Synthesis of Bridged Macrocyclic Polyethers of High Complexing Ability with Group 1a Salts

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Two members of a new type of bridged macrocyclic polyether having carbon bridgeheads have been synthesised by bridging the hydroxy groups of cis-dihydroxydibenzo-14-crown-4 (3a) with 3,6-dioxaoctane-1,8-diyl and 3,6,9-trioxaundecane-1,11-diyl links. These ligands show high complexing ability in water with sodium, potassium, and rubidium salts.

THE cryptands described by Lehn [1] show particularly high stability constants for their complexes with the Group 1a and 2a metal salts; these values are considerably higher than those obtained for complexes formed by the monocyclic polyethers [2] having the same number of oxygen atoms, with corresponding salts.[3] Replacing oxygen atoms of the monocyclic crown compounds by nitrogen atoms causes a fall in the stability constant [3] of complexes with the Group 1a metals, so it seemed reasonable to assume that the stability of the cryptates was due largely to the oxygen atoms, and that the nitrogen atoms played only a minor role in the binding; the main consideration was that the ligand should be relatively rigid and that the cavity should be the correct size to fit the cation. Recently Stoddart [4] has described a bridged macrocyclic polyether, but this has proved to have an unexpectedly low complexing ability for the Group 1a metals; this is believed to be due to the cavity being ellipsoidal,[5] resulting in the nine oxygen atoms of the ligand being unable simultaneously to co-ordinate the cation—a requisite for strong binding.

We have now synthesised two bridged macrocyclic polyethers having bridgehead carbon atoms, with the aim of producing rigid ligands of suitable cavity sizes capable of strongly binding Group 1a metal cations.

EXPERIMENTAL

1,2-Bis-(o-hydroxyphenoxy)propan-2-ol (2).—A mixture of o-benzyloxyphenol (160 g) and 1,3-dichloropropan-2-ol (52 g) was warmed to 90 °C and treated with sodium hydroxide pellets (35 g) in portions during 40 min with stirring. The temperature was then allowed to rise to 126 °C in 1 h as the epichlorohydrin produced was consumed. The product was poured while still mobile into water (1 000 ml), and ether (200 ml) was added to assist crystallisation. The buff-coloured product was collected, washed with water, and recrystallised (charcoal) from propan-2-ol (1 200 ml) giving colourless needles of the dibenzyl compound (1) (146 g), m.p. 65°. Crystallisation from wet cyclohexane gave a *hydrate* (Found: C, 74.8; H, 6.2. $C_{29}H_{28}O_5, \frac{1}{2}H_2O$ requires C, 74.8; H, 6.3%). This material in ethanol (600 ml) containing 10% palladium–charcoal (500 mg) was subjected to hydrogenolysis at 60—70 °C and atmospheric pressure. Hydrogen absorption was complete after 2 h. The solution

[1] B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Tetrahedron Letters*, 1969, 2885, 2889; B. Dietrich, J. M. Lehn, J. P. Sauvage, and J. Blanzat, *Tetrahedron*, 1973, **29**, 1629; J. M. Lehn, *Structure and Bonding*, 1973, **16**, 1.

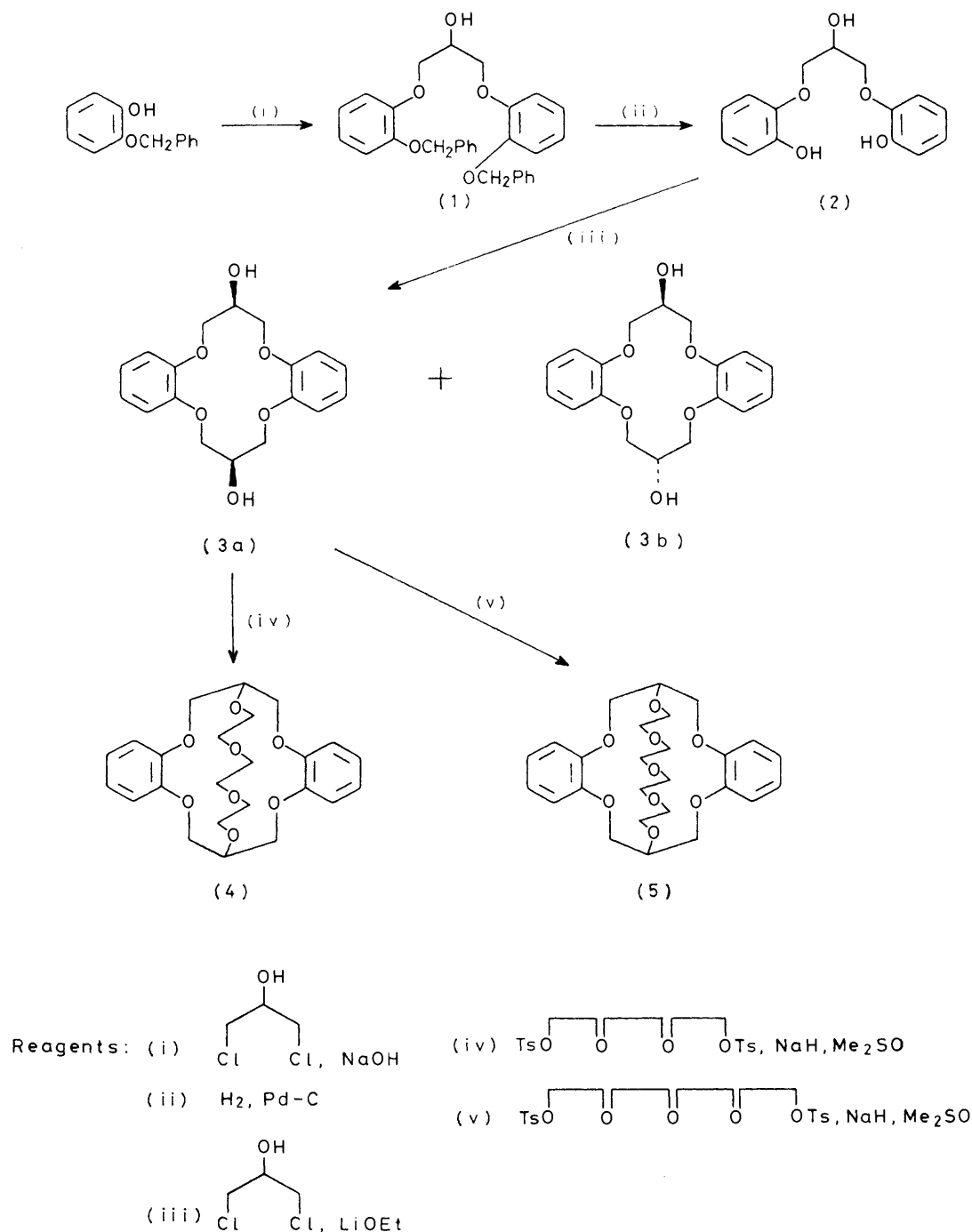[2] C. J. Pedersen, *J. Amer. Chem. Soc.*, 1967, **89**, 7017.

[3] H. K. Frensdorff, *J. Amer. Chem. Soc.*, 1971, **93**, 600.

[4] A. C. Coxon and J. F. Stoddart, *J.C.S. Chem. Comm.*, 1974, 537.

[5] A. C. Coxon and J. F. Stoddart, *J.C.S. Perkin I*, 1977, 767.

was filtered and concentrated to 250 ml, affording the *triol* (2) (83.1 g), m.p. 172—173° [further concentration yielded another 5.8 g, m.p. 169—173° (79.9% overall)] (Found: C, 65.1; H, 5.8. $C_{15}H_{16}O_5$ requires C, 65.2; H, 5.8%).

of the triol separated; 1,3-dichloropropan-2-ol (11 g) was then added to the stirred mixture heated under reflux. After 1½ h when much of the lithium salt had dissolved, a second addition of the lithium ethoxide solution (60 ml) was

Reagents: (i)
 Cl   Cl, NaOH

(ii)   H₂, Pd–C

(iii)
 Cl   Cl, LiOEt

(iv) TsO   O   O   OTs, NaH, Me₂SO

(v) TsO   O   O   O   OTs, NaH, Me₂SO

cis- (3a) *and* trans- (3b) 7,8,16,17-*Tetrahydro*-6H,15H-*dibenzo*[b,i][1,4,8,11]*tetraoxacyclotetradecin*-7,16-*diol*.— The triol (2) (82 g) in hot propan-1-ol (800 ml) was treated with lithium ethoxide solution (60 ml) [from lithium (4.2 g) in ethanol (240 ml)]. A thick suspension of the lithium salt

made, followed by another 11 g of the dichloro-compound. A pale yellow clear solution was obtained after 16 h heating. At this stage excess of lithium ethoxide solution was added (60 ml) followed gradually by more dichloro-compound (11 g). T.l.c. showed that all the triol had reacted after

a total of 26 h. The product was concentrated, poured into water, and strongly acidified (2N-HCl), and the amorphous precipitate was collected. This was extracted with boiling ethyl acetate, chromatographed through calcined alumina, further purified by treatment of a methanolic solution with charcoal. Evaporation gave a mixture of mainly *cis*- and *trans*-diols (42 g).

Separation of cis- *and* trans-*diols*. A mixture of the isomers (12 g) in methanol (150 ml) was subjected to column chromatography on Florisil (250 g; 5 × 40 cm; 100—200 U.S. mesh) and eluted with methanol. The trans-*isomer* (3b) (3.9 g) was eluted in 400 ml of solvent before the *cis*-isomer was detected, and crystallised from wet toluene as a hydrate, m.p. 164° (loss of water *ca.* 100°; sublimes above 140°) (Found: C, 64.85; H, 6.1. $C_{18}H_{20}O_6$ requires C, 65.0; H, 6.1%). Further elution gave a mixture of the *cis*- and *trans*-isomers, but since the rate of elution of the *cis*-isomer remained low, only a small amount had been eluted before all the *trans*-isomer had been removed (another 2.9 g of mainly *trans*-isomer was collected in another 350 ml of methanol). The column was then eluted with 70% v/v methanol–water containing 1% of lithium perchlorate and the remaining cis-*isomer* was obtained from aqueous methanol as a hydrate, m.p. 133° (with loss of water and resolidification); anhydrous material, m.p. 160° (Found: C, 64.5; H, 6.4%). In another preparation of the cyclic diol with propan-2-ol as solvent, part of the *cis*-diol crystallised from the reaction mixture as its lithium chloride complex, from which the *cis*-diol was easily obtained pure; however, an attempt to separate the mixture of *cis*- and *trans*-diols by selective complexation with lithium chloride or perchlorate was not successful, a mixture of both complexes being obtained.

7,8,16,17-*Tetrahydro*-6H,15H-5,9,14,18,19,22,25,28-*octaoxa*-7,16-*decanodibenzo*[a,h]*cyclotetradecene* (4).—The *cis*-diol (3a) (4.5 g) in dimethyl sulphoxide (50 ml) was treated with sodium hydride (50% in oil; 0.9 g). After the initial reaction had subsided, triethylene glycol ditosylate (9.2 g) was added and the mixture warmed to 50 °C and stirred for 1 h; a second addition of sodium hydride (50%; 0.9 g) was made and the mixture again stirred for 1 h at 50 °C. After cooling overnight, the solution was poured into water (150 ml) and extracted with chloroform (5 × 50 ml) (removing the product as a sodium tosylate complex); the extract was washed once with water and concentrated to yield an oil. This in methanol was subjected to column chromatography on alumina (neutral; 20 × 2 cm) eluted with methanol. After concentration, the product in methanol (50 ml) was treated with potassium thiocyanate (4.0 g). An immediate precipitate of the potassium complex was obtained which was collected and washed with methanol (yield 4.3 g; concentration gave another 0.3 g). The i.r. spectrum of this material showed it to be a mixture of the potassium thiocyanate and potassium tosylate complexes. This mixture suspended in 50% aqueous methanol (100 ml) was eluted through Amberlite IRA 400 (F⁻) resin (35 × 2 cm). In contact with the ion-exchange resin the complex dissolved; it was washed through the column with 50% aqueous methanol (1.5 l). The potassium fluoride complex was collected after concentration, and dried by azeotropic distillation of ethanol and toluene. The residue was suspended in toluene and heated under reflux for 30 min. After filtering off the potassium fluoride, evaporation yielded the bridged compound as a crystalline mass (3.1 g, 36%); crystallisation from methanol gave *needles* (2.3 g),

m.p. 154°. A second crop (0.3 g) was obtained on concentration (Found: C, 64.3; H, 6.8. $C_{24}H_{30}O_8$ requires C, 64.55; H, 6.8%).

7,8,16,17-*Tetrahydro*-6H,15H-5,9,14,18,19,22,25,28,31-*nonaoxa*-7,16-*tridecanodibenzo*[a,h]*cyclotetradecene* (5).—The diol (3a) (6.6 g) in dimethyl sulphoxide (60 ml) was treated with sodium hydride (50% in oil; 1.0 g) and then with tetraethylene glycol ditosylate (12 g) for 30 min at 50 °C; a second addition of sodium hydride (50%; 1.0 g) was then made. After stirring for 3 h at 50 °C the product was poured into water (250 ml) and the aqueous solution containing the ligand complexed with sodium tosylate was decanted. Extraction with chloroform (4 × 100 ml) yielded an oil (5.5 g), which was chromatographed through alumina in ethyl acetate. The recovered oil dissolved in aqueous methanol (60 ml) was eluted through Amberlite IRA 400 (F⁻) resin and the crude sodium fluoride complex was collected after concentration and drying. The complex was dissociated in boiling toluene; the sodium fluoride was filtered off and the product recovered from the toluene, recrystallisation from cyclohexane yielding the ether (5) as *needles* (0.97 g), m.p. 117° (Found: C, 63.5; H, 7.0. $C_{26}H_{34}O_9$ requires C, 63.7; H, 7.0%). In another preparation the ether was isolated from the crude oil by extraction into hot aqueous caesium chloride; the *complex*, m.p. 212°, crystallised on cooling (Found: C, 45.1; H, 5.4; Cl, 5.3. $C_{26}H_{34}O_9,CsCl,2H_2O$ requires C, 44.9; H, 5.5; Cl, 5.1%).

Attempted Oxidation of a Mixture of cis- *and* trans-*Diols*.—A mixture of the diols (3a and b) (2.0 g) in dimethyl sulphoxide (10 ml) was treated with acetic anhydride (8.0 ml) and stirred vigorously at 30 °C for 18 h. The product was poured into water and the colourless gum which separated washed first with warm water then with dilute ammonia. The resulting semi-solid in ethyl acetate was subjected to column chromatography on alumina; the eluate (ethyl acetate) (250 ml) was concentrated, and a solution in methanol (20 ml) was cooled to 3 °C. Needles of the *trans*-diacetate (550 mg), m.p. 134°, were obtained; the *cis*-diacetate (350 mg), m.p. 129°, then crystallised. The diacetates were identified by comparison of their i.r. and n.m.r. spectra with samples obtained by acetylation of the pure *cis*- and *trans*-diols.

Acetylation of a Mixture of Diols.—A mixture of the diols (3a and b) was purified by conversion into the calcium thiocyanate complex, and isolated after boiling in water and extraction of the diols into chloroform. The dried diols (10 g) in acetic acid (40 ml) containing sulphuric acid (0.2 g) were treated dropwise with acetic anhydride (20 ml) and warmed at 80 °C for 1 h. The product was stirred into water, and the oil extracted with ethyl acetate (150 ml). The extract was washed with sodium hydrogen carbonate solution and concentrated to yield a pale yellow oil (12.9 g). This oil in methanol (60 ml) was seeded with the *trans*-isomer. The product which separated (6.3 g), m.p. 115—130°, was shown by t.l.c. to be a mixture of the *cis*- and *trans*-isomers in roughly equal proportions. Recrystallisation twice from methanol failed to affect materially the ratio of isomers present.

Stability Constants.—Free cation concentration was measured using cation-sensitive electrodes in combination with a reference silver/silver chloride electrode in saturated sodium chloride in methanol, electrical contact with the solution under test being made through a ceramic plug.[6]

[6] E. J. Harris, B. Zaba, M. R. Truter, D. G. Parsons, and J. N. Wingfield, *Arch. Biochem. Biophys.*, 1977, **182**, 311.

From these values the stability constants K_e were calculated according to equation (1) using concentrations and not activities of the species present where C is the ligand and M^+

$$K_e = [M^+C]/[M^+][C] \text{ l mol}^{-1} \qquad \text{(i)}$$

the cation. The e.m.f. measurements obtained in methanol for sodium and potassium chloride with (4) showed that if the ligand to metal ratio was low ($<0.6:1$) the free cation concentration present was less than the theoretical value for apparent 1 : 1 complexation; this suggested that either some ligand molecules were associated with two metal ions, or that released anion was bonded in the form $X^-(M-X)$ as a

Stability constants [log $(K_e/\text{l mol}^{-1})$] of chlorides in water

	(4)	(5)	Dibenzo-18-crown-6 [*]	18-Crown-6 [*]	Diazabicyclo[2.2.2]-cryptand [†]
Na+	5.4 [a]	3.5	1.1	<0.3	3.9
	5.7 [b]				
	5.3 [c]				
K+	5.7 [a]	4.3	1.6	2.06	5.4
	5.8 [b]				
	5.7 [c]				
Rb+	3.8 [a]	4.4	1.1		4.35
	3.7 [b]				
	3.7 [c]				

[a] 20mM; [b] 10mM; [c] 2mM.

[*] Ref. 6. [†] J. M. Lehn and J. P. Sauvage, *Chem. Comm.*, 1971, 440.

complex anion; as the ligand to metal ratio approached unity, a typical 1 : 1 titration curve was obtained. The apparent presence of more than one form of complexed cation has made estimation of stability constants in methanol difficult, but for ligand (4) with sodium and potassium chloride, the value of log K_e is >7. Two different techniques were used for the determination of the stability constants of (4) and (5) in water. The low solubility of (4) in water (0.26×10^{-3} M) caused difficulty; since the ligand dissolved only slowly in the salt solution, several hours were required to reach equilibrium; during this period drift in electrode response could cause error. A technique similar to that of Jagur-Grodzinski [7] was tried. Excess of (4) over a 1 : 1 ratio of the salt present in solution was added, together with a few drops of methylene chloride, in order rapidly to reach equilibrium. After stirring for 1 h and after the methylene chloride had evaporated off the change in e.m.f. was recorded. The solution at this stage was assumed to be saturated with the ligand, and therefore the stability constant could be calculated. This method assumes the solubility of the ligand to be the same in the presence of the aqueous complex as in water; the results obtained therefore are doubtful. We found, however, that stability constants obtained in salt concentrations of 2, 10, and 20mM were in reasonable agreement. The results obtained for (4) in aqueous solution gave high values for sodium and potassium chlorides, falling off rapidly with rubidium chloride. Ligand (5), being more water soluble than (4), reached equilibrium more rapidly and the usual portionwise method of addition of ligand was used.[3] The stability constant increases along the series from sodium to rubidium.

The stability constants we have obtained must be regarded as only approximate; however, they serve to show

that the values are considerably higher than those of the macromonocyclic ethers and that (4) complexes best with sodium and potassium salts whereas the larger cavity of (5) is better for rubidium salts.

DISCUSSION

The use of space-filling molecular models in the design of the cryptands showed that a molecule based on the fairly rigid symmetrical dibenzo-14-crown-4 ring and bridged with a ten-membered chain containing four oxygen atoms would provide a cavity of diameter about 2.4 Å and therefore be suitable for the complexation of ions of the size of sodium or potassium, while a thirteen-membered bridge containing five oxygen atoms would provide a cavity about 3.2 Å in diameter. In the uncomplexed state it would be expected that the oxygen atoms of the bridge would assume a staggered conformation; however, a small change of the torsion angles between the bridge atoms would be sufficient to change the conformation of the molecule so that the oxygen atoms could be directed inwards and be positioned approximately equidistant from a central point in the cavity. Thus, the incorporation of a cation into the cavity would require only a small conformational change in order that bonding between all the oxygen atoms and the cation could occur. Once the cation had been encapsulated, displacement of the ligand by solvent molecules would be difficult, thus giving rise to complexes of high stability.

In the synthetic approach to the bicyclic compounds it was important to isolate the pure *cis*-diol (3a) in reasonably large amounts; after a number of attempted separations of the *cis*- and *trans*-isomers, a chromatographic separation on magnesium silicate was found to be the most effective. An unusual method was required for the isolation of (4) and (5) owing to the high stability of their complexes. Use was made of the high lattice energies of sodium and potassium fluorides, together with the low solubilities of these salts in toluene, enabling an irreversible dissociation of the anhydrous complex to be achieved.

Reaction of the sodium salt of benzyloxyphenol with 1,3-dichloropropanol to give the intermediate (1) was best carried out without solvent. Dibenzylation of (1) gave the triol (2) which, after conversion into its lithium salt, reacted with a second molecule of 1,3-dichloropropanol affording a mixture of the *cis*- and *trans*-diols (3a and b). Direct reaction of catechol with 1,3-dichloropropanol yielded only the seven-membered ring, none of the diol being isolated. Attempted separation by fractional crystallisation resulted in only a partial enrichment of the isomers; fractional crystallisation of the complex with lithium chloride or lithium thiocyanate was also not successful, and no suitably crystalline products could be obtained with sodium,

[7] E. Shchori, N. Nae, and J. Jagur-Grodzinski, *J.C.S. Dalton*, 1975, 2381.

potassium, calcium, or magnesium salts. The isomers were well resolved by t.l.c. on silica gel, but separation was best achieved on a Florisil (magnesium silicate) column. One isomer was rapidly eluted with methanol, but the second was retained much more strongly, being eluted by methanol at a low but constant rate. The second isomer was rapidly eluted from the Florisil on adding lithium perchlorate (1%) to aqueous methanol. This suggested that the second isomer was bonding more strongly to the magnesium ions, and addition of the lithium salt resulted in a transfer of bonding from the magnesium to the lithium. The stronger bonding of the second isomer suggested that it might be the *cis*, and this proved to be correct, since it was this isomer which gave the bicyclic compounds (4) and (5) on reaction with triethylene and tetraethylene glycol ditosylate, respectively.

In the hope that it might be possible to convert the *trans*- into the *cis*-diol, an attempt was made to oxidise a mixture of the *trans*- and the *cis*-diol to a common cyclic ketone. On treatment with the acetic anhydride–dimethyl sulphoxide reagent, no ketone was produced, but a mixture of the diacetates was obtained; fortuitously the *cis*- and *trans*-diacetates crystallised separately and were obtained in their pure states. Unfortunately, when a mixture of the diols was acetylated with acetic anhydride and a trace of acid, the *cis*- and *trans*-diacetates co-crystallised and no separation was achieved. The lack of oxidation of the secondary diols was attributed to steric constraint within the fourteen-membered ring; we have had no difficulty in oxidising the similar hydroxydibenzo-19-crown-6 and hydroxydibenzo-16-crown-5 systems under identical conditions.[8] Attempted separation of a mixture of the *cis*- and *trans*-ditosylates by fractional crystallisation was also unsuccessful.

The *cis*-diol (3a) in dimethyl sulphoxide was treated

with triethylene and tetraethylene glycol ditosylates in the presence of sodium ions to give the bridged compounds (4) and (5), respectively. The high stability of (4) and (5) with sodium and potassium salts caused some difficulty in isolating the pure ligand; the bicyclic compounds have a low solubility in water, but readily dissolve in aqueous salt solution due to the formation of hydrated complexes. Thus (4) dissolves in aqueous sodium chloride at 1 : 1 molar ratios, but addition of an excess of sodium chloride or hydrochloric acid caused a salting out of the sodium chloride complex. An attempt to remove potassium thiocyanate from its complex with (4) by elution of the complex in 70% methanol through a mixed-bed ion-exchange resin resulted in absorption of most of the ligand on to the resin bound to potassium ions. The ligand was released from the column by washing with hydrochloric acid and collecting the potassium chloride complex. The successful procedure for (4) was to purify the reaction products on an alumina column, and to precipitate the bridged compound as a mixture of its potassium thiocyanate and tosylate complexes from methanol. The thiocyanate and tosylate ions were exchanged for fluoride on an ion-exchange resin, from which the anhydrous potassium fluoride complex was isolated. This, on boiling in toluene, gradually dissociated, enabling the potassium fluoride to be filtered off, leaving the bridged crown compound in solution. The bridged crown (5) could be isolated from the crude product by extraction with hot aqueous cesium chloride, the hydrated complex crystallising on cooling. Hydrated complexes of (4) and (5) are not inconsistent with structures in which the cation is centrally placed within the cryptand; the cation is not entirely surrounded by the ligand and areas of the cation large enough for hydration to occur are still exposed.

[8] D. G. Parsons, unpublished work.