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Preliminary communication

Synthesis of a [2]-cryptand with carbon bridgeheads

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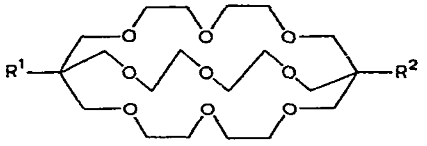
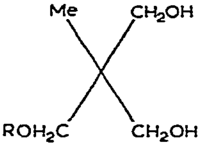
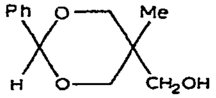
Recently, we described[1] the synthesis of the macrobicyclic polyethers **1**, **2**, and **3** from pentaerythritol. Attempts to effect hydrogenolysis of the dimethanesulphonate **3** with lithium aluminium hydride gave the diol **2**, together with small proportions of the alcohol **4**. Since none of the dimethyl [2]-cryptand **5*** was obtained from this reaction, we have devised independent routes to compound **5** which we now report.



1 $R^1 = R^2 = CH_2OCH_2Ph$
2 $R^1 = R^2 = CH_2OH$
3 $R^1 = R^2 = CH_2OMs$
4 $R^1 = Me; R^2 = CH_2OH$
5 $R^1 = R^2 = Me$



6 $R = H$
8 $R = PhCH_2$



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1,1,1-Tris(hydroxymethyl)ethane (**6**) can be converted[3] into its *O*-benzylidene derivative (**7**)** which, on treatment with lithium aluminium hydride–boron trifluoride[4] in ether, gave the monobenzyl ether **8**, m.p. 48–49°, in good yield. Treatment of diol **8** with sodium hydride and diethyleneglycol ditoluene-*p*-sulphonate[5] in methyl sulphoxide afforded products with constitutions **9** and **10**. Hydrogenolysis of this mixture of products over a palladium catalyst yielded the alcohol **11** as a colourless oil, and a crystalline mixture

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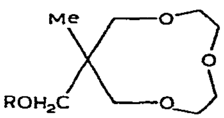
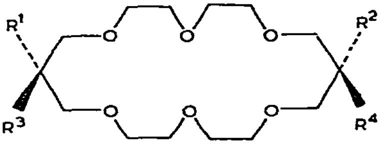
*Professor J.-M. Lehn has suggested the use of the term cryptand to us to describe all types of cavity-containing ligands. See also Ref. 2.

**The product is a mixture of diastereoisomers which can be separated chromatographically. For the present purpose, we have used the mixture.

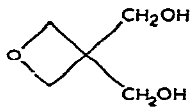
(m.p. 51–53°) of the diastereomeric diols **12a** and **12b*****, after chromatography (ether–methanol) on silica gel. Since all attempts, including high-pressure liquid chromatography, to separate **12a** and **12b** have so far been unsuccessful, the mixture of diols (**12**) was reacted with sodium hydride and diethyleneglycol ditoluene-*p*-sulphonate[5] in dimethoxyethane to give the dimethyl [2]-cryptand **5** [m.p. 59–60°; ^{1}H-n.m.r. data ($CDCl_3$): δ 3.62 (s, 24H, $-OCH_2CH_2O$-protons), 3.46 (s, 12H, other CH_2 protons), and 0.91 (s, 6H, 2 x Me)] in 7% yield after chromatography.



9 R = CH_2Ph
11 R = H



10a $R^1 = R^2 = Me; R^3 = R^4 = CH_2OCH_2Ph$
10b $R^1 = R^4 = Me; R^2 = R^3 = CH_2OCH_2Ph$
12a $R^1 = R^2 = Me; R^3 = R^4 = CH_2OH$
12b $R^1 = R^4 = Me; R^2 = R^3 = CH_2OH$



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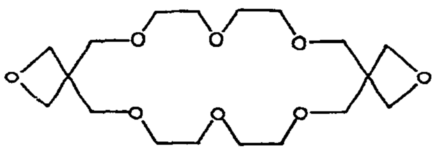

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The dimethyl [2]-cryptand **5** can also be obtained in a five-step synthesis from pentaerythritol. 3,3-Bis(hydroxymethyl)oxetane (**13**) is readily obtainable[6] from monobromopentaerythritol[7]. Treatment of diol **13** with sodium hydride and diethyleneglycol ditoluene-*p*-sulphonate[5] in methyl sulphoxide afforded the dispiro-compound **14**[8], m.p. 85–86°. Reductive ring-opening of the oxetane rings in **14** with lithium aluminium hydride in ether yielded the diastereomeric diols **12a** and **12b*****, from which the dimethyl [2]-cryptand **5** was obtained in 17% yield as previously described.

Inspection of Corey–Pauling–Koltun space-filling models indicates that **5** has a cavity size compatible with a sphere whose radius is between the ionic radii[9] of potassium (1.33 Å) and rubidium (1.49 Å) ions.

Although the dimethyl [2]-cryptand **5** will dissolve salts of alkali metals in organic solvents (*e.g.*, benzene or chloroform), stability constants defined by the equilibrium constants (K in $l. mol^{-1}$) for complex formation according to equation (*1*), and measured[10] potentiometrically with an ion-selective electrode, were found to be surprisingly low

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***The noise-decoupled ^{13}C-n.m.r. spectrum in $CDCl_3$ exhibits *seven* signals, indicating that both diastereoisomers are present. The spectrum of the pure *cis*-diol (**12a**), which has been obtained in low yield by a stereospecific synthesis, exhibits *six* signals.

[K^+($\log K = 2.2$), Rb^+($\log K = 1.9$), and Cs^+($\log K = 1.6$)] in methanol solution. The corresponding values [K^+($\log K = 1.8$), Rb^+($\log K = 1.4$), and Cs^+($\log K = 0.8$)] obtained for the dispiro-compound **14** indicate that the strength of the complexes increases only marginally in methanol on going from [1]-cryptand **14** to the [2]-cryptand **5**.

$$[2]\text{-C} + M^+, n \text{ solvent} \underset{k_b}{\overset{k_f}{\rightleftharpoons}} [2]\text{-CM}^+ + n \text{ solvent} \qquad (1)$$

However, ^{1}H-n.m.r. spectroscopy indicates that **5** and potassium thiocyanate form a strong complex in solution in $CDCl_3$–CS_2 (2:1). At room temperature, a sharp singlet was observed at δ 0.88 for the methyl protons. On addition of an equimolar amount of potassium thiocyanate, a new, well-resolved singlet was observed at δ 0.76 for the methyl protons. When ~ 0.5 molar equivalent of potassium thiocyanate was added, the methyl protons resonated as a well-resolved singlet at δ 0.80. Decreasing the temperature of the solution resulted in broadening of the signal and eventually the appearance (Fig. 1) of two singlets (δ 0.76 and 0.90) at −60°. This temperature-dependent behaviour can be associated with

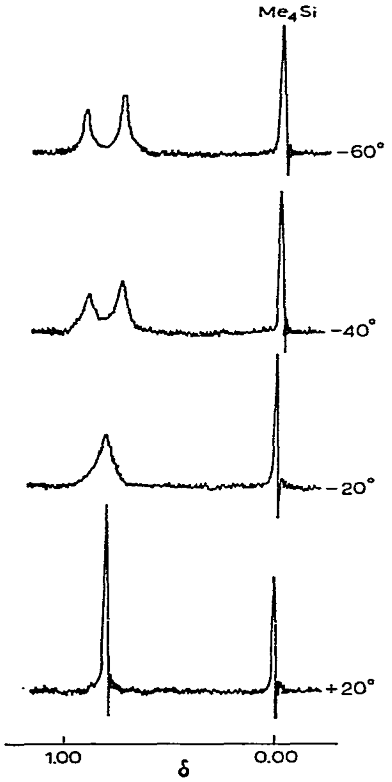

Fig. 1. The temperature dependence of the partial ^{1}H-n.m.r. spectrum (100 MHz) of a $CDCl_3$–CS_2 (~2:1) solution containing approximately equimolar amounts of the dimethyl [2]-cryptand **5** and the corresponding potassium ion complex.

exchange of potassium ions between the complex and the cryptand, where the rate-limiting step is the dissociation of the complex, *i.e.*, $k_b < k_f$. Rate constants (k_b) were obtained at several different temperatures between −16 and −51° by carrying out line-shape analyses with a computer program suitable for simulating n.m.r. line-shapes resulting from exchange of nuclei between two sites with no mutual coupling. The corresponding free energies of activation, obtained from the Eyring equation in the usual manner, gave a value for $\Delta G_b^{\ddagger}$ of 12.3 ±0.3 kcal. mol^{-1}. Thus, it would appear that the dimethyl [2]-cryptand 5 forms strong complexes with potassium ions in $CDCl_3$—CS_2 solution. Whether or not complexation is associated with cryptate[9] formation (*i.e.*, encapsulation of the potassium ion by the [2]-cryptand) must await the result of an X-ray crystal structure analysis.

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