Novel Thiophene-based Macrocycles related to Azacrown Ethers

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A range of compounds containing two 3-oxygenated thiophene rings linked through the oxygen atoms by a variety of alkyl and heteroalkyl chains has been prepared and subjected to electrophilic substitution, at C(2) and C(2′), giving, *inter alia*, bis-Mannich bases containing 14- to 22-membered rings; preliminary X-ray diffraction studies of representative metal complexes are in hand.

As far as we are aware the thiophene-based azacrown ethers described are of a novel type, and we can find no previous record of the use of the Mannich reaction for the synthesis of such systems. The preparation of polyether macrocycles containing thiophene rings has been described recently,[1] and there have been some reports of the synthesis of large rings *via* Schiff base formation from thiophene dialdehydes.[2]

The reaction sequence (Scheme 1) leading to the bis(3-thienyl) ethers **1** proceeds in good yield at each stage; the hydroxythiophene ester starting material is commercially available.† The ethers are susceptible to decomposition (apparently through cleavage of the ether linkages) under all but the mildest electrophilic substitution conditions. However, the bis(2-aldehydes) **2a** and Mannich bases[3] **2b** are produced in good yields (64–92%, and 72–100%, respectively). With formaldehyde and either *N*,*N*′-dimethylethylenediamine or piperazine in acetic acid, **1** undergoes a double Mannich reaction, at the 2- and 2′-positions, leading to macrocyclic compounds. Primary amines can also enter into the formation of cyclic systems from **1** under these conditions. The mass spectra of the products isolated indicate that they are formed from one molecule of amine or diamine and one of the ether, *i.e.* they are monomeric; dimers and higher polymers are formed to some extent, but are removed by chromatography during purification.

Cyclisations of this type could be achieved with ethers **1** containing both alkyl and hetero-substituted alkyl linking

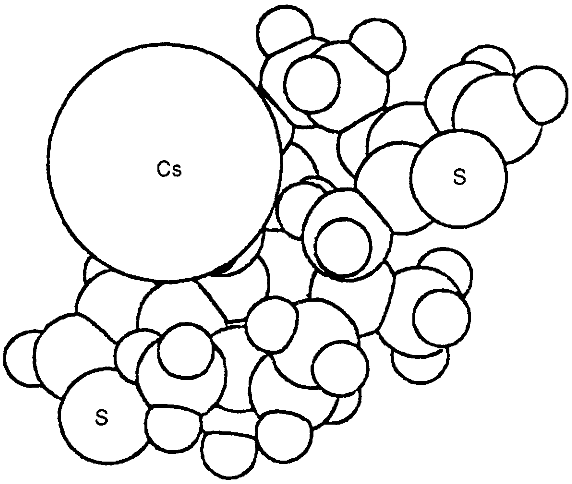

Fig. 1 Caesium complex of **3a**

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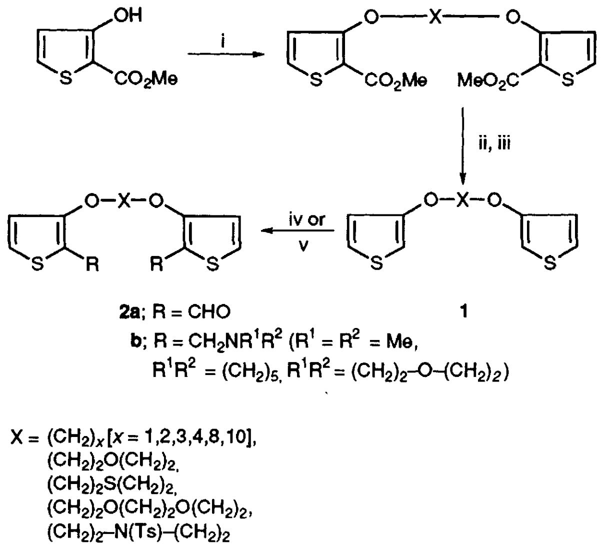
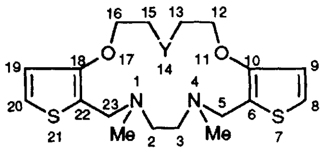
† Synthetic Chemicals Ltd, Four Ashes, Wolverhampton, UK WV10 7BP.



Scheme 1 *Reagents and conditions*: i, TsO–X–OTs (Ts = toluene-*p*-sulfonyl) or Br–X–Br, K_2CO_3, Me_2CO or DMF (dimethylformamide); ii, KOH, EtOH, H_2O, then H^+ iii, heat, Cu_2O, pyridine; iv, DMF, $POCl_3$, $Cl(CH_2)_2Cl$, then NaOAc, H_2O; v, R^1R^2NH, CH_2O, AcOH



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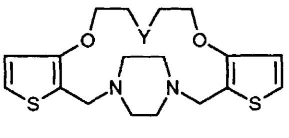
(Numbering for **3a**)



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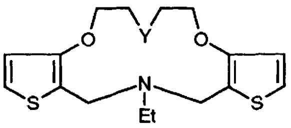

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a, Y = O; **b**, Y =O(CH2)2O; **c**, Y = S

groups (X), but the latter class are of greater interest, because of their relationship to crown ethers. Monomeric macro-ring formation took place in much better yields when the linking chain included sulfur or oxygen atoms than when it was purely alkyl. We suggest that a possible explanation for this observation is as follows: the initial product is that in which just one of the vacant thiophene 2-positions has undergone substitution; an appropriately placed linking-group hetero-atom may then coordinate with the positively charged 'free' end of the diamine chain, acting as an internal template and holding the electrophile in the vicinity of the remaining free C(2) position. Some evidence for this is that the cyclisations proceed reasonably well under normal dilution, although yields are improved (*e.g.* from 46 to 62% in a typical case) under high dilution conditions. Application of the Pedersen extraction method[4] to the azacrown ether relatives (**3**–**5**) has shown that they form dichloromethane-soluble complexes with Li^+, Na^+, K^+, Cs^+, Ag^+, Mg^{2+}, Ca^{2+} and Sr^{2+}. A summary of the picrate extraction results is presented in Table 1. In order to obtain comparisons, the greatest organic phase UV absorbance value obtained (Ca^{2+} with **4b**) was taken as a reference point; the other values given, which include those for 18-crown-6 **6**, are percentages of this maximum. It can be seen that the compounds are much more effective transfer agents than **6**, but that they do not exhibit greater selectivity.

Table 1 Relative organic phase UV absorbances *vs.* Ca^{2+}/**4b** of compounds **3a**, **3b**, **4a**, **4b**, **5a**, **5b** and 18-crown-6 **6** metal picrates

Metal ion	Relative absorbance						
	3a	**3b**	**4a**	**4b**	**5a**	**5b**	**6**
Li^+	40	30	46	13	49	9	1.2
Na^+	38	60	46	60	49	13	1.2
K^+	35	74	50	49	51	17	6.1
Cs^+	46	60	53	75	53	12	4.7
Ag^+	49	86	60	56	64	15	1.5
Mg^{2+}	41	44	43	88	51	17	0.1
Ca^{2+}	44	76	50	100	54	29	0.1
Sr^{2+}	49	88	57	80	60	11	1.3

Molecular modelling[5] of the energy-minimised conformation of the caesium complex‡ show that the ligand is approximately planar, with the caesium atom bound to one side of the macrocycle (Fig. 1). Work is continuing to obtain good single crystals for full structure determination of selected compounds.

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‡ The preparation of **3a** and its caesium complex are typical. A solution of *N,N'*-dimethylethylenediamine (0.3 g, 4.1 mmol), formaldehyde (37% aq. solution; 0.61 ml, 2.2 equiv.) and the ether (**1**; X = CH_2OCH_2; 1 g, 3.7 mmol) in glacial acetic acid (25 ml) was stirred at room temp. for 24 h. The mixture was made basic with sodium hydroxide (4 mol dm^{-3}), with cooling, and extracted with dichloromethane (2 × 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated, to give an orange oil (1.34 g), which was chromatographed on alumina (Brockman Grade 1, neutral, 60–120 mesh), using 1 : 1 chloroform–toluene as eluant. Compound **3a** was obtained, (0.66 g, 47%), as an orange oil, *m/z* (CI, CH_4) 383 (M+1), δ_H ($CDCl_3$) 7.10 (2H, d, *J* 6 Hz, 8-H+20-H), 6.80 (2H, d, *J* 6 Hz, 9-H+19-H), 4.11 (4H, m, 12-H+16-H), 3.71 (4H, m, 13-H+15-H), 3.80 (4H, s, 5-H+23-H), 2.58 (4H, s, 2-H+3-H) and 2.34 (6H, s, 2 × Me), δ_c($CDCl_3$) 154.4 (C-10+C-18), 122.55 (C-8+C-20), 116.8 (C-6+C-22), 116.55 (C-9+C-19), 71.0 (C-12+C-16), 70.0 (C-13+C-15), 52.4 (C-5+C-23), 50.3 (C-2+C-3) and 42.4 (Me), ν_{max} (film) 1555.9 (C=C) cm^{-1}, λ_{max} (MeOH) 202.3 (log ε_{max} 3.71), 227.0 (log ε_{max} 3.30) and 256.7 (log ε_{max} 2.99) nm.

To a solution of the ligand **3a** (0.76 g, 2 mmol) in methanol (40 ml) was added a solution of caesium iodide (0.52 g, 2 mmol) in 70% methanol-water (10 ml). The solution was maintained at 40 °C for 1.5 h, then allowed to evaporate at room temp. until the caesium complex (0.25 g, 21%) crystallised, m.p. 174–176 °C, δ_H ($CDCl_3$) 7.28 (2H, d, *J* 5 Hz, 8-H+20-H), 6.86 (2H, d, *J* 5 Hz, 9-H+19-H), 4.18 (4H, m, 12-H+16-H), 3.82 (4H, m, 13-H+15-H), 4.25 (4H, s, 5-H+23-H), 2.99 (4H, s, 2-H+3-H) and 2.61 (6H, s, 2 × Me), δ_c($CDCl_3$) 156.3 (C-10+C-18), 125.7 (C-8+C-20), 108.6 (C-6+C-22), 115.7 (C-9+C-19), 70.1 (C-12+C-16), 69.7 (C-13+C-15), 49.4 (C-5+C-23), 49.4 (C-2+C-3) and 40.9 (Me), ν_{max} (KBr) 1549.1 (C=C) cm^{-1}, λ max (MeOH) 201.6 (log ε_{max} 3.26), 221.6 (log ε_{max} 3.41) and 256.8 (log ε_{max} 2.84) nm.