	$\log_{10}K_e(\pm 0.2)(\lambda_{max})$					
	5a[a]	$(\lambda_{max})^b$	**5b**[a]	$(\lambda_{max})^b$	**5c**[a]	$(\lambda_{max})^b$
Li^+	−9.34	(606)	−9.34	(594)	−9.91	(586)
Na^+	−7.06	(610)	−8.40	(606)	−9.57	(610)
K^+	−7.14	(612)	−6.99	(616)	−7.34	(612)
Rb^+	−8.38	(614)	−6.67	(620)	−6.63	(620)
Cs^+	−9.14	(614)	−6.53	(620)	−6.64	(620)

[a]Calculated with the expression $K_e = [H^+]_{aq}.[ML]_{org}/[M^+]_{aq}.[HL]_{org}$ for a solution of **5** at *ca* 6×10^{-5} M in CH_2Cl_2 and M^+Cl^- in H_2O at pH 8.

[b]For extraction of aqueous MOH (1 M) by a solution of **5** at *ca* 6×10^{-5} M.

greater selectivity. Thus, at pH 8 the hemispherand **5c** shows high selectivity for K^+ over Na^+ (K_{K+}/K_{Na+} *ca* 170) and Li^+ (K_{K+}/K_{Li+} ca 370) although Rb^+ and Cs^+ are extracted more efficiently than K^+. The more flexible hemispherand **5b** shows significantly less selectivity than **5c** for K^+ as compared with Na^+ (K_{K+}/K_{Na+} *ca* 26) and its structure can evidently adapt more readily to the smaller size of the sodium cation than can the more rigid benzo-fused structure of **5c**. Neither of the hemispherands **5b** and **5c** shows measurable extraction of Mg^{2+}, Ca^{2+}, or Sr^{2+}, presumably because the corresponding 1 : 1 complexes (*cf* **16**) would require the presence of a poorly solvated anion in the organic phase. However both azophenols extract Ba^{2+} although the resulting complex has an absorption spectrum that is quite distinct from those of the salts **16**. The reason for this is not clear but we note that ion pairing for $Ba^{2+} \cdot X^-$ occurs rather more readily than for the other doubly charged cations. The hemispherand derivative **5a** does not show useful K^+/Na^+ selectivity which is not unexpected in view of the reported K_a's for the corresponding metal picrates [18] by the related trimethoxy hemispherand.

Note

[1]This paper is submitted to honour the memory of the late Charles J. Pedersen. It would not have been possible to carry out this work without the inspiration of the many ideas and discoveries that have resulted from his discovery of the crown ethers.

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