The Synthesis of Phenolic Cryptands—Efficient Acid Catalysis in a Molecular Cavity

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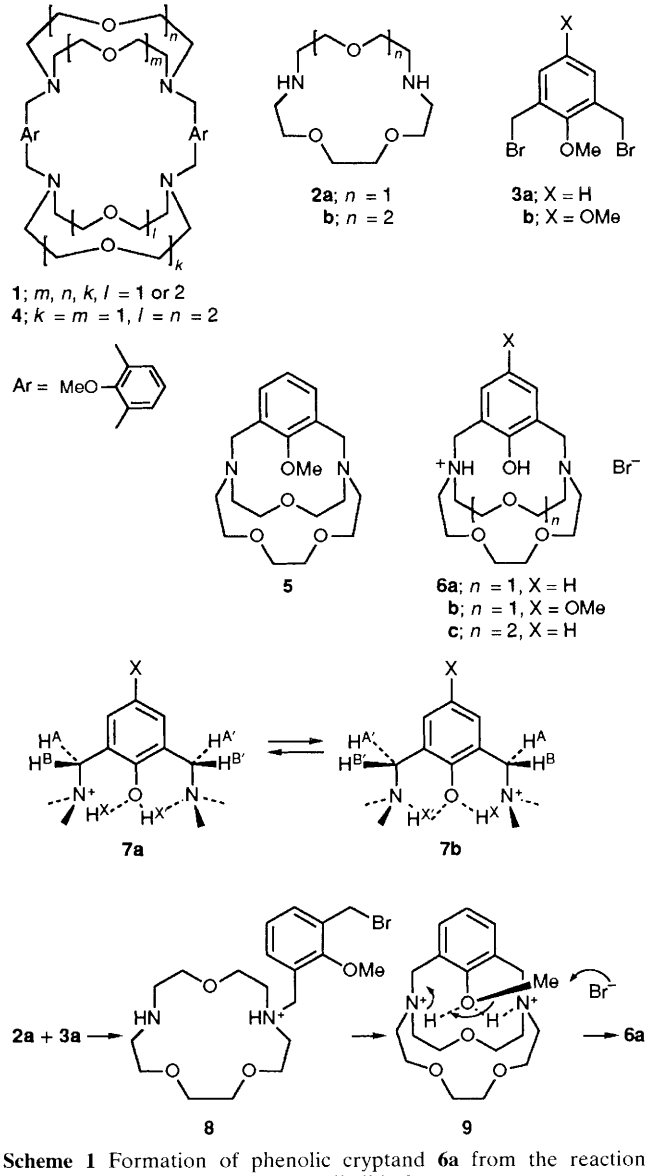
The reaction of 1,3-bisbromomethyl-2-methoxy benzene with diaza-15-crown-5 or diaza-18-crown-6 in acetonitrile gives the phenolic cryptands **6a** and **6c**; it is shown that the formation of **6a** involves the methoxy cryptand salt **9** which undergoes efficient demethylation by bromide anion as a result of acid catalysis within the cavity of the cryptand system.

Cryptand[1] synthesis has been carried out by direct alkylation of bis-primary amines with dihalides[2] and by alkylation of diaza-crown ethers with dihalides,[3] for example for the synthesis of the face-to-face crown ethers **1**. Usually these reactions have been carried out in the presence of base and sometimes a metal cation has been used[2] as a template. Accordingly, the reaction of the diaza-15-crown-5 (1,4,10-trioxa-7,13-diazacyclopentadecane) **2a** with the dihalide **3a** was used as an approach to the methoxy cryptand **4**. In the presence of an excess of potassium or caesium carbonate in acetonitrile at 80 °C a complex mixture of products was obtained which included small amounts of the required cryptand **4** and the bicyclic cryptand **5**, but in the absence of base the major reaction product was the phenolic cryptand **6a** (86% yield based upon diaza crown **2a**).



Scheme 1 Formation of phenolic cryptand **6a** from the reaction between diaza-15-crown-5 **2a** and dihalide **3a**

The structure of the product **6a** follows from mass spectrometry [FAB MS *m/z* 337 (M^+)], ^1H and ^{13}C NMR spectra, and elemental analysis for the dihydrobromide salt **6a**·HBr. In particular the fluxional hydrogen bonded system **7a** ⇋ **7b** (X = H) gives an ABX system ($\delta_X/\delta_{X'}$ 10.51, averaged coupling constants $J_{AB}/J_{A'B'}$ 13.0 Hz, $J_{AX}/J_{A'X'}$ 4.5 Hz, $J_{BX}/J_{B'X'}$ not detectable), this analysis is confirmed by the COSY spectrum which also provides evidence for 2ABCD systems associated with the NCH_2CH_2O units. The protons H^X and $H^{X'}$ exchange slowly with deuterium when a $CDCl_3$ solution of **6a** is shaken with D_2O, and the spectrum of the intermediate monodeuterio derivative shows a signal for the fluxional N^+–D···O–H···N ⇋ N···D–O···H–N^+ system which is shifted

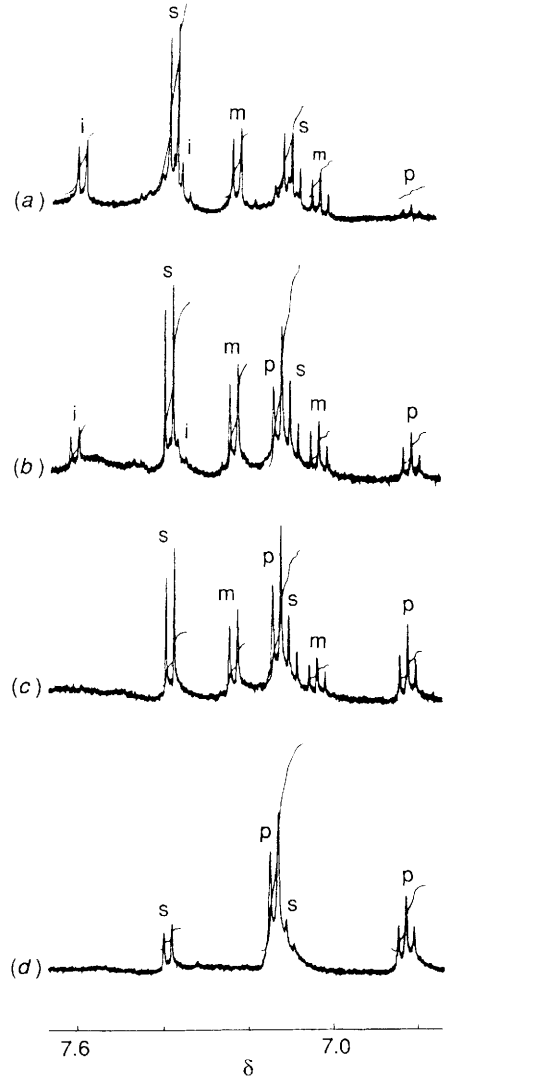


Fig. 1 ^1H NMR spectrum (400 MHz, δ 6.8–7.6) of a solution of the diaza-crown ether **2a** and an excess of dibromide **3a** in CD_3CN at 80 °C after (*a*) 10 min, (*b*) 30 min, (*c*) 100 min and (*d*) 17 h. The AX_2 systems from the aromatic protons are labelled according to their assignment: s for starting material **3a**, i for intermediate **8**, m for methyl ether **9** and p for product **6a**.

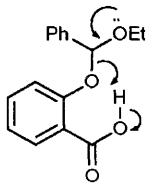
downfield (δ 10.91) as compared with the diprotio system. This is presumably a consequence of unequal populations of the two different monodeuterio species.

An analogous reaction between the dihalide **3b** and diaza-15-crown-5 **2a** gives the phenolic cryptand salt **6b**; the ^{1}H NMR spectrum of this product shows a similar ABX spectrum for the fluxional system **7a** ⇋ **7b** (X = OMe) and also a single OMe signal, confirming that the methoxy group at C-2 of the aromatic ring has been selectively demethylated. The dihalide **3a** also reacts with diaza-18-crown-6 (1,4,10,13-tetraoxa-7,16-diazacyclooctadecane) **2b** to give a good yield (82%) of the phenolic cryptand salt **6c**, but in this case the ^{1}H NMR spectrum shows an A_2X spectrum for the fluxional system **7a** ⇋ **7b** (X = H) due to the symmetry of the macrocycle.

The demethylation involved in the formation of the phenolic cryptands is unexpected. The formation of the cryptand **6a** was therefore investigated in more detail by following the course of the reaction in CD_3CN at 80 °C using ^{1}H NMR spectroscopy. Relevant spectra of the aromatic protons are shown in Fig. 1. These spectra provide evidence for the formation of two intermediates during the reaction which ultimately leads to a high yield of the cryptand **6a**. The second of these intermediates has been identified as the dihydrobromide **9** of the methyl ether **5** by comparison with the spectrum of an authentic sample obtained from the reaction of the dihalide **3a** with diaza-15-crown-5 **2a** in dichloromethane. The first intermediate is tentatively identified as the mono-alkylated crown ether **8**. Thus, the formation of **6a** evidently involves the reaction sequence shown in Scheme 1, with the demethylation occuring after the formation of the bicyclic salt **9**. This demethylation should result in the formation of methyl bromide and a signal at δ 2.65 in the ^{1}H NMR spectrum of the reaction mixture is consistent with this. We note that the dealkylation process, which is the reverse of the normal base-catalysed methylation of a phenol, involves acid catalysis by the $^+$NH groups within the molecular cavity of the cryptand salt. The high yield of the bicyclic product (see final spectrum in Fig. 1) is possibly a result of developing hydrogen bonding between the NH and OMe groups during the reaction **8** → **9**.

Intramolecular acid catalysis has been discussed;[4] moderately high effective molarities (EM) have been observed[5] for acetal cleavage reactions such as **10** and **11**, but in these cases there is a conjugated system between the reacting centres. In the absence of a good intermolecular analogy it is not possible to determine the EM for the process **9** → **6a** but it is of interest that the analogous demethylation of aryl methyl ethers requires fusion with pyridine hydrochloride at 220 °C whereas the reaction **9** → **6a** proceeds in acetonitrile at 80 °C using a <0.0115 mol dm^{-3} concentration of reactants.

The salt **9** can be obtained from the reaction of dihalide **3a** with diaza-15-crown-5 **2a** in refluxing dichloromethane. Heating a 0.0115 mol dm^{-3} solution of **9** in acetonitrile for 22 h gives phenolic cryptand **6a** exclusively. The geometrical relationship between reactant **9** and product **6a** has been checked by searches for the low energy conformations of both compounds using the programs QUANTA and CHARMm (supplied by the Polygen Corporation). Both **6a** and **9** have similar low energy conformations so that a low energy conformation of **9** can pass directly into a low energy conformation of **6a** by the acid catalysed nucleophilic displacement indicated in Scheme 1. The highly effective intramolecular acid catalysis involved in the reaction is consistent with a process that occurs in a strongly hydrogen bonded system that is preorganised within a cryptand cavity. This is reminiscent of the rapid general base catalysed hydrogen exchange recently reported[6] for the amino bis-sulfone **12** in organic solvents. In both the general base catalysed and acid catalysed processes the 'concentration independent and sustained contact with no intervening solvent'[6] is evidently a key factor. Highly efficient examples of both processes are therefore likely to involve a hydrophobic molecular cavity which is preorganised for catalysis and these may be good models for general base and general acid catalysis by enzymes.[7]



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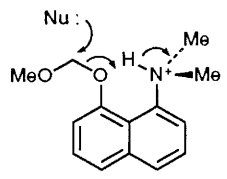

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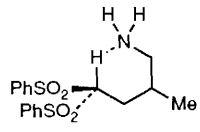

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Received, 8th June 1992; Com. 2/03026H

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