# Synthesis of Mixed Aza, Oxa and Thia Crown Ethers

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Two series of monoaza-15-crown-5 compounds containing either a fused benzo group or sulfur donor atoms in the macrocycles have been synthesised by 1:1 cyclisation of diols or dithiols with ditosylates in the presence of sodium hydride; the molecular structure of 2,3-benzo-10-*N*-(4′-methoxyphenyl)-1,4,7,13-tetraoxa-10-azacyclopentadecane (**8**) has also been determined by single-crystal X-ray analysis.

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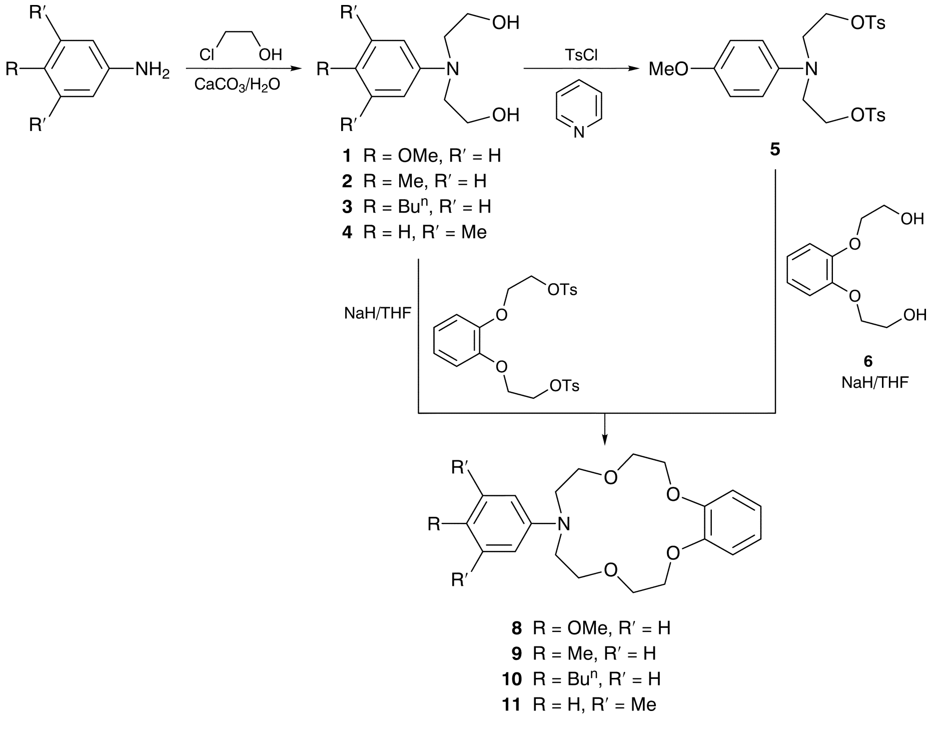
Owing to their unique complexing ability, aza crown ethers have been widely used in catalysis, molecular recognition, and chromatographic separation of metal cations.[1–3] Different functionalities can be introduced readily to the nitrogen atoms as pendant arms that can tailor the properties of these macrocyclic compounds.[4–6] The incorporation of oxygen and sulfur donor atoms in the macrocycles will also markedly affect their complexing properties because of the hard (O, N) and soft (S) character of the donor atoms and the exodentate tendency of the sulfide linkages.[7,8] Despite a potential application as selective complexing agents, these mixed-donor crown ethers have not been fully examined.[9–13] Here, we describe the synthesis of a series of azabenzo-15-crown-5 compounds and a related series containing mixed N-, O-, and S-donor atoms. The molecular structure of one of the azabenzo crown ethers is also reported.

The synthetic routes to the azabenzo crown ethers **8**–**11** are shown in Scheme 1. The *N*,*N*-bis(2′-hydroxyethyl)anilines **1**–**4** were prepared by treating the corresponding anilines with calcium carbonate and 2-chloroethanol in water.[14] The use of weak base promoted *N*-alkylation rather than *O*-alkylation as reported by Bradshaw *et al.*[15] The methoxyaniline **1** was then converted to the ditosylate **5** using 4-toluenesulfonyl chloride and pyridine. Treatment of this ditosylate with 1,2-bis(2′-hydroxyethoxy)benzene (**6**) and sodium hydride in tetrahydrofuran (THF) led to the formation of **8** in moderate yield. An alternative method to these azabenzo crown ethers such as **9**–**11** involved the condensation of the diols **2**–**4** with the ditosylate **7**. The reaction yields using these two pathways were comparable. All of the new compounds were characterised with a range of spectroscopic methods and elemental analyses or accurate mass measurements. The molecular structure of **8** (Fig. 1) was also determined by single-crystal X-ray analysis. All of the bond distances and angles (Table 1, see full text) are as expected.

Another series of aza crown ethers **16**–**19**, containing also oxygen and/or sulfur donor atoms were prepared in an analogous manner. Thus reaction of the ditosylate **5** with the diols or dithiols **12**–**15** and sodium hydride resulted in the formation of the corresponding macrocycles in 31–40% yields (Scheme 2). Compound **16** was prepared previously by the condensation of the diol **1** and triethylene glycol dimesylate in 30% yield.[16]

The $^1$H and $^{13}$C NMR data for **16**–**19** were consistent with the proposed structures. It is worth noting that the triplets arising from the methylene protons between the



**Scheme 1**

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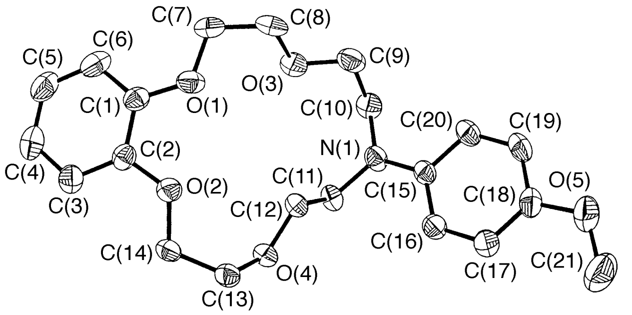

**Fig. 1** Molecular structure of **8** showing the atom numbering system. H atoms have been omitted for clarity, and thermal ellipsoids are drawn at the 35% probability level

nitrogen and sulfur atoms of **18** and **19** show broadening and complex splitting in their $^1$H NMR spectra. It may suggest that the macrocycles are puckered and the conformational changes involve a substantial amount of energy. This is in accord with model studies reported previously for some macrocyclic oxathia ethers.[17]

## Experimental

*Crystal Data for* **8**.—$C_{21}H_{27}NO_5$, $M_r = 373.4$, $F(000) = 800$, orthorhombic, $a = 8.682(1)$, $b = 8.246(1)$, $c = 27.922(3)$ Å, $V = 1999(1)$ Å$^3$, space group $Pna2_1$ (no. 33), $Z = 4$, $D_c = 1.241$ g cm$^{-3}$, $\mu$(Mo-K$\alpha$) = 0.088 mm$^{-1}$. Data collection was performed at 294 K on a MSC/Rigaku RAXIS IIc imaging-plate system using Mo-K$\alpha$ radiation ($\lambda = 0.710\,73$ Å) from a Rigaku RU-200 rotating-anode generator operating at 50 kV and 90 mA ($2\theta_{min} = 3°$, $2\theta_{max} = 55°$, 45 4° oscillation frames in the range of 0–180°, exposure 12 min. per frame).[23–25] The structure was solved by the direct method. The final $R$ value was 0.0432 ($R_w = 0.0465$). The estimated standard deviation for the geometrical parameters involving non-hydrogen atoms lie within the following ranges: bond lengths, 0.003–0.005 Å; bond angles, 0.2–0.3°.

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Techniques used: $^1$H and $^{13}$C NMR, MS, X-ray diffraction

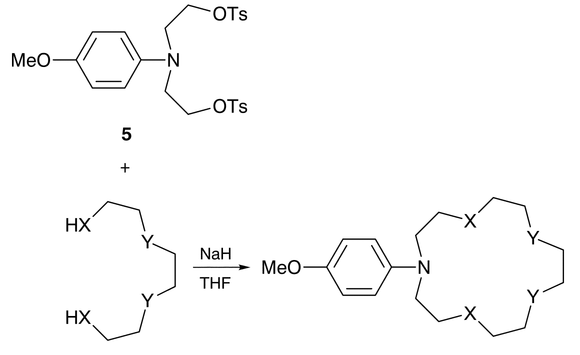
References: 30

Table 1: Selected bond distances (Å) and angles (°) for compound **8**

Table 2: Crystallographic data for compound **8**

Table 3: Atomic coordinates (×10$^4$) for compound **8**

Appendix: Tables of H-atom coordinates, thermal parameters and a full listing of molecular dimensions and a packing diagram for **8**



**12** X = Y = O
**13** X = O, Y = S
**14** X = S, Y = O
**15** X = Y = S

**16** X = Y = O
**17** X = O, Y = S
**18** X = S, Y = O
**19** X = Y = S

**Scheme 2**

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