

An effective self-templating ring closure method for mixed donor thiophene-based macrocycles

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Joan Halfpenny* and Zachary S. Sloman

Department of Chemistry and Physics, Nottingham Trent University, Clifton Lane, Nottingham, UK NG11 8NS

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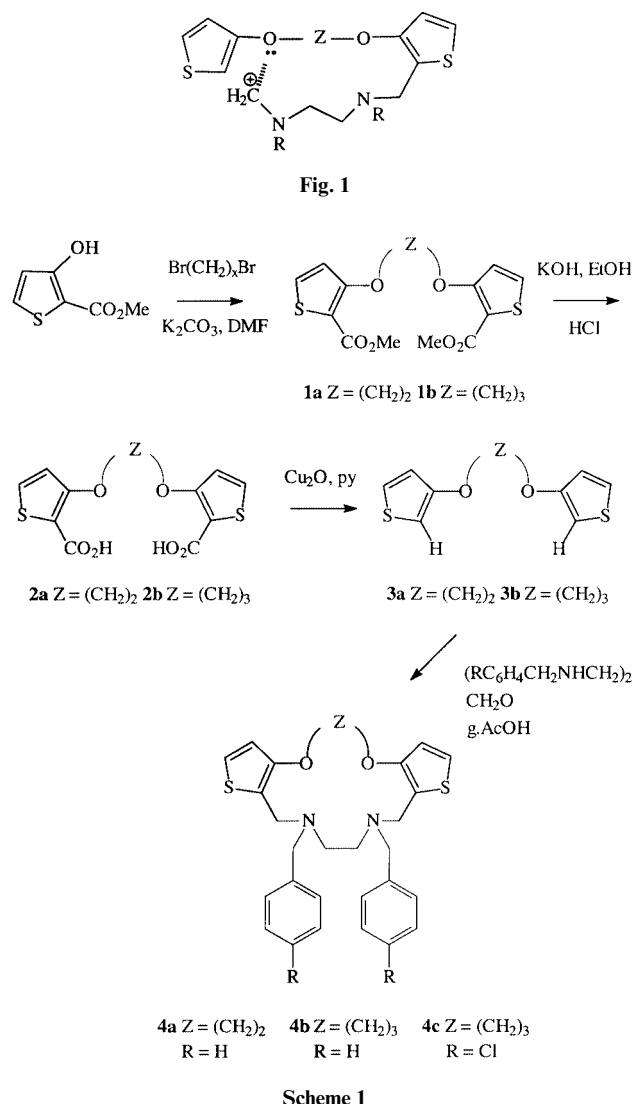
The synthesis *via* the Mannich reaction of a series of 14- and 15-membered ring mixed donor thiophene-containing macrocycles is reported. The macrocycles each incorporate two oxygen and two nitrogen donor atoms and were obtained in high yields without any requirement for high dilution techniques or metal ion templates. The compounds can be purified by simple recrystallisation. The crystal structure of the 15-membered ring macrocycle $C_{29}H_{32}N_2O_2S_2$ (**4b**) has been determined. The structure shows that the bulky benzyl substituents have a major effect on the macrocyclic ring geometry.

Introduction

The chemistry of macrocycles containing aromatic units has been well documented but heteroaromatic systems^{1,2} have been less widely studied, despite the fact that different substitution patterns are possible and the heteroatom may act as a binding site in some cases. As part of our continuing studies³ on mixed donor thiophene-containing macrocycles derived *via* the Mannich reaction we have studied the synthesis of a series of 14- and 15-membered ring mixed donor thiophene-containing macrocycles, which have the potential to act as selective complexation reagents for transition metal ions. The distinguishing feature of this work is the simple and effective method of ring closure. One of the most common problems encountered in the synthesis of macrocyclic compounds is the formation of higher oligomers or polymers⁴ as well as the desired macrocycle. High dilution and 'metal ion template' techniques may help but the yields are often low and purification *via* column chromatography is often necessary. The method of ring closure reported here avoids all of these problems *via* its self-templating mechanism. The Mannich reaction involves electrophilic substitution at the 2-position of the thiophene ring by reaction of the mildly electrophilic condensate of formaldehyde and a secondary amine.⁵ The formation of oligomers/polymers is limited, presumably due to an electrostatic interaction between one of the ether oxygens and the electropositive methylene carbon of the reaction intermediate (Fig. 1). This has the effect of bringing the reactive electrophilic arm proximate to the thiophene ring of the same molecule where reaction takes place. The fact that high yields of the [1 + 1] macrocycles are obtained at normal dilution and that there is no oligomeric or polymeric byproduct suggests that intermolecular electrostatic interactions are minimal.

Results and discussion

The 14- and 15-membered ring macrocycles **4a–c** were synthesised as shown in Scheme 1. The first stage of the synthesis involves the coupling of two molecules of methyl 3-hydroxythiophene-2-carboxylate *via* Williamson ether synthesis using the appropriate dibromoalkane. The resulting α,ω -bis(2-methoxycarbonyl-3-thienyloxy)alkanes (**1**) were digested in hot solvent to yield the pure products. These were then saponified to the α,ω -bis(2-carboxy-3-thienyloxy)alkanes (**2**) by refluxing



with KOH in 80% ethanol and subsequent treatment with concentrated hydrochloric acid. The α,ω -bis(2-carboxy-3-thienyloxy)alkanes (**2**) readily decarboxylate in the presence of

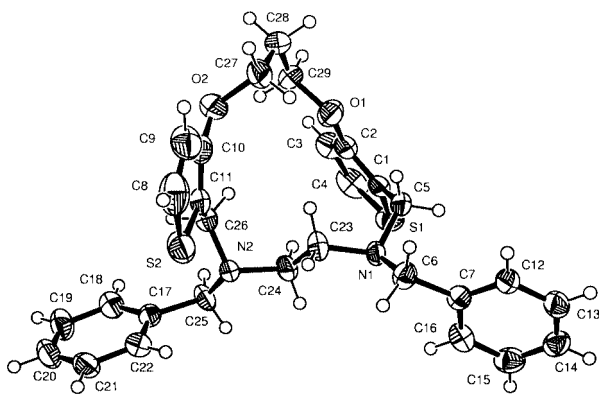


Fig. 2 The molecular conformation of $C_{29}H_{32}N_2O_2S_2$ showing 50% probability displacement ellipsoids for non-H atoms. Hydrogen atoms are shown as spheres of an arbitrary radius. Selected bond lengths (Å) and angles ($^\circ$): S1–C1 1.712(4), S1–C4 1.659(5), C1–C2 1.349(5), C2–C3 1.387(5), C3–C4 1.345(6), S2–C8 1.706(5), S2–C11 1.701(4), C8–C9 1.348(6), C9–C10 1.402(6), C10–C11 1.353(5), C1–C5 1.456(5), C5–N1 1.459(5), N1–C23 1.471(4), C23–C24 1.494(5), C24–N2 1.468(4), N2–C26 1.451(4), C10–O2 1.375(5), O2–C27 1.432(5), C27–C28 1.488(6), C28–C29 1.492(6), C29–O1 1.405(4), O1–C2 1.365(4); C1–S1–C4 92.2(2), S1–C4–C3 112.7(3), S1–C1–C2 109.7(3), C1–C2–C3 113.7(4), C2–O1–C29 118.0(3), O1–C29–C28 108.9(3), C29–C28–C27 113.8(4), C28–C27–O2 108.9(4), C27–O2–C10 113.9(3), C1–C5–N1 113.1(3), C5–N1–C23 110.7(3), N1–C23–C24 109.8(3), C23–C24–N2 112.5(3), C24–N2–C26 112.4(3), N2–C26–C11 114.8(3), C8–S2–C11 92.2(2), S2–C8–C9 112.5(4), C8–C9–C10 110.3(4), C9–C10–C11 115.5(4), C10–C11–S2 109.5(3).

copper(I) oxide in refluxing pyridine. It was necessary to remove the solvent *in vacuo* and digest the residue to obtain the α,ω -bis(3-thienyloxy)alkane products (**3**) in ca. 74% overall yield. The bis(3-thienyloxy)alkanes (**3**) were then macrocyclised using formaldehyde and the appropriate bis(secondary amine) in glacial acetic acid at room temperature. The high yields and simplicity of the reactions mean that these macrocycles can now be synthesised on multigram scales. The compounds are soluble in a wide range of organic solvents and can be readily recrystallised. Compound **4a** was recrystallised in 63% yield from methanol and obtained as a light yellow powder. Compound **4b** was obtained in 69% yield as light yellow crystalline needles which did not require recrystallisation. Compound **4c** was obtained in 36% yield as a white powder after recrystallisation from ethanol. The IR spectra, 1H NMR spectra, mass spectra, microanalyses and, for **4b**, crystal structure all conform with the proposed products. The X-ray analysis of **4b** (Fig. 2) was undertaken to establish the effect of the bulky benzyl substituents on the geometry of the macrocyclic cavity. The molecule was found to be non-planar with the greatest cross-molecule distances occurring between the two thiophene rings [C4–C8 = 8.66(3) Å] and the two phenyl rings [C13–C20 = 12.78(3) Å]. The large separation of the two phenyl rings influences the geometry of the macrocyclic cavity by ensuring that the thiophene rings and therefore the oxygen and nitrogen donor atoms do not lie in the same plane. The largest cross-cavity distances are C28–N2 = 5.85(3) Å and C1–C11 = 5.28(3) Å. The macrocyclic cavity was found to contain two approximately planar regions, each conveniently defined by a least-squares plane through the atoms of a thiophene ring. Deviations from these planes[†] show that N2 lies much closer to least-squares plane 2 than N1 to plane 1. The N2...S2 distance is 3.115(4) Å. This distance, much shorter than the sum of the van der Waals radii (3.45 Å), and also considerably shorter than N1...S1 [3.328(4) Å],

[†] Plane 1, S1 0.004(1), O1 –0.001(3), C1 –0.006(4), C2 0.007(4), C3 –0.004(5), C4 0.000(5), C5 –0.149(4), N1 –1.473(3) and plane 2, S2 –0.002(1), O2 –0.030(2), C8 0.005(4), C9 –0.008(4), C10 0.006(4), C11 –0.003(4), C26 –0.160(4), N2 0.509(3).

suggests a non-bonded S...N interaction similar to that previously reported for other 2-substituted thiophenes.⁶ Support for this view is provided by the smaller S2–C11–C26 external angle of 121.7(3) $^\circ$ compared with C10–C11–C26 128.4(3) $^\circ$ and the smaller torsion angle S2–C11–C26–N2 of –37.9(4) $^\circ$ compared with S1–C1–C5–N1 –68.6(4) $^\circ$. Some distortion in the thiophene ring bond lengths and angles is observed in many substituted thiophene compounds, the most obvious effect being the asymmetric nature of the S–C bonds.⁶ In the present compound the ring associated with the S2...N2 interaction has nearly symmetrical S–C bond lengths, possibly due to the movement of some electron density towards N2, whereas the ring containing S1 shows the usual distortion. In many of the examples quoted by Koziol, Palenik and Palenik⁶ the nitrogen is sp^2 hybridised rather than sp^3 as in the present compound, and therefore the C–N distance is shorter, facilitating the S...N interaction. Considering the steric restrictions imposed in the present compound by the C and N atoms being part of the large macrocyclic ring, the existence of such a short S...N contact is quite remarkable.

Experimental

The 1H NMR spectra were recorded with a JEOL EX-270 MHz spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard; J values are given in Hz. Mass spectroscopic determinations were carried out by Shell Research Ltd., Sittingbourne and the University of Nottingham. Elemental analyses were performed by the microanalysis unit at the University of Nottingham. Methyl 3-hydroxythiophene-2-carboxylate was supplied by Synthetic Chemicals Ltd.

General procedure for the preparation of the α,ω -bis(2-methoxycarbonyl-3-thienyloxy)alkanes **1a,b**

A stirred solution of methyl 3-hydroxythiophene-2-carboxylate, anhydrous potassium carbonate (0.55 equiv.) and the appropriate dibromoalkane (0.55 equiv.) in anhydrous DMF ($5\text{ cm}^3\text{ g}^{-1}$ of thiophene ester) was heated at 95–100 $^\circ\text{C}$ for 5 h. The reaction mixture was poured into ice and the resulting precipitate filtered off, washed with water and digested in hot solvent (**1a** = methanol, **1b** = acetone). The residual solid was filtered off and washed with the same solvent.

1,2-Bis(2-methoxycarbonyl-3-thienyloxy)ethane 1a. Solid (89%), mp 188.8–191.0 $^\circ\text{C}$; ν_{max} (KBr)/ cm^{-1} 3108, 3103, 2952, 2890, 1709 and 1542; δ_{H} 3.71 (6 H, s, OCH_3), 4.48 (4 H, s, CH_2O), 7.18 (2 H, d, J 5.6, ThH) and 7.81 (2 H, d, J 5.6, ThH); m/z 343 ($M^+ + 1$) (Found: C, 49.1; H, 4.3. $C_{14}H_{14}O_6S_2$ requires C, 49.11; H, 4.12%).

1,3-Bis(2-methoxycarbonyl-3-thienyloxy)propane 1b. Solid (80%), mp 138.1–139.9 $^\circ\text{C}$; ν_{max} (KBr)/ cm^{-1} 3108, 3102, 2949, 2884, 1712 and 1542; δ_{H} 2.13 (2 H, m, CH_2), 3.70 (6 H, s, OCH_3), 4.31 (4 H, t, J 6.5, CH_2O), 7.12 (2 H, d, J 5.5, ThH) and 7.80 (2 H, d, J 5.5, ThH); m/z 357 ($M^+ + 1$) (Found: C, 50.8; H, 4.6. $C_{15}H_{16}O_6S_2$ requires C, 50.55; H, 4.52%).

General procedure for the preparation of the α,ω -bis(2-carboxy-3-thienyloxy)alkanes **2a,b**

A solution of the α,ω -bis(2-methoxycarbonyl-3-thienyloxy)-alkane (**1a,b**) and potassium hydroxide (4.0 equiv.) in 80% aqueous ethanol ($20\text{ cm}^3\text{ g}^{-1}$ of bis-ester) was boiled under reflux for 2 h. The solution was filtered through glass wool into a stirred mixture of ice and a slight excess of hydrochloric acid. The resulting solid was filtered off, washed with water and dried *in vacuo* at 60 $^\circ\text{C}$ for at least 3 days.

1,2-Bis(2-carboxy-3-thienyloxy)ethane 2a. Solid (93%), mp 218.9–219.6 $^\circ\text{C}$; ν_{max} (KBr)/ cm^{-1} 3106, 3100, 2945, 2886, 2600,

1688 and 1541; δ_{H} 4.46 (4 H, s, CH₂O), 7.18 (2 H, d, *J* 5.6, ThH) and 7.75 (2 H, d, *J* 5.6, ThH); *m/z* 271 (M⁺ - 43) (Found: C, 45.8; H, 3.3. C₁₂H₁₀O₆S₂ requires C, 45.85; H, 3.21%).

1,3-Bis(2-carboxy-3-thienyloxy)propane 2b. Solid (98%), mp 214.1–214.3 °C; ν_{max} (KBr)/cm⁻¹ 3105, 3100, 2943, 2886, 2600, 1685 and 1538; δ_{H} 2.18 (2 H, m, CH₂), 4.36 (4 H, t, *J* 6.0, CH₂O), 7.15 (2 H, d, *J* 5.5, ThH) and 7.79 (2 H, d, *J* 5.5, ThH); *m/z* 285 (M⁺ - 43) (Found: C, 47.6; H, 3.7. C₁₃H₁₂O₆S₂ requires C, 47.55; H, 3.68%).

General procedure for the preparation of the α,ω -bis(3-thienyloxy)-alkanes 3a,b

A mixture of the α,ω -bis(2-carboxy-3-thienyloxy)alkane (**2a,b**) and copper(I) oxide (1.2 wt. equiv.) in pyridine (10 cm³ g⁻¹ of diacid) was boiled under reflux for 1 h. The solvent was removed under reduced pressure and the residue was extracted repeatedly with DCM. The combined organic extracts were washed with dilute hydrochloric acid, then with saturated sodium hydrogen carbonate solution, dried (MgSO₄) and evaporated to give the crude product.

1,2-Bis(3-thienyloxy)ethane 3a. Solid recrystallised from MeCN (73%), mp 156.2–158.7 °C; ν_{max} (KBr)/cm⁻¹ 3116, 3100, 3090, 2936, 2932, 2890 and 1543; δ_{H} 4.36 (4 H, s, CH₂O), 6.30 (2 H, m, ThH), 6.79 (2 H, m, ThH) and 7.15 (2 H, m, ThH); *m/z* 227 (M⁺ + 1) (Found: C, 52.9; H, 4.6. C₁₀H₁₀O₂S₂ requires C, 53.07; H, 4.45%).

1,3-Bis(3-thienyloxy)propane 3b. Solid recrystallised from MeOH (85%) mp 65.0–66.6 °C; ν_{max} (KBr)/cm⁻¹ 3116, 3101, 3085, 2937, 2931, 2856 and 1544; δ_{H} 2.17 (2 H, p, *J* 6.0, CH₂), 4.08 (4 H, t, *J* 6.0, CH₂O), 6.20 (2 H, m, ThH), 6.70 (2 H, m, ThH) and 7.10 (2 H, m, ThH); *m/z* 241 (M⁺ + 1) (Found: C, 54.7; H, 5.1. C₁₁H₁₂O₂S₂ requires C, 54.97; H, 5.03%).

General procedure for the preparation of the macrocycles 4a–c

A solution of the α,ω -bis(3-thienyloxy)alkane (**3a,b**), the appropriate *N,N'*-dibenzylalkyldiamine (1.1 equiv.) and formaldehyde (2.2 equiv.) in glacial acetic (100 cm³ g⁻¹ of bis-ether) was stirred for 24–72 h. The solution was basified with 4 M NaOH and extracted with DCM. The organic extracts were dried (MgSO₄) and the solvent evaporated under reduced pressure.

12,15-Dibenzyl-2,5-dioxa-9,18-dithia-12,15-diazatricyclo-[15.3.0^{6,10}]heneicosa-1^{17,6},7,19-tetraene 4a. Solid recrystallised from MeOH (63%), mp 84.7–85.6 °C; δ_{H} 2.72 (4 H, s, NCH₂), 3.71 (4 H, s, PhCH₂), 3.73 (4 H, s, ThCH₂), 4.32 (4 H, s, CH₂O), 6.84 (2 H, d, *J* 5.6, ThH), 7.14 (2 H, d, *J* 5.6, ThH) and 7.20–7.40 (10 H, m, PhH); *m/z* 491 (M⁺ + 1) (Found: C, 68.5; H, 6.4; N, 5.8. C₂₈H₃₀N₂O₂S₂ requires C, 68.54; H, 6.16; N, 5.71%).

13,16-Dibenzyl-2,6-dioxa-10,19-dithia-13,16-diazatricyclo-[16.3.0^{7,11}]heneicosa-1^{18,7},8,20-tetraene 4b. Solid (69%), mp

128.5–129.9 °C; δ_{H} 2.18 (2 H, p, *J* 5.3, CH₂), 2.67 (4 H, s, NCH₂), 3.66 (4 H, s, PhCH₂), 3.75 (4 H, s, ThCH₂), 4.25 (4 H, t, *J* 5.3, CH₂O), 6.87 (2 H, d, *J* 5.5, ThH), 7.15 (2 H, d, *J* 5.5, ThH) and 7.20–7.40 (10 H, m, PhH); *m/z* 505 (M⁺ + 1) (Found: C, 68.7; H, 6.5; N, 5.6. C₂₉H₃₂N₂O₂S₂ requires C, 69.01; H, 6.39; N, 5.55%).

Crystal data for 4b.† Crystals were obtained directly from the reaction work-up and were suitable without further recrystallisation. The density was measured by flotation of a number of well-formed crystals in a mixture of methanol and dichloromethane. C₂₉H₃₂N₂O₂S₂, *M_r* = 504.69, monoclinic, *a* = 12.504(11), *b* = 11.299(10), *c* = 19.80(2) Å, β = 113.30(10)°, *U* = 2570(4) Å³, space group *P*2₁/*c* (no. 14), *Z* = 4, *D_x* = 1.305 g cm⁻³, *D_m* = 1.31 g cm⁻³, μ (Mo-K α) = 0.237 mm⁻¹, *T* = 293(2) K. 3225 independent reflections, *R_{int}* = 0.0496. The structure was solved by direct methods using MULTAN87⁷ and refined on *F*² by full-matrix least-squares (SHELXL97)⁸ using all unique data to final *R*₁ (on *F*, *F_o* > 2 σ *F_o*) = 0.0609 and *wR*₂ (on *F*²) = 0.1498 [non-H atoms anisotropic, H atoms in calculated positions (riding model)]. Weighting scheme: *w* = 1/[$\sigma^2(F_o^2)$ + (0.0805*P*)² + 0.3142*P*], where *P* = (*F_o*² + 2*F_c*²)/3. Fig. 2 was produced using PLATON.⁹

13,16-Bis(*p*-chlorobenzyl)-2,6-dioxa-10,19-dithia-13,16-diazatricyclo-[16.3.0^{7,11}]heneicosa-1^{18,7},8,20-tetraene 4c. Solid (36%), mp 109.0–111.1 °C; δ_{H} 2.20 (2 H, p, *J* 5.4, CH₂), 2.60 (4 H, s, NCH₂), 3.60 (4 H, s, PhCH₂), 3.70 (4 H, s, ThCH₂), 4.25 (4 H, t, *J* 5.4, CH₂O), 6.85 (2 H, d, *J* 5.6, ThH), 7.15 (2 H, d, *J* 5.6, ThH) and 7.25–7.30 (8 H, m, PhH); *m/z* 573 (M⁺ + 1) (Found: C, 60.7; H, 5.3; N, 4.9. C₂₉H₃₀Cl₂N₂O₂S₂ requires C, 60.73; H, 5.27; N, 4.88%).

† CCDC reference number 207/431. See <http://www.rsc.org/suppdata/p1/b0/b002029j/> for crystallographic files in .cif format.

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