1,6,13,18,25,30-Hexaoxa[6.6.6](1,3,5)cyclophane. Attempted Synthesis of a [4]Cryptand

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The hexaoxa[5.5.5](1,3,5)cyclophane (12) has been synthesised from phloroglucinol and 1,4-dibromobutane by using a stepwise approach. All attempts to effect catalytic hydrogenation of both aromatic rings in the hexaoxa-[6.6.6](1,3,5)cyclophane (12) to give the desired [4]cryptand (14) have proved unsuccessful.

In the preceding paper [1] we described the synthesis of the [2]cryptands (1)—(5) with bridgehead carbon atoms (Scheme) from diethylene glycol ditosylate (6) and either pentaerythritol (7) or 1,1,1-tris(hydroxymethyl)ethane (8). A ligand with topological properties (see Scheme) very similar to those of the [2]cryptands (1)—(5) is the [4]cryptand (10). Although this ligand can be derived formally from diethylene glycol ditosylate (6) and all-*cis*-cyclohexane-1,3,5-triol (9),[2] it was anticipated that it might be more easily approached by catalytic hydrogenation of the aromatic rings of 1,4,7,14,17,20,-27,30,33-nonaoxa[7.7.7](1,3,5)cyclophane (11).† In order to ascertain if cyclophanes of this type are obtainable from phloroglucinol, it was decided initially to employ 1,4-dibromobutane in base-promoted condensations with an appropriately substituted phloroglucinol derivative. In this paper, we describe (i) the synthesis of the hexaoxa[6.6.6](1,3,5)cyclophane (12), (ii) the evidence for catalytic hydrogenation of one of the two aromatic rings of (12) to give the hexahydrohexaoxa-[6.6.6](1,3,5)cyclophane (13), and (iii) our unsuccessful attempts to hydrogenate catalytically both aromatic rings of (12) to give the [4]cryptand (14).

† In this cyclophane all the phenolic oxygen atoms are necessarily oriented such that their lone pairs are directed away from the central cavity of the ligand. If it were to occur, catalytic hydrogenation would have to involve stereospecific addition of hydrogen to the *outer* faces of the aromatic rings in the cyclophane (11). This would lead to the generation of all-*cis*-1,3,5-oxygen atoms, which would be expected to assume *syn*-axial orientations on the cyclohexyl rings of the newly formed [4]cryptand (10). The oxygen atoms which were previously phenolic would then be able to orient themselves such that the lone pairs would be directed towards the middle of the cavity in the [4]cryptand (10).

EXPERIMENTAL

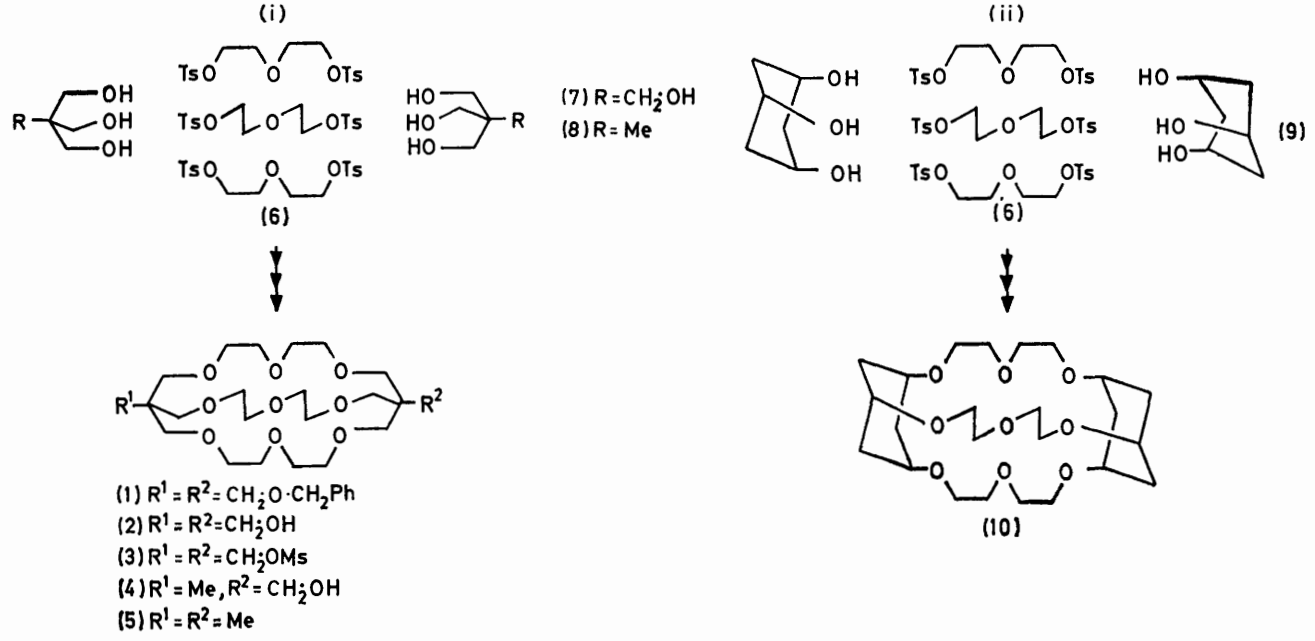
The general methods have been discussed elsewhere.[1,3]

1,3,5-*Trisbenzyloxybenzene* (15).—A solution of benzyl bromide (143 g) in *NN*-dimethylformamide (150 ml) containing potassium carbonate (90 g) was stirred under nitrogen. A solution of phloroglucinol dihydrate (45 g)

[1] A. C. Coxon and J. F. Stoddart, preceding paper.
[2] H. Stetter and K. H. Steinacker, *Chem. Ber.*, 1952, **85**, 451.
[3] I. J. Burden, A. C. Coxon, J. F. Stoddart, and C. M. Wheatley, *J.C.S. Perkin I*, 1977, 220.

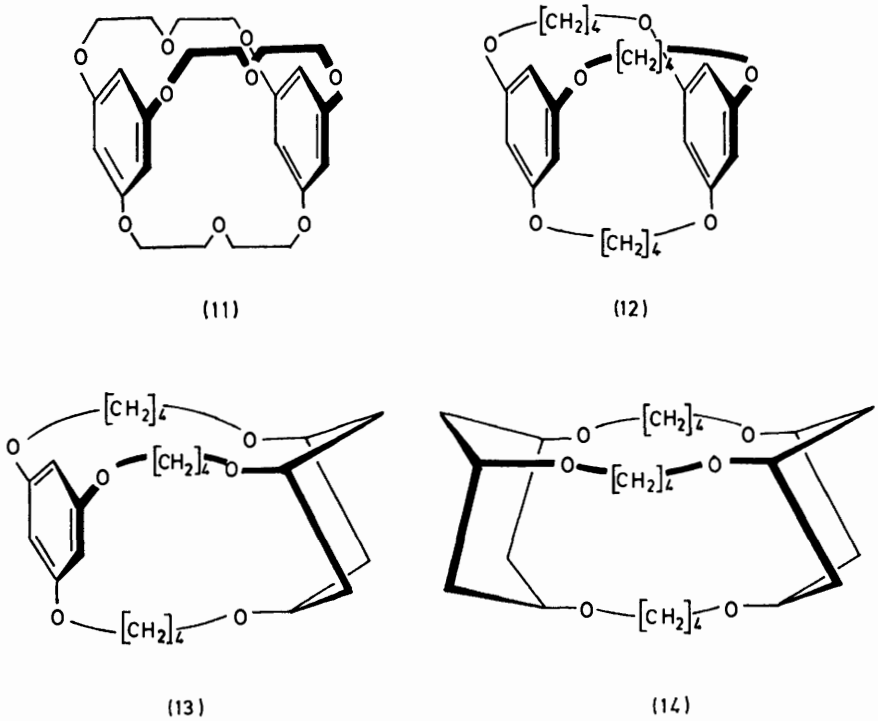
in *NN*-dimethylformamide (150 ml) was added during 3 h and the mixture was stirred for 16 h, filtered, and concentrated. The residue was partitioned between toluene and water; the organic layer was extracted with 6N-sodium hydroxide, then washed with water, dried ($MgSO_4$), and filtered. Concentration afforded a red oil which crystallised. The crude product was washed and then recrystallised from ethanol to afford the *tribenzyl ether* (15) (23 g, 21%), m.p. 92—94° [Found: C, 81.7; H, 6.35%; *M* (mass spec.), 396. $C_{27}H_{24}O_3$ requires C, 81.8; H, 6.1%; *M*, 396], τ ($CDCl_3$) 2.54—2.86 (15 H, m, 3 × $C_6H_5{\cdot}CH_2$), 3.77 (3 H, s, H-2, -4, and -6), and 5.06 (6 H, s, 3 × $C_6H_5{\cdot}CH_2$).

3,5-Bisbenzyloxyphenol (16).—(*a*) The tribenzyl ether (15) (5 g) was added with stirring to a mixture of methanol (400 ml) and dioxan (100 ml). When it had almost completely dissolved, sodium methoxide (0.98 g) and 10%



SCHEME

Schematic representations of the formation of (i) the [2]cryptands (1)—(5) from diethylene glycol ditosylate (6) and pentaerythritol (7) or 1,1,1-tris(hydroxymethyl)ethane, and (ii) the [4]cryptand (10) from diethylene glycol ditosylate (6) and all-*cis*-cyclohexanetriol (9)



palladium–charcoal (0.3 g) were added. The mixture was subjected to hydrogenolysis until 1.0 mol. equiv. of hydrogen had been consumed, and was then filtered, acidified with 2N-hydrochloric acid, and concentrated to a crystalline residue. Recrystallisation from toluene afforded the *dibenzyl ether* (16) (3.5 g, 93%), m.p. 92—94° [Found: C, 78.1; H, 6.2%; *M* (mass spec.), 306. $C_{20}H_{18}O_3$ requires C, 78.4; H, 5.9%; *M*, 306], τ ($CDCl_3$) 2.62—2.92 (10 H, m, 2 × C_6H_5·CH_2), 3.84 (1 H, t, *J* 2.3 Hz, H-4), 4.01 (2 H, d, *J* 2.3 Hz, H-2 and -6), 5.00br (1 H, s, OH), and 5.13 (4 H, s, 2 × C_6H_5·CH_2).

(*b*) The tribenzyl ether (15) (8.0 g) was dissolved in diethyl ether (500 ml) and 10% palladium–charcoal (1.25 g) was added. The mixture was subjected to hydrogenolysis until 1.0 mol. equiv. of hydrogen had been consumed. The catalyst was filtered off and the filtrate was concentrated. Column chromatography of the residue on silica gel [ethyl acetate–light petroleum (b.p. 60—80°) (1 : 4) as eluant] gave three fractions. Fraction 1 was unchanged tribenzyl ether (15) (4.54 g, 57%), fraction 2 the dibenzyl ether (16) (1.18 g, 19%), and fraction 3 the monobenzyl ether (17) (0.40 g, 9%), an oil which crystallised at 0 °C; *M* (mass spec.) 216.

(*c*) A solution of phloroglucinol (15.4 g) in *NN*-dimethylformamide (200 ml) was stirred under nitrogen, and potassium carbonate (40 g) was added. A solution of benzyl bromide (21.6 ml) in *NN*-dimethylformamide (70 ml) was added dropwise during 15 min and the mixture was stirred for 16 h. Filtration followed by concentration of the filtrate afforded a residue which was subjected to column chromatography on silica gel. Elution with ethyl acetate–light petroleum (b.p. 60—80°) (1 : 9) gave the tribenzyl ether (15) (1.0 g, 3%) and the dibenzyl ether (16) (1.37 g, 5%) amongst other products. Elution with ethanol–light petroleum (b.p. 60—80°) (1 : 9) gave the monobenzyl ether (17) (1.5 g, 7%).

1,3,5-*Tris*-(4-*bromobutoxy*)*benzene* (18).—A suspension of potassium carbonate (40 g) in 1,4-dibromobutane (100 ml) and *NN*-dimethylformamide (80 ml) was stirred under nitrogen. A solution of phloroglucinol (15 g) in *NN*-dimethylformamide (60 ml) was added during 2 h. The mixture was stirred for 16 h, filtered, and concentrated, and the residue was subjected to column chromatography on alumina (300 g) [Laporte type H, deactivated with water (15 ml)]. Elution with toluene–light petroleum (b.p. 60—80°) (1 : 3) gave a crude crystalline product which was recrystallised from dichloromethane–ethanol to afford the pure *tribomide* (18) (31.8 g, 65%), m.p. 43—44° [Found: C, 40.5; H, 5.2; Br, 45.3%; *M* (mass spec.), 528/530/532/534. $C_{18}H_{27}Br_3O_3$ requires C, 40.7; H, 5.1; Br, 45.1%; *M*, 528/530/532/534], τ ($CDCl_3$) 3.97 (3 H, s, C_6H_3), 6.06 (6 H, t, *J* 6.0 Hz, 3 × $OCH_2[CH_2]_3Br$), 6.54 (6 H, t, *J* 6.0 Hz, 3 × O·$[CH_2]_3$·CH_2Br), and 7.77—8.25 (12 H, m, 3 × O·CH_2·CH_2·CH_2·CH_2Br).

1-[3,5-*Bis*-(4-*bromobutoxy*)*phenoxy*]-4-(3,5-*bisbenzyloxyphenoxy*)*butane* (19).—A solution of the tribromide (18) (25 g) in *NN*-dimethylformamide (50 ml) containing suspended potassium carbonate (5 g) was stirred under nitrogen. The dibenzyl ether (16) (1.9 g) in *NN*-dimethylformamide (10 ml) was added during 1 h. The mixture was stirred for 16 h, filtered, and concentrated, and the residue was partitioned between dichloromethane and water. The organic layer was washed, dried ($MgSO_4$), filtered, and adsorbed on alumina (20 g) [Laporte type H (100 g), deactivated with 10% acetic acid (5 ml)], which was then added to the top of a column of deactivated alumina (80 g). Elution with toluene–light petroleum (b.p. 60—80°) (7 : 3) afforded some unchanged tribromide (18). Elution with toluene–light petroleum (b.p. 60—80°) (3 : 2) gave the crude product (5.5 g). Further column chromatography on alumina followed by recrystallisation from toluene–ethanol gave the pure *polyether* (19) (3.8 g, 82%), m.p. 59—61° [Found: C, 60.6; H, 6.05; Br, 21.1%; *M* (mass spec.), 754/756/758. $C_{38}H_{44}Br_2O_6$ requires C, 60.3; H, 5.85; Br, 21.1%; *M*, 754/756/758], τ ($CDCl_3$) 2.52—2.82 (10 H, m, 2 × C_6H_5·CH_2), 3.73—4.06 (6 H, m, 2 × C_6H_3), 5.03 (4 H, s, 2 × C_6H_5·CH_2), 6.09br (8 H, t, *J* 6.0 Hz, 2 × O·CH_2·$[CH_2]_3Br$ and O·CH_2·$[CH_2]_2$·CH_2·O), 6.57 (4 H, t, *J* 6.0 Hz, 2 × O·$[CH_2]_3CH_2Br$), and 7.84—8.28 (12 H, m, 2 × O·CH_2·CH_2·CH_2·CH_2Br and O·CH_2·CH_2·CH_2·CH_2·O).

1-[3,5-*Bis*-(4-*bromobutoxy*)*phenoxy*]-4-(3,5-*bishydroxyphenoxy*)*butane* (20).—(*a*) The coupled product (19) (1.0 g) was dissolved in ethyl acetate (100 ml) and ethanol (200 ml) was added. A slurry of 10% palladium–charcoal (150 mg) in water was added and the mixture was subjected to hydrogenolysis until 2.0 mol. equiv. of hydrogen had been absorbed. The mixture was filtered and the filtrate was concentrated to afford the *diphenol* (20) (0.72 g, 95%) as an oil, *M* (mass spec.) 574/576/578, τ ($CDCl_3$) 3.82—4.16 (6 H, m, 2 × C_6H_3), 6.11br (8 H, t, *J* 6.0 Hz, 2 × O·CH_2·$(CH_2)_3Br$ and O·CH_2·$[CH_2]_2$·CH_2·O), 6.59 (4 H, t, *J* 6.0 Hz, 2 × O·$[CH_2]_3$·CH_2Br), and 7.82—8.40 (12 H, m, 2 × O·CH_2·CH_2·CH_2·CH_2Br and O·CH_2·CH_2·CH_2·CH_2·O).

(*b*) The coupled product (19) (3.84 g) was dissolved in toluene (8 ml) and diethyl ether (20 ml). The solution was stirred as 45% hydrogen bromide in acetic acid (8 ml) was added. The mixture was left for 16 h then diluted with diethyl ether and washed with water. The ether layer was dried ($MgSO_4$), filtered, and concentrated. The oily residue (3.4 g) was subjected to column chromatography on Woelm acidic alumina [100 g, deactivated with water (50 ml)]. Elution with dichloromethane gave the diphenol (20) (1.7 g, 58%) as an oil.

1,6,13,18,25,30-*Hexaoxa*[6.6.6](1,3,5)*cyclophane* (12).—(*a*) The diphenol (20) (535 mg) was stirred under nitrogen in *NN*-dimethylformamide (350 ml), and potassium carbonate (4.0 g) and Amberlite IR-4B (CO_3^{2-} form) resin (6.0 g) were added. The mixture was stirred for 36 h, filtered, and concentrated to give the crude product, which was subjected to column chromatography on silica gel (25 g). Elution with dichloromethane gave the *hexaoxa*[6.6.6](1,3,5)*cyclophane* (12) (255 mg, 56%), m.p. 218—221° [Found: C, 69.9; H, 7.7%; *M* (mass spec.), 414. $C_{24}H_{30}O_6$ requires C, 69.5; H, 7.3%; *M*, 414], τ ($CDCl_3$) 4.25 (6 H, s, 2 × C_6H_3), 5.87br (12 H, t, *J* 5.0 Hz, 3 × O·CH_2·$[CH_2]_2$·CH_2·O), and 7.92—8.26 (12 H, m, 3 × O·CH_2·CH_2·CH_2·CH_2·O), δ_C ($CDCl_3$) 158.7 (6 quarternary aromatic carbons), 94.7 (6 tertiary aromatic carbons), 66.7 (3 × O·CH_2·CH_2·CH_2·CH_2·O), and 23.5 (3 × O·CH_2·CH_2·CH_2·CH_2·O).

(*b*) A solution of the diphenol (20) (0.72 g) in *NN*-dimethylformamide (200 ml) was stirred with potassium carbonate (4.0 g) for 16 h. The mixture was then filtered and concentrated, and the residue was dissolved in dichloromethane. The dichloromethane solution was washed with water, dried ($MgSO_4$), filtered, and concentrated, and the crude product was shown by mass spectrometry and t.l.c. to comprise mainly phloroglucinol and 1,3,5-tris-(4-bromobutoxy)benzene (18). When this crude product was subjected to preparative t.l.c. on silica gel (dichloromethane as eluant) in a double development procedure, the

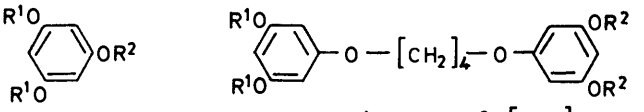
hexaoxa[6.6.6](1,3,5)cyclophane (12) (32 mg, 6%) was obtained in low yield.

Attempted Catalytic Hydrogenations of 1,6,13,18,25,30-*Hexaoxa*[6.6.6](1,3,5)*cyclophane* (12).—Ruthenium (5%) on alumina (100 mg) was stirred under hydrogen (500 lb in^{-2}) for 1 h at 100 °C in dry dioxan (60 ml). This mixture was allowed to cool for 30 min and then a solution of the hexaoxa[6.6.6](1,3,5)cyclophane (12) (50 mg) in dry dioxan (15 ml) was added. The temperature was raised to 100 °C and the hydrogen pressure was increased to 1 600 lb in^{-2}. The mixture was stirred for 16 h, allowed to cool, and filtered, and the filtrate was concentrated. The residue was subjected to chromatography on alumina (Laporte type H). Elution with light petroleum (b.p. 60—80°)–chloroform (1 : 4) gave three fractions. Fraction 1 was unchanged hexaoxa[6.6.6](1,3,5)cyclophane (12) (t.l.c. and mass spectrometry). Fraction 2, *m/e* 420 ($C_{24}H_{36}O_6$) was tentatively identified as the hexahydrohexaoxa[6.6.6](1,3,5)-cyclophane (13). Fraction 3, *m/e* 422 ($C_{24}H_{38}O_6$), could arise from hydrogenolysis of one carbon–oxygen bond in the hexahydrohexaoxa[6.6.6](1,3,5)cyclophane (13). No product of higher molecular weight was isolated.

Other conditions were investigated for ruthenium (5%) on alumina as catalyst in the hydrogenation of (12). They included (*a*) ethanol as solvent at 80 °C and 100 atm of hydrogen for 30 h, (*b*) butan-1-ol as solvent at 100 °C and 10 atm of hydrogen for 30 h, and (*c*) dioxan as solvent at 75 °C and 100 atm of hydrogen for 16 h. None of these led to either hydrogenation or hydrogenolysis. Raney nickel was also ineffective as a catalyst in high temperature–high pressure attempted hydrogenations of (12) in ethanol–chloroform.

RESULTS AND DISCUSSION

At the outset it was decided that the preparation of the [4]cryptand (14) could best be carried out by a route which involved catalytic hydrogenation of the hexaoxa-[6.6.6](1,3,5)cyclophane precursor (12) as the final step. Since preliminary attempts to condense phloroglucinol with 1,4-dibromobutane in the presence of base led to polymeric products, a stepwise route was devised in which two of the three phenolic hydroxy-groups of phloroglucinol were protected initially. This was achieved by (i) partial hydrogenolysis (1.0 mol. equiv. of hydrogen) of the tribenzyl ether (15), which was obtained on benzylation of phloroglucinol, to give the dibenzyl ether (16) in two steps, and (ii) partial benzylation of phloroglucinol with 1.9 mol. equiv. of benzyl bromide to afford the dibenzyl ether (16) directly, albeit in admixture with the tribenzyl (15) and monobenzyl (17) ethers. In fact, the two-step procedure, involving a highly selective (93%) partial hydrogenolysis of the tribenzyl ether (15) in dioxan in the presence of sodium methoxide,[4] proved the more convenient method for obtaining the dibenzyl ether (16). Condensation of phloroglucinol with a gross excess of 1,4-dibromobutane in *NN*-dimethylformamide, with potassium carbonate as base, gave the tribromide (18) in good yield. Coupling between this tribromide (18) and the dibenzyl ether (16) proceeded efficiently with the same solvent and base system. Removal of the benzyl ether groups in the coupled product (19) to give the diphenol (20) was achieved by (i) catalytic hydrogenolysis and (ii) acid catalysed de-*O*-benzylation with hydrogen bromide in acetic acid. The double intramolecular condensation of the diphenol (20) in *NN*-dimethylformamide with potassium carbonate as base gave the hexaoxa[6.6.6]-(1,3,5)cyclophane (12) in low yield. Since the major products of this reaction were phloroglucinol and the tribromide (18), it was suspected that the bromide ions produced during the reaction were acting as nucleophiles towards the unchanged diphenol (20), the intermediate condensation products, and the hexaoxa[6.6.6](1,3,5)-cyclophane (12) itself. Addition of an anion exchange resin to the mixture with the objective of complexing the bromide ions and thus reducing their concentration in solution resulted in a dramatically increased (6 ⟶ 56%) yield of the hexaoxa[6.6.6](1,3,5)cyclophane (12) in the base-promoted condensation of the diphenol (20).



(15) $R^1 = R^2 = CH_2Ph$
(16) $R^1 = CH_2Ph$; $R^2 = H$
(17) $R^1 = H$, $R^2 = CH_2Ph$
(18) $R^1 = [CH_2]_4Br$

(19) $R^1 = CH_2Ph$, $R^2 = [CH_2]_4Br$
(20) $R^1 = H$, $R^2 = [CH_2]_4Br$

All attempts to hydrogenate catalytically both aromatic rings of the hexaoxa[6.6.6](1,3,5)cyclophane (12) were unsuccessful. The best that could be achieved with 5% ruthenium–alumina, which was successfully employed [5] in the catalytic hydrogenation of dibenzo-18-crown-6 to yield a mixture of the *cis,syn,cis*- and *cis,-anti,cis*-isomers of dicyclohexyl-18-crown-6, was mass spectral evidence that one aromatic ring of (12) could be reduced to give the hexahydrohexaoxa[6.6.6](1,3,5)-cyclophane (13). Subsequently, mass spectral evidence indicated that hydrogenolysis of a carbon–oxygen bond proceeded faster than hydrogenation of the second aromatic ring of (13). Thus, the desired [4]cryptand (14) was not obtained by this approach. Other possible lines of attack for preparing the [4]cryptand (14), and ultimately (10), have not been pursued because of the relative weakness of the complexes formed between the topologically related [2]cryptands (1), (2), and (5) and the alkali metal chlorides in methanolic solution.[1]

We thank R. M. King for technical assistance. An S.R.C.-CASE Studentship (to W. D. C.) is acknowledged.

[6/1303 *Received*, 5*th July*, 1976]

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