New Pocket Ionophores with Potential for Simultaneous Chelation of Anions and Cations. Synthesis and Scope of Chelating Properties

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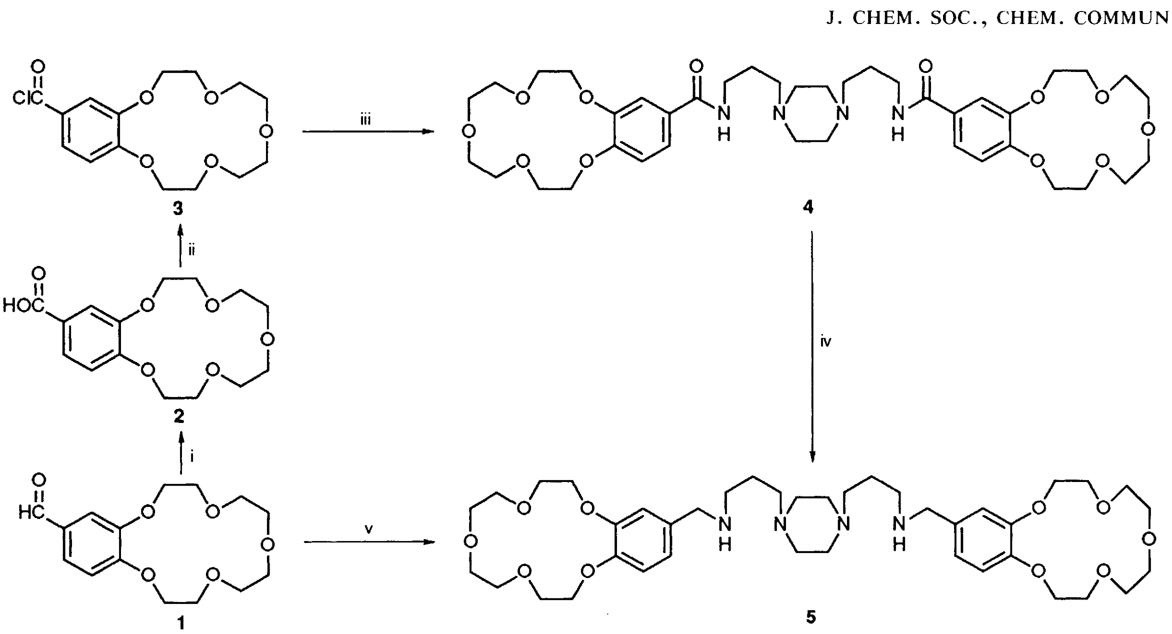
This paper reports the synthesis and characterisation of the first multi-receptors [bis(crowns) with polyamine linkers] to exhibit multiple binding to anions and their counterions simultaneously.

It has been known for some time that molecules containing two crown ether moieties, separated by a linking group, will sandwich potassium cations,[1] and it has been postulated that the linker between the two crown rings will form a pocket.[2] It occurred to us that if the linker were formed from a polyamino residue, then in hydroxylic solvents, even at neutral pH, where it would be partly protonated, such a molecule should be capable of complexing the counterion of its potassium 'filling'. This paper reports a synthetic route, and the separation and characterisation of the first such multi-recep-



Scheme 1 *Reagents*: i, $KMnO_4$, H_2O, acetone, 40 °C; ii, $SOCl_2$, toluene, reflux; iii, 1,4-bis(3-aminopropyl)piperazine, Et_3N, toluene, room temperature then reflux; iv, $LiAlH_4$, THF, reflux; v, 1,4-bis(3-aminopropyl)piperazine, $NaBH(OAc)_3$, AcOH, dichloroethane, room temperature

tors, which are then shown to be capable of multiple binding to anion and counterion at one and the same time.

Two routes to the synthesis[†] of the example **5** are shown in Scheme 1. We used reductive amination to prepare **5** in good yields in one step (step v, Scheme 1) in addition to the four-step route (steps i–iv). Other, less satisfactory, routes were also investigated.

The behaviour of the new multi-receptors towards alkali-metal cations, and towards anions was investigated chiefly by NMR spectroscopy. The quadrupolar nuclei ^{39}K and ^{35}Cl were used to demonstrate complexation *via* the characteristic line-broadening[‡] following the arguments of Shchori and coworkers (potassium),[4] and Kintzinger and coworkers (chloride).[5]

The complexation of chloride by protonated ligand **5** was demonstrated in the following series of experiments. Table 1 shows the shifts and linewidths of chloride signals in solutions of the tetrahydrochloride salt **6** of ligand **5** when titrated with sodium sulfate. Under the conditions used, the amine was expected to be fully protonated in solution. The tetrahydrochloride **6** in D_2O (observed pD 1.72) had a ^{35}Cl linewidth (119 ± 2.7 Hz) considerably wider than that of sodium chloride at the same pD (see Table 1). On titration with sodium sulfate (shown in Fig. 1) this linewidth progressively narrowed until sulfate equivalent to three-quarters of the amount of chloride present had been added, then remained at a value of *ca.* 70 Hz: however, this residual linewidth is still much wider than expected for free chloride. The corresponding chemical shift data, also shown in Table 1, changed with the composition in a parallel fashion, and the final shift was still 2 ppm different from that of the standard. This implies *two* possible complexed chloride environments, a unique one, in which one chloride associates with each tetraprotonated amine, and cannot apparently be displaced by sulfate, and a further environment in which additional chloride associates

Table 1 ^{35}Cl Chemical shifts (δ) and linewidths (*W*) for Cl^- in the presence of the tetrahydrochloride **6**

Nucleus	δ_{obs}[a]	W_{obs}/Hz[a]	Na_2SO_4/ mol dm^{-3}	pD[b]
$^{35}Cl^c$	4.2	119.2		1.7
$^{35}Cl^c$	2.6	92.6	0.050	
$^{35}Cl^c$	1.6	75.2	0.100	
$^{35}Cl^c$	1.2	67.9	0.150	2.7
$^{35}Cl^c$	0.9	61.2	0.300	3.05
$^{35}Cl^c$	1.0	59.1	0.400	3.15
$^{35}Cl^d$	4.2	119.2		1.7
$^{35}Cl^d$	1.1	75.0	0.150	1.7
$^{35}Cl^d$	0.9	67.7	0.300	1.7
$^{35}Cl^d$	1.1	70.3	0.400	1.7

[a] *W* ± 3 Hz, δ ± 0.11 ppm. [b] pD = pH* + 0.4,[11] where pH* is the pH meter reading in D_2O solution. [c] **6** (0.050 mol dm^{-3}) in D_2O with no pD control, reference NaCl (0.200 mol dm^{-3}) in D_2O, linewidth for reference ^{35}Cl signal is 8.2 Hz. [d] **6** (0.050 mol dm^{-3}) in D_2O pD controlled at 1.7, reference NaCl (0.200 mol dm^{-3}) in D_2O, linewidth for reference ^{35}Cl signal is 8.2 Hz.

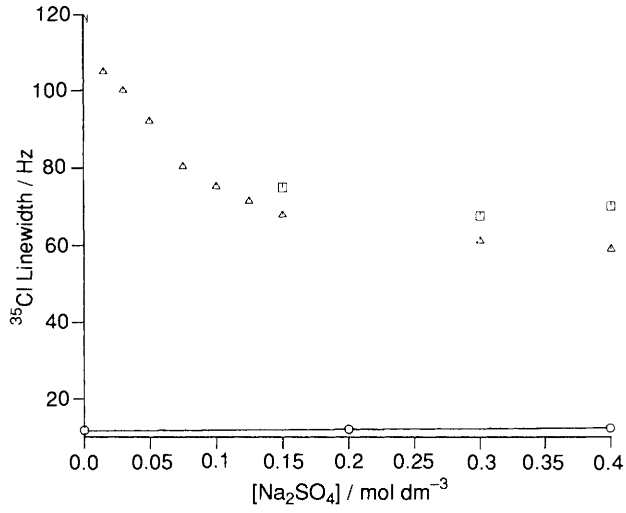


Fig. 1 A plot of the change in linewidth of the ^{35}Cl signal upon addition of Na_2SO_4 (*a*) to a solution of **6** (0.05 mol dm^{-3} in D_2O) with pD controlled at 1.7 (□): (*b*) as (*a*), starting at pD 1.7, with no pD adjustment (△): and (*c*) to a solution of NaCl (0.2 mol dm^{-3}), with no pD adjustment (○)

[†] Satisfactory analyses, NMR and MS data were obtained for compounds **1**, **2**, **4**, **5** and **6**. The acid chloride **3** was used without isolation.

[‡] In conditions of fast exchange, quadrupolar nuclei of spin 3/2 usually exhibit one broad signal, the weighted time-average of that of the narrow line for the solvated, usually symmetrical, environment of the free ion, and the wider line for the complexed, usually asymmetrical environment(s) of the complexed ion.

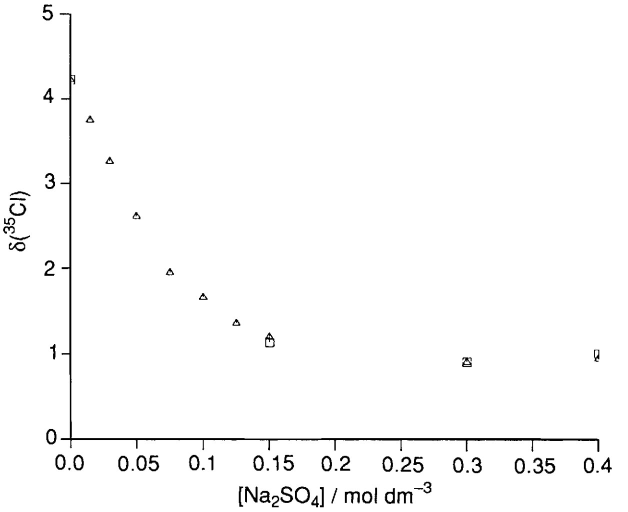


Fig. 2 A plot of the change in ^{35}Cl chemical shift upon addition of Na_2SO_4 (*a*) to a solution of **6** (0.05 mol dm^{-3} in D_2O) with pD controlled at 1.7 (□): (*b*) as (*a*), starting at pD 1.7, with no pD adjustment (△)

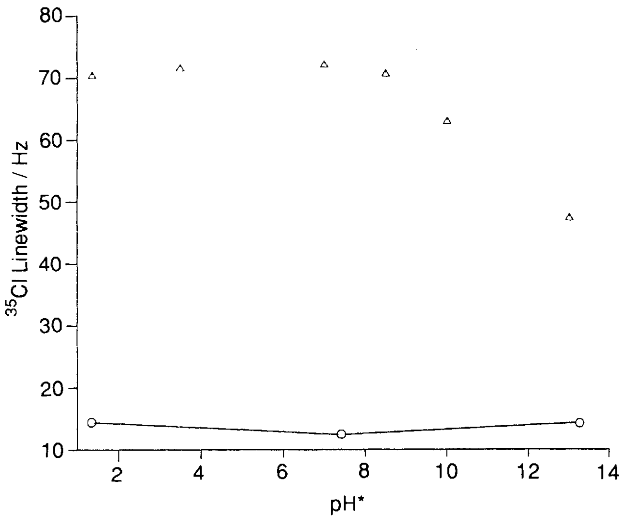


Fig. 3 A plot of the change in linewidth of the ^{35}Cl signal as pH* is varied (*a*) in a solution 0.2 mol dm^{-3} in NaCl, 0.4 mol dm^{-3} in Na_2SO_4 (○): (*b*) in a solution 0.05 mol dm^{-3} in **6**, and 0.4 mol dm^{-3} in Na_2SO_4 (△)

with the protonated amine, but from which it can be displaced by sulfate. The titration was performed firstly by adding successive quantities of sodium sulfate to a solution of amine hydrochloride **6**, when the pD of the final solution shown in Table 1 was found to be raised to 3.15. Following a referee's suggestion, the titration was performed again with pD fixed at 1.7. These results, also in Table 1 (and Figs. 1 and 2) offer the same conclusion. For comparison, the change in the chloride linewidth with pD was also measured for chloride in a D_2O solution, 0.2 mol dm^{-3} in NaCl, and 0.4 mol dm^{-3} in Na_2SO_4, and for complexed chloride (final solution from the titration with sodium sulfate) as pD was raised from 1.7 to 8.4 (Fig. 3). The signal of the free chloride was invariant while that of bound chloride remained at *ca.* 70 Hz until pD *ca.* 8.4, when its linewidth rapidly decreased. Since a stronger coulombic interaction is expected for the doubly charged sulfate ion, relative to the singly charged chloride, it may be surmised that the first, more strongly bound, chloride environment provided by deuteriated forms of **5** must occupy a space which is too small for sulfate, while the second is less specific. The chloride NMR technique was used previously by Hosseini and coworkers to demonstrate chloride binding.[6] Log *K* for the binding of chloride to various comparable[7] fully-protonated polyammonium linear and macrocyclic systems is of the order of 2 to 3.

Table 2 ^{35}Cl Chemical shifts (δ) and linewidths (*W*) for Cl^- in NaCl (0.100 mol dm^{-3}) in D_2O, in the presence of the tetratosylate **7**[a]

[**7**]/mol dm^{-3}	δ_{obs}	W_{obs}/Hz
0.000	−1.71	12.8
0.025	−0.79	28.7
0.050	−0.39	39.6
0.175	0.24	54.5
0.100	0.47	69.5
0.130	1.57	97.0

[a] Shifts in this table differ from those of the previous spectra as the deuterium lock used to set the relative chemical shifts was in a different field at the start of the experiment. No pD control was attempted: pD at the end of the experiment was 0.52.

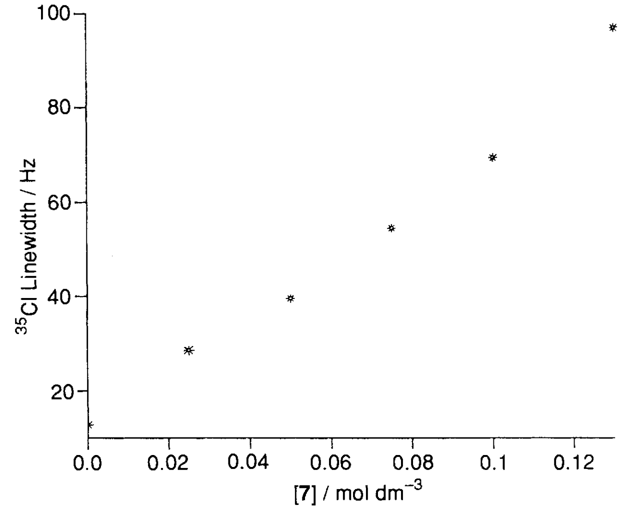


Fig. 4 A plot of the change in linewidth of the ^{35}Cl signal upon addition of **7** to a solution in D_2O of NaCl (0.1 mol dm^{-3}), with no pH adjustment

Table 3 ^{35}Cl and ^{39}K chemical shifts δ and linewidths (*W*) for Cl^- and K^+ in the presence of compounds **5** and **6**

Nucleus	Ligand	δ_{obs}	W_{obs}/Hz
$^{35}Cl^a$	5	−31.7	124.7
$^{35}Cl^b$	5,6	−23.0	546.7
$^{39}K^a$	5	0.1	90.0
$^{39}K^b$	5,6	−9.25	303.0
$^{39}K^c$	5	2.1	175.0

[a] **5** (0.0079 mol dm^{-3}) + KCl (0.032 mol dm^{-3}) in CD_3OD, reference KCl (0.032 mol dm^{-3}) in CD_3OD, linewidths for reference ^{39}K and ^{35}Cl signals are 14.6 and 97.3 Hz, respectively. [b] **5** (0.012 mol dm^{-3}) + **6** (0.004 mol dm^{-3}) + KCl (0.032 mol dm^{-3}) in CD_3OD, reference KCl (0.032 mol dm^{-3}) in CD_3OD, linewidths for reference ^{39}K and ^{35}Cl signals are 14.6 and 97.3 Hz, respectively. [c] **5** (0.040 mol dm^{-3}) + KSCN (0.100 mol dm^{-3}) in CD_3OD, reference KSCN (0.040 mol dm^{-3}) in CD_3OD, linewidth for reference ^{39}K signal is 19.2 Hz.

A solution of sodium chloride was titrated with the amine **5** as its tetratosylate **7** (see Table 2 and Fig. 4) the ^{35}Cl linewidth increased smoothly to 70 Hz, at a ratio of one tetraprotonated amine to one chloride: subsequent additions of **7** progressively increased the chloride linewidth, suggesting the incursion of a second chloride environment. The solubilities of the relevant salts prevented further examination of this system. The conclusion is that chloride is bound, probably in two ways, in this system in D_2O.

The complexation of potassium counterions by the ligand **5** was investigated in [$^2H_4$]methanol (see Table 3). Although it was anticipated that the amine would be partially N-deuteriated in solution in [$^2H_4$]methanol, the experiment was also conducted using a mixture of **5** and **6** in the ratio of 3 : 1, to ensure at least one deuteriated nitrogen per molecule of **5**. An evaluation of the ^1H NMR spectra suggested that the potassium was bound to the crown in a sandwich fashion.[2,3] The ^{39}K NMR linewidth, which is the weighted average of free and bound ^{39}K linewidths, increased (either in KNCS or KCl solutions) relative to that of free potassium ions under comparable conditions (Table 3). ^{35}Cl NMR of the same system also showed considerably broadened lines for the chloride present. The clear indication is that both potassium and chloride are coordinated to the same ligand at the same time.

While variable-temperature potassium NMR showed (from the familiar *Z*-curve) that potassium exchange was becoming slow on the NMR time-scale at *ca.* 260 K, in no instance was a *Z*-curve obtained in the chloride spectra. It seems probable that the potassium dissociates more slowly from the ligand than does the chloride. This differential will be important in providing selective materials for applications such as three-phase transport and ion-selective electrodes, in which the complexation at the interface of two or more phases is important to the selectivity.[8] Clearly, the sandwiching cation requires to be more firmly attached, since it is intended to provide the stable 'pocket' environment into which the chloride (or other anions) is to enter. Two recent papers employ a similar principle, with a copper–amine interaction providing the closure for a water-soluble metalloreceptor which can incorporate lipophilic substrates in a pocket.[9,10]

The design is capable of considerable extension, of both sandwich and linker, to allow complexation of more complicated anions. Further evaluation of its modified potential for recognition and binding of anionic substrates in the presence of potassium and other ions is proceeding.

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