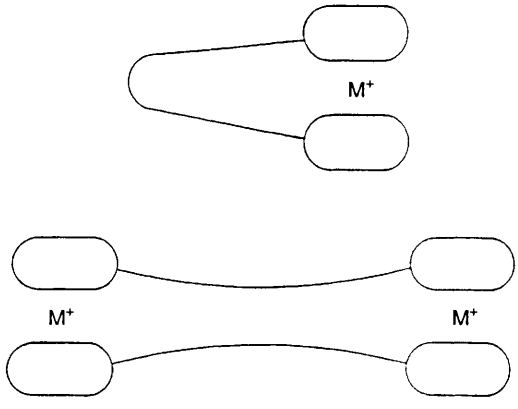
Design and Synthesis of Ionophores with Multiple Receptor Sites: Solution Nuclear Magnetic Resonance Studies of Their Interaction with Chloride, Sodium and Potassium Ions†

Kenneth I. Kinnear, David P. Mousley, Ezzidin Arafa and Joyce C. Lockhart*
Chemistry Department, The University of Newcastle upon Tyne, Newcastle upon Tyne NE1 7RU, UK

Ionophores of the bis(crown ether) type, with polyamine linkers, examples of which are known to bind simultaneously to a cation and its counter anion, have been prepared. One-pot reductive amination, used to couple a benzo-crown aldehyde with aliphatic (both linear and cyclic) and aromatic polyamines, proved to be the most efficient route. A strong inhibition of one synthetic route (amine benzylation) was observed. The competitive interaction between chloride and other anions for binding with the protonated ionophores was examined using ^{35}Cl NMR spectroscopy. Sandwich complexing of potassium contrasting with single-face complexation of sodium was demonstrated by ^{13}C NMR spectroscopy.

Biological systems frequently organise a molecule with two distinct subunits by a strong ionic or co-ordinative type interaction with a metal ion, which holds the units in position for some other biological strategy. For example the two halves of the iron protein of the nitrogenase complex are organised by an Fe_4S_4 cluster linked to cysteines coming from each half, forming a receptor site into which fits the ATP/ADP unit involved in energy transfer for the hydrogenation of di-nitrogen.[1] Such examples have prompted chemical mimicry. In this work a promising bis(crown ether) structure[2] was designed to co-ordinate anions within a cavity produced by organisation of the two ends of the molecule with a strong interaction. In the examples tried[2] this 'organisation' is a sandwiching of an alkali-metal cation between two crown ethers. Molecules containing two crown ether moieties, separated by a linking group, are known to sandwich potassium cations,[3,4] but crystallographic evidence of the structure has been sparse. A recent crystal structure determination of a rubidium complex of a Schiff-base-linked bis(crown ether) shows a double sandwich structure, not previously demonstrated.[5] This has a potential binding site between the two aromatic fragments which link the two crowns of each individual bis(crown ether), which may be represented as shown in Scheme 1, which we have used previously to describe our design intention.[2,3] The 1:1 sandwich structure (see Scheme 1) has also been demonstrated crystallographically.[6] This paper gives details of synthetic routes to, and the separation and characterisation of, multireceptors which should exhibit multiple binding as outlined by us previously in a preliminary report.[2]



Scheme 1 The make-up of 1:1 and 2:2 sandwich structures

Experimental

NMR Studies.—Characterising ^1H and ^{13}C NMR spectra were run on a Bruker WM 300-WB or WP200 spectrometer, using deuteriochloroform as solvent unless otherwise noted. The chlorine-35 studies were performed in D_2O at determined pD values on the Bruker WM 300-WB spectrometer. Complexation studies with potassium and sodium thiocyanates used ^{13}C NMR spectra taken for the relevant crown ether in deuteriated acetonitrile, on the same instrument. In all carbon-13 titrations the concentration of the crown ether was 0.08 mol dm^{-3} and aliquots of metal salts were added sequentially. At each stage a complete (δ 0–200) spectrum was obtained, and details are recorded in SUP 57040.

Preparations.—14-*Formyl*-2,3,5,6,8,9,11,12-*octahydro*-1,4,7,10,13-*benzopentaoxyacyclopentadecine* **1b**. To a stirred solution of 2,3-dihydroxybenzaldehyde (3.45 g, 2.5×10^{-2} mol) in dry tetrahydrofuran (thf) (500 cm^3) under nitrogen was added sodium hydride (1.32 g, 5.5×10^{-2} mol). The solution was brought to reflux for 30 min, cooled to room temperature and stirred for 3 h. A solution of 1,4-bis(*p*-tolylsulfonyloxy)butane (15.00 g, 3.0×10^{-2} mol) in dry thf (50 cm^3) was added dropwise and the mixture refluxed for 48 h. It was then cooled, the excess of hydride destroyed by careful addition of distilled water (1 cm^3) and the mixture filtered. The filtrate was reduced in volume *in vacuo*, taken up in chloroform (100 cm^3) and washed with aqueous sodium hydroxide solution (5%, 2×50 cm^3). The organic phase was dried over $MgSO_4$, filtered and concentrated in the presence of Celite, prior to flash chromatography on silica gel (Merck TLC grade). Elution with ethyl acetate yielded 0.75 g (10%) of the desired *product* **1b**. An analytical sample was prepared by recrystallisation of a portion of this solid from ethanol, m.p. 91.2–91.8 °C [Found: C, 60.30; H, 6.95%; *m/z* 296 (M^+). $C_{15}H_{20}O_6$ requires C, 60.80; H, 6.80%; *m/z* 296 (M^+)]. NMR ($CDCl_3$): ^1H (200 MHz), δ 10.40 (1 H, s, CHO), 7.42–7.35 (2 H, m, aromatic), 7.10–7.05 (2 H, m, aromatic), 4.30 (2 H, t, OCH_2 bound to benzo), 4.18–4.10 (2 H, m, OCH_2), 3.97 (2 H, t, OCH_2 bound to benzo), 3.95–3.86 (2 H, m, OCH_2), 3.77–3.63 (8 H, m, 4 × OCH_2); ^{13}C (50 MHz), δ 190.152 (CHO), 152.227

† *Supplementary data available* (No. SUP 57040, 5 pp): ^{13}C NMR shifts. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1994, Issue 1, pp. xxiii–xxviii.

(aromatic C), 129.927 (aromatic C), 123.974 (aromatic C), 119.304 (2 aromatic C), 118.841 (aromatic C), 74.502 (OCH_2), 71.302 (OCH_2), 71.008 (OCH_2), 70.342 (OCH_2), 70.236 (OCH_2), 70.155 (OCH_2), 69.206 (OCH_2) and 68.326 (OCH_2).

Acid **2**. To a solution of the formyl crown[3] **1a** (1.55 g, 5.20×10^{-3} mol) in acetone at 40 °C was added dropwise with stirring over 0.5 h a freshly prepared solution of potassium permanganate (1.43 g, 9.06×10^{-3} mol) in acetone–water (10 cm^3: 20 cm^3). The mixture was stirred for 2 h and then filtered. The filtrate was reduced in volume on an evaporator. Cooling (ice-bath) and acidification with concentrated hydrochloric acid resulted in the precipitation of a white solid which was washed with water, dried and shown to be the desired acid **2** (1.10 g, 67%).[7,8]

Bis(crown ether) piperazine **4**. To a solution of the acid[7] **2**, (1.10 g, 3.53×10^{-3} mol) in hot toluene (200 cm^3) was added thionyl chloride (2 cm^3). After heating this mixture at reflux overnight the solvent and excess of thionyl chloride were removed under vacuum. The solid acid chloride **3** thus obtained was used without further purification in the preparation of compound **4**. Compound **3** (1.00 g, 3.03×10^{-3} mol) suspended in toluene (100 cm^3) was added dropwise with stirring to a solution containing triethylamine (2 cm^3) and *N*,*N*′-bis(3-aminopropyl)piperazine (0.30 g, 1.50×10^{-3} mol). The mixture was then stirred at room temperature for 4 h prior to heating overnight at reflux. On cooling a white solid which had formed was filtered off. This solid was redissolved in chloroform (30 cm^3) and the resultant solution washed with distilled water (2×20 cm^3). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a solid. Recrystallisation of this solid from Pr^iOH–methanol gave compound **4** as a colourless powder (710 mg, 60%), m.p. 198–199 °C [Found: C, 58.3; H, 7.6; N, 6.4%; *m*/*z* 788 (M^+). $C_{40}H_{60}N_4O_{12}\cdot 2H_2O$ requires C, 58.2; H, 7.8; N, 6.8%; *m*/*z* 788 (M^+)]. ^1H NMR (200 MHz, $CDCl_3$): δ 7.86 (2 H, br s, 2 NH), 7.41 (2 H, s, aromatic), 7.28 (2 H, d, aromatic), 6.80 (2 H, d, aromatic), 4.30–4.00 (8 H, m, 4 OCH_2 bound to benzo), 4.00–3.80 (8 H, m, 4 OCH_2), 3.80–3.58 (16 H, m, 4 OCH_2CH_2O), 3.57–3.30 (4 H, m, 2 NCH_2), 2.90–2.10 (12 H, m, piperazine ring, 2 NCH_2) and 1.90–1.64 (4 H, m, 2 CH_2).

Reduced compound **5a**. Compound **4** (300 mg, 1.0×10^{-4} mol) in dry thf (500 cm^3) was heated to reflux with stirring under N_2. To the refluxing solution was carefully added $LiAlH_4$ (50 mg, 1.32×10^{-3}), and the mixture was then maintained at this temperature for 3 d. After cooling, the reaction mixture was poured onto distilled water (30 cm^3) then treated with NaOH solution (20%, 10 cm^3). The two layers which formed were separated and on concentration *in vacuo* the organic phase yielded a colourless syrup (280 mg). This was chromatographed on silica gel (Merck TLC grade) and final elution with freshly prepared NH_4OH–MeOH–CH_2Cl_2 (1:5:5) gave the desired product as a colourless syrup. This crystallised on standing to give compound **5a** as a colourless solid (150 mg, 52%), m.p. 78–80 °C {Found: C, 62.30; H, 8.70; N, 7.30%; *m*/*z* 761 ($[M + 1]^+$). $C_{40}H_{64}N_4O_{10}\cdot 0.5H_2O$ requires C, 62.40; H, 8.50; N, 7.30%; *m*/*z* 760 (M^+)}. NMR: ^1H (200 MHz, $CDCl_3$) δ 6.79 (2 H, s, aromatic), 6.74 (4 H, s, aromatic), 4.09–4.03 (8 H, m, 4 OCH_2 bound to benzo), 3.94–3.81 (8 H, m, 4 CH_2O), 3.81 (16 H, s, 4 OCH_2CH_2O), 3.62 (4 H, m, 2 CH_2NH bound to benzo), 2.57 (4 H, apparent t, 2 $NHCH_2$, $N = 7$) (*N* is the sum of the coupling constants for an AA′BB′ system) 2.35 (8 H, br s, piperazine ring), 2.31 (4 H, apparent t, 2 $NHCH_2$, $N = 7$), 2.15 (2 H, s, 2 NH, D_2O exchangeable), 1.62 (4 H, apparent qnt, 2 $NHCH_2$, $N = 7$); (CD_3OD), δ 7.17 (2 H, s, aromatic), 7.16 (4 H, s, aromatic), 4.34–4.26 (8 H, m, 4 OCH_2, bound to benzo), 4.08–4.02 (8 H, m, 4 CH_2O), 3.90 (16 H, s, 4 OCH_2CH_2O), 3.80 (4 H, m, 2 CH_2NH bound to benzo), 2.80 (4 H, apparent t, 2 $NHCH_2$, $N = 7$), 2.67 (8 H, br s, piperazine ring), 2.57 (4 H, apparent t, 2 $NHCH_2$, $N = 7$) and 1.90 (4 H, apparent qnt, 2 $NHCH_2$, $N = 7$ Hz); ^{13}C (50 MHz, $CDCl_3$), δ 149.148 (aromatic C), 148.082 (aromatic C), 133.655 (aromatic C), 120.810 (aromatic C), 114.039 (2 aromatic C), 71.080 (OCH_2), 70.546 (OCH_2), 69.683 (OCH_2), 69.207 (OCH_2), 69.020 (OCH_2), 57.077 (NCH_2), 53.721 (NCH_2), 53.327 (NCH_2), 48.072 (NCH_2) and 26.955 (CH_2); (CD_3OD), δ 150.761 (aromatic C), 149.948 (aromatic C), 134.097 (aromatic C), 122.867 (aromatic C), 115.967 (aromatic C), 72.165 (OCH_2), 71.727 (OCH_2), 70.944 (OCH_2), 70.511 (OCH_2), 70.406 (OCH_2), 58.104 (NCH_2), 54.374 (NCH_2), 54.149 (NCH_2), 48.674 (NCH_2) and 27.140 (CH_2).

A portion of the syrup (130 mg) was dissolved in the minimum of Pr^iOH and treated with concentrated hydrochloric acid (eight drops). The heavy white precipitate which formed was filtered off and shown to be the tetrahydrochloride of compound **5a** (103 mg, 66%), m.p. 213–216 °C (Found: C, 50.9; H, 7.6; N, 5.7%. $C_{40}H_{64}N_4O_{10}\cdot 4HCl\cdot 2H_2O$ requires C, 51.0; H, 7.7; N, 5.9%). ^1H NMR (200 MHz, D_2O): δ 7.04 (2 H, s, aromatic), 7.00 (4 H, s, aromatic), 4.14 (12 H, m, 4 OCH_2 bound to benzo and 2 CH_2), 3.87 (8 H, s, 4 CH_2O), 3.69 and 3.65 (16 H, 2s, 4 OCH_2CH_2O), 3.48 (8 H, s, 2 CH_2CH_2), 3.19 (4 H, apparent t, 2 CH_2, $N = 7.5$), 3.09 (4 H, apparent t, 2 CH_2, $N = 8.0$ Hz) and 2.09 (4 H, m, 2 CH_2).

Alternatively, to a solution of compound **1a** (2.96 g, 1.0×10^{-2} mol), *N*,*N*′-bis(3-aminopropyl)piperazine (1.00 g, 5.0×10^{-3} mol) and glacial acetic acid (30 cm^3) in 1,2-dichloroethane (40 cm^3) was added sodium triacetoxyhydroborate (4.0, 1.89×10^{-2} mol), following the method of Abdel-Magid and Marynoff.[9] The resultant solution was stirred overnight at room temperature and then made basic with a saturated solution of sodium hydrogencarbonate. This aqueous solution was extracted with ethyl acetate (2×100 cm^3) to remove any unreacted **1a** prior to extraction with chloroform (3×70 cm^3). The combined chloroform extracts were concentrated *in vacuo* to afford compound **5a** as a colourless syrup (2.4 g, 64%). Purification of this material for analytical purposes was achieved *via* flash chromatography (silica gel, Merck TLC grade) as previously described.

Reduced compound **5b** *using reductive amination*. The preparation of compound **5b** from **1b** (0.75 g, 2.5×10^{-3} mol) and *N*,*N*′-bis(3-aminopropyl)piperazine (0.26 g, 2.6×10^{-3} mol) carried out in a similar manner to that of **5a**, gave a colourless syrup (0.4 g, 40%); *m*/*z* 761 ($[M + 1]^+$) [calc. 760 (*M*)]. NMR (CD_3OD): ^1H (200 MHz), δ 6.98–6.64 (6 H, m, aromatic), 4.17–4.08 (8 H, m, 4 OCH_2 bound to benzo), 3.96–3.86 (8 H, m, 4 OCH_2), 3.79–3.55 (20 H, m, 4 OCH_2CH_2O and 2 CH_2), 2.58 (4 H, apparent t, 2 CH_2, $N = 6.8$ Hz), 2.41–2.29 (12 H, br m, 6 CH_2) and 1.71–1.61 (4 H, br m, 2 CH_2); ^{13}C NMR (50 MHz), δ 151.829 (aromatic C), 146.793 (aromatic C), 134.075 (aromatic C), 123.778 (aromatic C), 121.761 (aromatic C), 112.027 (aromatic C), 72.817 (OCH_2), 71.228 (OCH_2), 70.894 (OCH_2), 70.676 (OCH_2), 70.305 (OCH_2), 70.163 (OCH_2), 69.503 (OCH_2), 67.884 (OCH_2), 56.978 (NCH_2), 53.289 (NCH_2), 48.897 (NCH_2), 47.922 (NCH_2), and 27.059 (CH_2). The syrup was dissolved in the minimum of Pr^iOH and treated with concentrated hydrochloric acid (approximately 10 drops). The white precipitate which formed was filtered off and shown to be the tetrahydrochloride of **5b** (180 mg, 38%), m.p. 219–223 °C (Found: C, 52.2; H, 7.6; N, 5.7. $C_{40}H_{64}N_4O_{10}\cdot 4HCl\cdot H_2O$ requires C, 51.95; H, 7.6; N, 6.05%). NMR (D_2O): ^1H (200 MHz), δ 7.30–7.17 (2 H, m, aromatic), 7.09–7.00 (1 H, m, aromatic), 4.28 (4 H, s, CH_2 bound to benzo), 4.25–4.20 (8 H, m, 4 OCH_2), 4.00–3.93 (8 H, m, 4 OCH_2), 3.76 (16 H, s, 8 OCH_2), 3.63 (8 H, s, 4 × piperazine CH_2), 3.30 (4 H, t, 2 NCH_2), 3.15 (4 H, t, 2 NCH_2) and 2.20–2.00 (4 H, m, 2 CH_2); ^{13}C (50 MHz), δ 152.66 (aromatic C), 147.90 (aromatic C), 126.95 (aromatic C), 125.88 (aromatic C), 124.28 (aromatic C), 116.93 (aromatic C), 74.50 (OCH_2), 71.67 (OCH_2), 71.32 (OCH_2), 71.19 (OCH_2), 70.27 (OCH_2), 70.05 (OCH_2), 69.02 (OCH_2), 55.06 (NCH_2), 50.57 (NCH_2), 47.89 (NCH_2), 45.30 (NCH_2) and 22.24 (CH_2).

The reductive amination technique was also employed as for compound **5a** to prepare the following representative bis(crown ether) compound.

Diethylenetriamine derivative **6**. Reaction of compound **1a** (750 mg, 2.53×10^{-3} mol) and diethylenetriamine (131 mg, 1.27×10^{-3} mol) in the presence of glacial acetic acid (8 cm^3) and sodium triacetoxyhydroborate (537 mg, 2.54×10^{-3} mol) in 1,2-dichloroethane (40 cm^3) afforded compound **6** as a colourless syrup (600 mg, 71%); *m/z* 664 ($[M + 1]^+$) [calc. 663 (*M*)]. NMR: ^1H (200 MHz, CD_3OD)], δ 7.29 (2 H, br s, aromatic), 7.19 (4 H, s, aromatic), 4.43 (8 H, s, 4 OCH_2, bound to benzo), 4.41 (8 H, s, 4 OCH_2), 4.02 (20 H, s, 4 OCH_2CH_2O and 2 CH_2N bound to benzo) and 3.02 (8 H, s, 2 NCH_2CH_2N); ($CDCl_3$), δ 6.80 (2 H, br s, aromatic), 6.74 (4 H, s, aromatic), 4.08–4.02 (8 H, m, 4 OCH_2 bound to benzo), 3.85–3.83 (8 H, m, 4 OCH_2), 3.68 (16 H, s, 4 OCH_2CH_2O), 3.64 (4 H, s, 2 CH_2N bound to benzo), 2.65 (8 H, s, 2 NCH_2CH_2N) and 2.10 (3 H, br s, 3 NH); ^{13}C (50 MHz, $CDCl_3$), δ 149.33 (aromatic C), 148.37 (aromatic C), 133.06 (aromatic C), 121.12 (aromatic C), 115.00 (aromatic C), 114.41 (aromatic C), 71.07 (OCH_2), 70.62 (OCH_2), 69.70 (OCH_2), 69.40 (OCH_2), 69.21 (OCH_2), 53.27 (NCH_2), 48.70 (NCH_2) and 48.26 (NCH_2); (75 MHz, CD_3OD), δ 150.77 (aromatic C), 149.94 (aromatic C), 134.30 (aromatic C), 122.90 (aromatic C), 116.12 (aromatic C), 115.74 (aromatic C), 72.07 (OCH_2), 71.69 (OCH_2), 70.90 (OCH_2), 70.59 (OCH_2), 70.46 (OCH_2), 53.96 (NCH_2), 49.00 (NCH_2) and 48.82 (NCH_2).

A portion of this syrup (100 mg, 1.51×10^{-3} mol) was dissolved in the minimum of Pr^iOH and treated with concentrated hydrochloric acid (seven drops). The pale yellow precipitate which formed was filtered off and recrystallised from methanol–Pr^iOH to give a solid (coloured faintly yellow) which was shown to be the trihydrochloride of compound **6** (98 mg, 84%), m.p. 210–216 °C (Found: C, 50.4; H, 7.3; N, 5.9. $C_{34}H_{53}N_3O_{10}\cdot 3HCl\cdot 2H_2O$ requires C, 50.5; H, 7.5; N, 5.3%). NMR (D_2O): ^1H (200 MHz), δ 7.04 (2 H, s, aromatic), 7.00 (4 H, s, aromatic), 4.18 (4 H, s, 2 NCH_2), 4.13 and 4.11 (8 H, 2 s, 4 OCH_2 bound to benzo), 3.86 (8 H, s, 4 OCH_2), 3.68 and 3.64 (8 H, 2 s, 8 OCH_2) and 3.43 (8 H, s, 4 NCH_2); ^{13}C (50 MHz), δ 150.43 (aromatic C), 149.51 (aromatic C), 124.96 (aromatic C), 124.34 (aromatic C), 115.90 (aromatic C), 114.71 (aromatic C), 71.28 (OCH_2), 70.76 (OCH_2), 70.12 (OCH_2), 69.42 (OCH_2), 69.27 (OCH_2), 52.90 (NCH_2), 44.99 (NCH_2) and 43.62 (NCH_2).

1,8-*Diamino*-3,6-*dioxaoctane derivative* **7**. The reaction of compound **1a** (1.48 g, 5.0×10^{-3} mol) and 1,8-diamino-3,6-dioxaoctane (0.37 g, 2.5×10^{-3} mol) by the method described for **5a** afforded compound **7** as a colourless syrup (1.6 g, 81%). Accurate *m/z* 708.3821; calc. for $C_{36}H_{56}N_2O_{12}$ 708.3833. NMR ($CDCl_3$): H^1 (200 MHz), 6.84–6.77 (m, 6 H, aromatic) 4.12–4.05 (m, 8 H, macrocyclic OCH_2), 3.67 (s, 4 H, CH_2N bound to benzo), 3.58–3.53 (m, 8 H, linker OCH_2), 2.73 (t, 4 H, J = 5.2 Hz, NCH_2), 2.10 (br s, 2 H, NH) and 1.80–1.70 (m, 4 H, NCH_2CH_2); ^{13}C (50 MHz), δ 149.19, 148.11, 133.52, 120.94, 114.15, 114.09 (aromatic C), 71.1, 70.59, 69.7, 69.27, 69.03 (crown ether C), 70.59, 70.29 (linker ether), 53.6 (CH_2N bound to benzo) and 48.59 (NCH_2CH_2O).

4,4′-*Methylenedianiline derivative* **8**. The reaction of compound **1a** (1.30 g, 4.39×10^{-3} mol) and 4,4′-methylenedianiline (416 mg, 2.10×10^{-3} mol) in the presence of glacial acetic acid (8 cm^3) and sodium triacetoxyhydroborate (1.76 g, 8.30×10^{-3} mol) in 1,2-dichloroethane (50 cm^3) afforded a yellowish white solid. Purification of this material for analytical purposes proved difficult but was achieved *via* flash chromatography (silica gel, Merck TLC grade) using ethyl acetate then triethylamine–ethyl acetate–light petroleum (b.p. 60–80 °C) (1 : 9 : 2) as eluent. The positive fractions from the column gave on concentration a syrup which solidified on standing to a cololourless *glass*, **8** (1.25 g, 78%), m.p. 36–40 °C [Found: C, 66.9; H, 7.6; N, 3.6%; *m/z* 758 (M^+). $C_{43}H_{54}N_2O_{10}\cdot H_2O$ requires C, 66.5; H, 7.3; N, 3.6%; *m/z* 758 (M^+)]. NMR ($CDCl_3$): ^1H (200 MHz), δ 6.95 (4 H, d, J = 8.35, aromatic), 6.87–6.81 (6 H, m, benzo crown ether aromatics), 6.53 (4 H, d, J = 8.35 Hz, aromatic), 4.17 (4 H, s, 4 CH_2NH bound to benzo), 4.10–4.08 (8 H, m, 4 OCH_2 bound to benzo), 3.90–3.84 (8 H, m, 4 OCH_2), 3.73 (18 H, s, 4 OCH_2CH_2O), 3.68 (2 H, s, CH_2 bound to aniline); ^{13}C (50 MHz), δ 149.33 (aromatic C), 148.30 (aromatic C), 146.42 (aromatic C), 132.82 (aromatic C), 131.17 (aromatic C), 129.62 (aromatic C), 120.33 (aromatic C), 114.23 (aromatic C), 113.49 (aromatic C), 113.05 (aromatic C), 71.12 (OCH_2), 70.58 (OCH_2), 69.71 (OCH_2), 69.65 (OCH_2), 69.26 (OCH_2), 68.99 (CH_2NH bound to benzo), 48.51 (NCH_2) and 40.18 (CH_2 bound to aniline).

1,4,7-*Triazacyclononane derivative* **9**. This material was obtained from a reaction of compound **1a** (687 mg, 2.32×10^{-3} mol) and 1,4,7-triazacyclononane (300 mg, 2.32×10^{-3}) in the presence of glacial acetic acid (0.6 cm^3) and sodium triacetoxyhydroborate (980 mg, 4.62×10^{-3} mol) in 1,2-dichloroethane (30 cm^3). After the usual work-up, the cyclic *compound* **9** was obtained as a colourless syrup (460 mg, 58%); *m/z* 689 ($[M + 1]^+$) [calc. 689 (*M*)]. NMR ($CDCl_3$): ^1H(300 MHz), δ 6.85–6.74 (6 H, m, aromatic), 4.14–4.08 (8 H, br m, 4 OCH_2 bound to benzo), 3.99–3.86 (8 H, m, 4 OCH_2), 3.72 (16 H, s, 4 OCH_2CH_2O), 3.58 (4 H, s, 2 CH_2) 2.97 (4 H, s, 2 CH_2), 2.79 (4 H, s, 2 CH_2) and 2.40 (4 H, s, 2 CH_2); ^{13}C (75 MHz), δ 149.30 (aromatic C), 148.96 (aromatic C), 130.77 (aromatic C), 122.16 (aromatic C), 115.61 (aromatic C), 114.28 (aromatic C), 69.65 (OCH_2), 69.60 (OCH_2), 69.50 (OCH_2), 69.28 (OCH_2), 69.18 (OCH_2), 60.76 (NCH_2), 50.92 (NCH_2), 48.44 (NCH_2) and 44.29 (NCH_2).

When 2 and 3 mole equivalents of compound **1a** were employed complex mixtures of products were obtained which were not further investigated.

Reaction of benzyl bromide with N,N′-*bis*(3-*tosylaminopropyl*)*piperazine* **10**. *N,N′*-Bis(3-tosylaminopropyl)piperazine **10** (3 g, 5.90×10^{-3} mol) and dry potassium carbonate (2 g, 2×10^{-2} mol) in dry dimethylformamide (dmf) (500 cm^3) were heated at 80 °C for 3 h. The mixture was cooled to room temperature, then benzyl bromide (2 g, 1.2×10^{-2} mol) in dry dmf (50 cm^3) was added dropwise with stirring; the reaction mixture was then heated at 80 °C for 2 d. The mixture was allowed to cool to room temperature, filtered and the filtrate concentrated *in vacuo* to yield a brown syrup. This was redissolved in chloroform (50 cm^3) and the resultant solution washed with distilled water (3 × 20 cm^3). The organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* in the presence of Celite prior to purification on a silica gel column (Merck TLC grade). Elution with ethyl acetate–light petroleum afforded the *N,N′*-bis{3-[benzyl(tosyl)amino]propyl}piperazine **12** as a colourless syrup (1.35 g, 33%), which crystallised from ethanol as a colourless powder, m.p. 133–135 °C [Found: C, 65.00; H, 7.10; N, 8.05%; *m/z* 688 (M^+). $C_{38}H_{48}N_4O_4S_2\cdot 0.5H_2O$ requires C, 65.40; H, 7.10; N, 8.05%; *m/z* 688 (*M*)]. NMR ($CDCl_3$): ^1H (200 MHz), δ 7.71 (4 H, d, aromatic, J = 8 Hz), 7.34–7.26 (14 H, m, aromatic), 4.28 (4 H, s, 2 CH_2N bound to phenyl), 3.10 (4 H, apparent t, 2 NCH_2, N = 7 Hz), 2.44 (6 H, s, 2 tosyl CH_3), 2.31–2.03 (12 H, m, 2 NCH_2) and 1.61–1.34 (4 H, m, 2 CH_2); ^{13}C (50 MHz), δ 143.30 (aromatic C), 136.87 (aromatic C), 136.54 (aromatic C), 129.77 (aromatic C), 128.60 (aromatic C), 128.46 (aromatic C), 127.83 (aromatic C), 127.28 (aromatic C), 55.43 (NCH_2), 52.88 (NCH_2), 52.41 (NCH_2), 46.50 (NCH_2), 25.62 (CH_3), and 21.58 (CH_2). The monobenzylated derivative **11** was also obtained as a colourless syrup (300 mg, 8.5%); *m/z* 598 ($[M - 1]^+$) [calc. 599 (*M*)]. ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (2 H, d, aromatic, J = 8), 7.70 (2 H, d, aromatic, J = 8 Hz), 7.34–7.22 (9 H, m, aromatic), 4.30 (2 H, s, CH_2N bound to phenyl), 3.10 (2 H, apparent t, NCH_2, N = 7), 3.03 (2 H, s, apparent t, NCH_2, N = 7), 2.43 (3 H, s, tosyl CH_3), 2.42 (3 H, s, tosyl CH_3), 2.37–2.11 (12 H, m, 6 NCH_2), 1.58 (2 H, apparent q, CH_2, N = 7), and 1.51 (2 H, apparent q, CH_2, N = 7 Hz).

Compound **10** was also treated with the bromomethyl analogue of **1a** using a variety of bases and solvents, but these reactions did not proceed smoothly and the desired intermediates were not obtained in a purity or quantity sufficient for further synthetic work (see Results and Discussion).

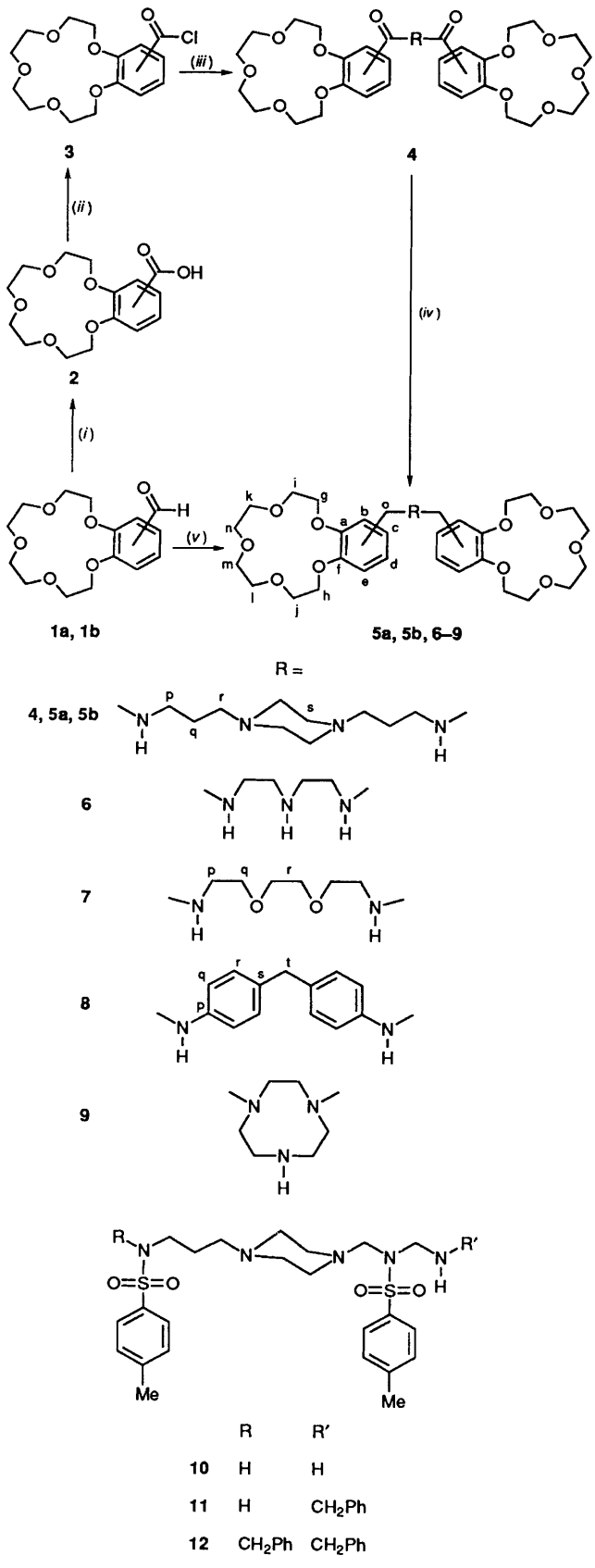
Results and Discussion

The general synthesis of the bis(crown ether) compounds **5–9** is shown in Scheme 1. We have sought to incorporate the technique of reductive amination[9] [(*v*) in Scheme 2], thus eliminating the need for the rather involved synthetic route (*i*)–(*iv*) which requires the isolation of the intermediates **2**, **3** and the bis(amide) **4**. The route to **4** incorporates the known[7,8] crown-5 carboxylic acid **2** and its acid chloride **3**. However we prepared **2** by direct oxidation from the aldehyde **1a** in acetone–water rather than by the more elaborate method from the acetophenone derivative as outlined by Smid and co-workers[7] and Toke *et al.*[8] Although the preparation of the amide **4** from this acid chloride **3** was relatively simple, the reduction of **4** to the desired reduced bis(crown ether) amine **5a** with $LiAlH_4$ proved to be slow and not entirely satisfactory. This fact along with the multi-step nature of the synthesis and the failure of other routes (mentioned in the Experimental section and further described below) moved us in the direction of reductive amination techniques. A review of the literature led us away from the normal hydride reagents, such as sodium cyanotrihydroborate, to employ sodium triacetoxyhydroborate, a reagent known to be effective in the reductive amination of weakly basic amines. This reagent was entirely satisfactory in bringing about the reductions we required in cheap, simple one-pot reactions.

A method for the reductive amination of substituted amines from their aldehyde and amine precursors using sodium triacetoxyhydroborate was outlined in a short paper by Abdel-Magid and Maryanoff.[9] We have extended this technique to synthesise a range of aromatic, aliphatic cyclic and acyclic amines incorporating within their structures crown ether moieties. We had originally planned to synthesise these compounds using a *simple* nucleophilic displacement reaction on the bromomethyl analogue of **1a** with tosylated polyamines, followed by deprotection of the amine sub-units of the bis(crown ether) amine tosylates. Extensive resources and synthetic strategies (NaH–thf–dmf, K_2CO_3–dmf and even CsF–dmf) were employed in the preparation and isolation of such bis(crown ether) amine tosylates but yields were disappointing and eventually these particular synthetic routes were abandoned.

It is interesting however that previous authors have experienced difficulties in bringing about nucleophilic displacements in the presence of crown ethers[10] and this inhibitory effect has been postulated to originate mainly from the increased steric effect compared with the electrostatic effects. The actual nucleophilic substitution reaction between a tosylated polyamine and benzyl bromide not surprisingly showed no such inhibition and both mono- and di-substituted benzylated tosylated polyamines were isolated from such a reaction, giving more evidence that it is the crown ether which somehow inhibits the displacement of the bromide. With the failure of this route our attention turned to other methods including acylation/reduction and as mentioned above reductive amination. Success was achieved with diamines having two primary or two secondary amine groups. The triamine (used for compound **6**) reacted only at its primary amine groups, while the 1,4,7-triazacyclononane (used for **9**) became substituted at two of its secondary amine residues. All other reactions with three or more different primary or secondary amino groups gave complex mixtures from which no clean product was obtained.

Solution NMR Studies.—The behaviour of the new bis(crown ethers) towards cations and anions was investigated[2] previously by NMR titrations, using multinuclear facilities. The competition between chloride and other anions for the binding site on the protonated compounds **5a** and **5b** was examined. Titrations of **5a**·4HCl in acidic aqueous solution were followed by ^{35}Cl NMR spectroscopy as described previously.[2] The titrations with potassium sulfate followed the pattern shown for sodium sulfate, although lower solubility of the potassium salt



	R	R′
10	H	H
11	H	CH_2Ph
12	CH_2Ph	CH_2Ph

Scheme 2 (*i*) $KMnO_4$, water, acetone, 40 °C; (*ii*) $SOCl_2$, toluene, reflux; (*iii*) *N*,*N*′-bis(3-aminopropyl)piperazine, NEt_3, toluene, room temperature then reflux; (*iv*) $LiAlH_4$, thf, reflux; (*v*) *N*,*N*′-bis(3-aminopropyl)piperazine, sodium triacetoxyhydroborate, glacial acetic acid, 1,2-dichloroethane, room temperature. The labelling of the crown ether carbons and protons used for NMR assignments in the text is shown

Table 1 Chlorine-35 NMR linewidths ($\Delta\nu_{\frac{1}{2}}$) upon titration of compounds **5a** and **5b**[a]

Starting compound	c/mol dm^{-3}	Titrant	Final concentration/mol dm^{-3}	$\Delta\nu_{\frac{1}{2}}$[b]/Hz	
				Initial	Final
5a·4HCl	0.05	Na_2SO_4	0.15	118[c]	67[c]
	0.025	Na_2SO_4	0.2	96	49
	0.025	K_2SO_4	0.2	96	49
5b·4HCl	0.025	K_2SO_4	0.125	85	42
5a·4HCl	0.05	$NaNO_3$	0.8	124	77.5
	0.05	NaBr	0.2	117	63
KCl	0.1	**5a**[d]	0.025	14	66
	0.0125	**5a**[d]	0.075	13	176

[a] At pD 1.3 as described in ref. 1. [b] ± 3 Hz. [c] From ref. 1. [d] As tetra(toluene-*p*-sulfonate).

Table 2 Chloride linewidths[a] before and after addition of potassium sulfate

Compound[b]	Linewidth		Ratio[c] (%)
	0 mol dm^{-3} K_2SO_4	0.2 mol dm^{-3} K_2SO_4	
Hexacyclen hexahydrochloride	≈308	19	6
Cyclam tetrahydrochloride	102	33	32
N,*N*′-Bis(3-aminopropyl)piperazine tetrahydrochloride	31	19	60
5a·4HCl	95	44	46
KCl (0.2 mol dm^{-3})	12	14	111

[a] ± 3 Hz. [b] Concentration 0.025 mol dm^{-3} unless otherwise stated. [c] Of linewidth at higher to that of lower sulfate concentration.

required that they be performed at half the concentration used previously. The results are shown in Table 1 where initial and final linewidths for the titration are quoted. In each instance, as previously, the chlorine-35 linewidth for the hydrochloride narrowed on titration to a value considerably greater than for free chloride ions under the same conditions (this linewidth is concentration dependent). The salts examined were sodium and potassium sulfates, sodium nitrate and bromide. Compound **5a** as its tetra(toluene-*p*-sulfonate) was also used to titrate chloride salts and the linewidth increased smoothly as noted previously.[2] The chloride has at least three possible sites in these titrations: (*a*) free chloride, (*b*) a special complexed site from which it cannot be displaced by any of the other anions used and (*c*) a general complexed site from which it can be removed by sulfate and other anions. It can be seen from Table 2 that whilst the linewidths of chloride in 1,4,8,11-tetraazacyclotetradecane (cyclam) tetrahydrochloride and 1,4,7,10,13,16-hexaazacyclooctadecane (hexacyclen) hexahydrochloride solutions (under conditions similar to those described for the new compounds in this study) were reduced substantially on addition of an excess of sulfate ion, that of the tetrahydrochloride of **5a** remained broad consistent with the proposal that it has a chloride-specific site.[2] The tetrahydrochloride of the linker *N*,*N*′-bis(3-aminopropyl)piperazine itself shows little of this effect, indicating the importance of the crown ethers in the operation of **5a** and **5b**. There is however no indication of a difference between sodium and potassium counter ions in producing the effect. Further evidence as to the nature of the specific chloride site awaits the determination of a crystal structure of the hydrochloride but thus far no crystalline samples have been obtained.

^{1}H *NMR spectra.* Spectral assignments were made using the labelling schemes shown in Scheme 1. Owing to coincidental, identical shifts, the ^{1}H aromatic section of each bis(crown ether) only shows two resonances with a 1:2 integral ratio. This can be explained as an overlap of the c and d doublets and the b singlet. Any *meta* coupling is usually not resolved. The polyamine linker protons are reasonably easy to assign, though distinguishing the two triplets of the p and r protons of compound **5a** and **5b** was arbitrary. Typically, the crown ether section of the ^{1}H NMR spectrum has the same pattern as that of the formyl precursor,[3] *i.e.* two overlapping pairs of AA′BB′ multiplets and a singlet upfield of these, the integral ratio of 1:1:2 confirming the assignment. The protons of the methylene group attached to the aromatic ring usually have a shift very close if not identical to that of the singlet of the crown ether region. The NMR shifts of the linker section are obviously different for each compound. The NH proton signals showed as broad singlets between δ 1.7 and 2.3. Many had integrals higher than 2 though lower than 4. The spectral changes, particularly of the crown ether and aromatic protons, on addition of potassium or sodium ions showed the difference which has customarily been interpreted[3,11] to signify 1:1 sandwich complexing (for K) or 2:1 complexing (for Na).

^{13}C *NMR spectra.* The ^{13}C NMR spectra could be assigned (*a*) by analogy with previous work[12] assisted (*b*) by the additional assignment of carbon c (linker carbon) as that with the altered shift, and (*c*) by HETCOR (heteronuclear correlation) analysis. The ^{13}C NMR titration also provided the means to distinguish types of complex in which the metal ion interacts with a single face from those where it is sandwiched.[12] In this work, compounds **5a**, **7** and **8** offered a wide range of linker which between them might give pointers to the likelihood of 1:1 or 2:2 sandwich structures in solution. Thus **5a** with the propylpiperazine linker is the most rigid and should have more chance of forming a 2:2 complex, while the most flexible **7** should be most likely to fold over to give a 1:1 sandwich structure. The intermediate **8** has a biphenyl methane unit which could potentially be planar, but is more likely to have a twisted torsion[13] and could thus form either a 2:2 or 1:1 sandwich. These compounds were subjected to ^{13}C NMR titration in deuteriated acetonitrile with added aliquots of metal thiocyanate (potassium or sodium) resulting in a distinctly different outcome for each metal ion. Typical sodium thiocyanate titrations are shown for compound **8** in Figs. 1 and 2. In Fig. 1 the aromatic carbons a–f are seen to change shift smoothly, ceasing at a ratio of 2 mol of sodium salt per ligand. The ether carbons (g–n in Fig. 2) likewise show clearly the formation of a 2:1 Na:L complex, with shifts between 1 and 2 ppm on complexation. The potassium thiocyanate titration of **8** in Fig. 3, shows the different behaviour towards potassium ions. A less smooth change of shift for the aromatic carbons a–f clearly indicates the formation of a 1:1 K:L complex, but the

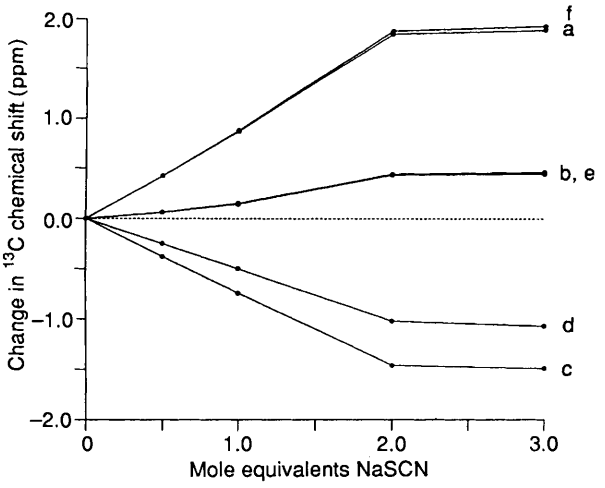


Fig. 1 Change in ^{13}C NMR shifts (aromatic section of compound **8**) upon addition of NaNCS

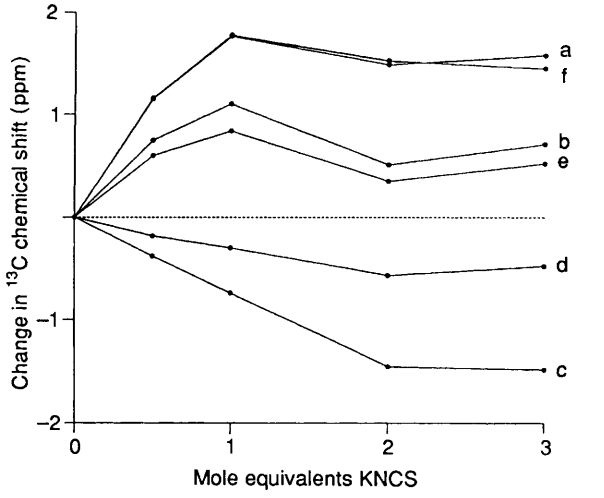


Fig. 3 Change in ^{13}C NMR shifts (aromatic section of compound **8**) upon addition of KNCS

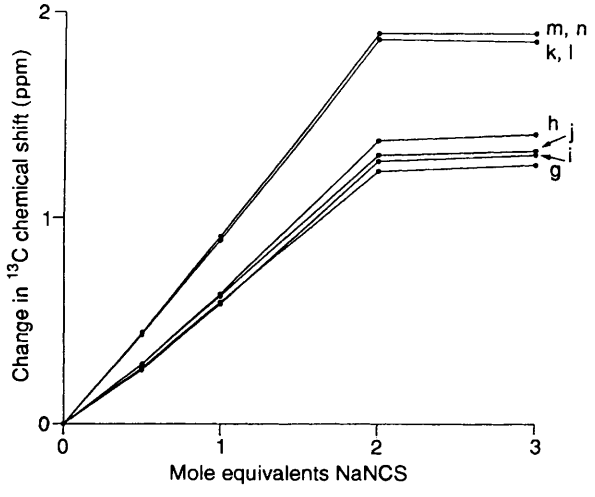


Fig. 2 Change in ^{13}C NMR shifts (ether section of compound **8**) upon addition of NaNCS

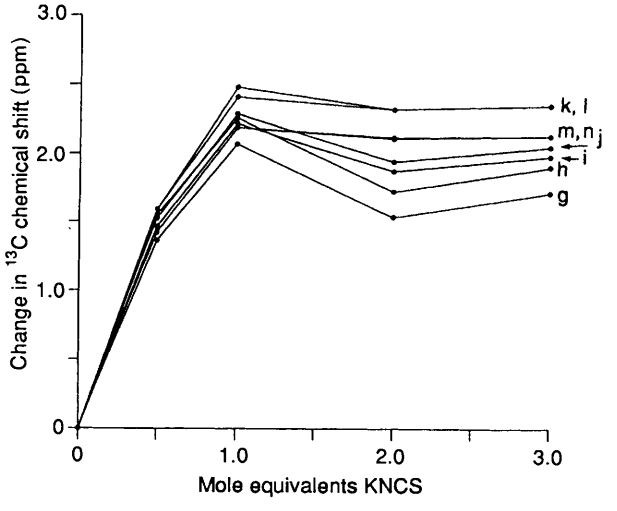


Fig. 4 Change in ^{13}C NMR shifts (ether section of compound **8**) upon addition of KNCS

further addition of potassium salt causes further changes suggesting the possibility of a 2:1 K:L complex at the appropriate composition of the solution. This is again shown in the plot for the shifts of the ether carbons g–n in Fig. 4. The formation of a 1:1 complex causes shifts of 2.0–2.5 ppm, but further addition of potassium ions causes the shifts to drift towards values suggestive of a 2:1 complex. The ability of bis(crown ethers) to sandwich potassium but not usually sodium ions in this way is well known [7] and its demonstration by NMR titration was established previously, although there is no agreement as to whether the sandwich is of the 1:1 or 2:2 form in any particular instance in solution.

Some features of the shift patterns found here are diagnostic for potassium or sodium complexation. The resonances of the aromatic carbons labelled b and e shift considerably in the presence of potassium, but not sodium, salts, while those of the c,d pair shift in the presence of sodium rather than potassium salts. In Fig. 3 it is evident that the shift increment for these carbons in the molecule **8** on complexation reverts close to the changes seen for a 2:1 sodium complex (as in Fig. 1) at the appropriate composition. Another feature which may prove diagnostic is the extent of shift change for the aliphatic carbons next to ether oxygens: the resonances of the k,l carbons shift proportionately more than those of the n,m pair for the potassium 1:1 complex, while for the sodium 2:1 complex the n,m carbon shift changes are proportionately more than those of the k,l ones. One can speculate that these diagnostics may reflect a conformational change of the molecule consequent on bending round to form the 1:1 type of complex for potassium salts. The trends are less clear for **5a** the most rigid compound. Further details of the results are evident in SUP 57040 and Figs. 1–4. However, the titration was carried beyond the 1:1 or 2:1 ratios just mentioned. Shift changes persisted beyond these points which could be attributed to the presence of complexes of different stoichiometry. This was particularly evident for crown **7** with sodium, where addition of an excess of sodium ions beyond the 2:1 Na:L ratio caused the resonances of the linker ether carbons to undergo shifts almost as great as that experienced by the crown ether carbons. This suggests further complexation of sodium by the bridge ether groups, and categorises them as less-effective donors than the crown ether oxygens. Potassium ions in excess had little effect on the signals of **7**. Note the variations in the shift increments/decrements observed for aromatic, the linker and the ether macrocycle carbons. These variations are rich in information related to conformational change but it has not proved possible to interpret the variations in more depth. A detailed attempt to interpret them in terms of ring currents and charge-related contributions failed to get a really satisfactory answer.[11] The present results do not actually distinguish between the 1:1 and 2:2 sandwich structures proposed in Scheme 1.

Conclusion

The bis(crown ether) polyamine multireceptors described had the capacity to complex anions, with a specific interaction with chloride ions. They also formed sandwich complexes with potassium ions, and complexes having two metal ions per ligand with sodium ions, and probably also with potassium ions at particular compositions.

Acknowledgements

We thank the SERC for financial support (to K. I. K. and D. P. M.) and for the provision of NMR and mass spectroscopic facilities, and the Libyan Government for support (to E. A.).

References

1 M. M. Georgiadis, H. Komiya, P. Chakrabarti, D. Woo, J. J. Kornuc and D. C. Rees, *Science*, 1992, **257**, 1653.
2 E. A. Arafa, K. I. Kinnear and J. C. Lockhart, *J. Chem. Soc., Chem. Commun.*, 1992, 61.
3 T. M. Handyside, J. C. Lockhart, M. B. McDonnell and P. V. S. Rao, *J. Chem. Soc., Dalton Trans*, 1982, 2331.
4 K. Toth, E. Lindner, M. Horváth, J. Jeney, I. Bitter, B. Agai, T. Meisel and L. Töke, *Anal. Lett.*, 1989, **22**, 1185.
5 S. Xiaoqiang, Wang Defen, W. Dengjin, H. Hongwen, Z. Zhongyuan and Y. Kaibei, *Wuji Huaxue Xuebao*, 1991, **7**, 58.
6 P. D. Beer, H. Sikanyika, A. M. Z. Slawin and D. J. Williams, *Polyhedron*, 1989, **8**, 879.
7 M. Bourgoin, K. H. Wong, J. Y. Hui and J. Smid, *J. Am. Chem. Soc.*, 1975, **97**, 3462.
8 L. Töke, I. Bitter, B. Agai, Z. Hell, E. Lindner, K. Toth, M. Horváth and E. Pungor, *Liebigs Ann. Chem.*, 1988, 549.
9 A. F. Abdel-Magid and C. A. Marynoff, *Synlett*, 1990, 537.
10 J. Suh and J. S. Heo, *J. Org. Chem.*, 1990, **55**, 5531 and refs. therein.
11 J. C. Lockhart, A. C. Robson, M. E. Thompson, P. D. Tyson and I. H. M. Wallace, *J. Chem. Soc., Dalton Trans.*, 1978, 611.
12 D. G. Parson, M. R. Truter and J. N. Wingfield, *Inorg. Chim. Acta*, 1980, **47**, 81.
13 J. C. Lockhart, D. P. Mousley, G. A. Forsyth, F. Teixidor, M. P. Almajano, L. Escriche, R. Sillanpää and R. Kivekäs, *J. Chem. Soc., Perkin Trans. 2*, 1994, 1309.

Received 27*th June* 1994; *Paper* 4/03860F