Straightforward synthesis of sulfur bridged oligopyrrolic macrocycles

David Sanchez-Garcia, Thomas Köhler, Daniel Seidel, Vincent Lynch and Jonathan L. Sessler*

Received (in Cambridge, UK) 18th January 2005, Accepted 17th February 2005
First published as an Advance Article on the web 1st March 2005
DOI: 10.1039/b500735f

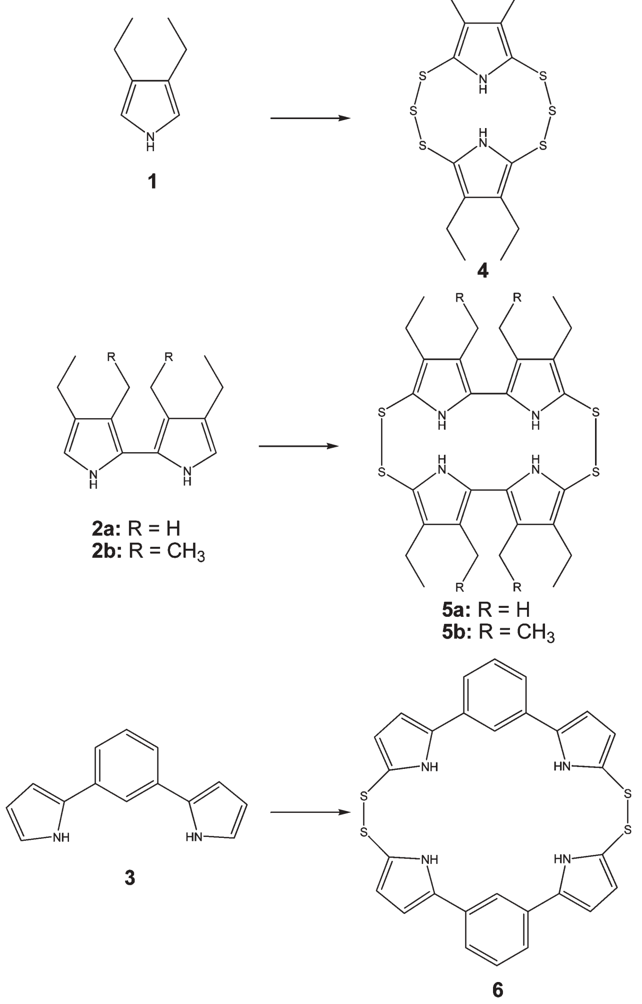
Di- and trisulfide linked oligopyrrolic macrocycles are obtained when appropriate α,α′-free pyrrolic precursors are reacted with sulfur dichloride; these systems represent the first examples of what might be a general new class of porphyrin analogues.

In recent years, novel porphyrinoids, synthetic analogues of naturally occurring blood pigments, have attracted considerable attention within the scientific community. This interest has been driven in part by the remarkable properties these new systems display, such as aromatic effects, unusual spectroscopic features, cation coordination, and anion recognition, to name but a few.[1–5] It has also been stimulated by potential applications in areas as diverse as photodynamic therapy, cancer chemotherapy, nonlinear optics, enzyme modelling, liquid crystal/materials research, and metal complexation.[1,2]

To date, efforts to prepare new porphyrinoids have relied in large measure, albeit not exclusively, on two general strategies. These consist of *i*) changing the nature and number of heterocyclic subunits and *ii*) increasing, decreasing, or rearranging the placement of the bridging carbon atoms linking these subunits (*i.e.*, the so-called *meso* carbons).[2–5] Another appealing strategy has involved replacing some or all of these latter bridging atoms by nitrogens, a strategy that has led, *inter alia*, to a large body of Schiff-base type oligopyrrolic macrocycles including several that display high stability and unusual chemical features.[6] However, relatively little attention has been paid to the development of porphyrin analogues containing linkages other than carbon or nitrogen.[7,8] Here, we detail a method for generating sulfur-linked pyrrolic macrocycles that is based on the simple reaction of a bis(α-free) pyrrolic fragment with S_2Cl_2. Specifically, we report the synthesis and single crystal X-ray diffraction structures of the bis(pyrrole) macrocycle **4** linked by two sets of three sulfur atom straps, as well as its bipyrrole derived congener **5a** that possesses bridges containing two sulfur atoms each. Also reported is a larger system, **6**, that is derived from a 1,3-bis(pyrrolyl)benzene subunit.

The use of sulfur to bridge pyrrolic subunits is not new. In early work, Broadhurst *et al.* reported a procedure involving ring closure around a single bridging sulfur atom, followed by sulfur extrusion and ring contraction, as a means of generating heterocyclic analogues of sapphyrin [pentaphyrin(1,1,1,1,0)].[9] This procedure was also applied to the synthesis of corrole.[10] More recently, Rees and co-workers reported the reaction of *N*-methylpyrrole with sulfur dichloride (S_2Cl_2) to produce a pyrrole (pentathiepin) whose β-pyrrole positions are "strapped" by a linked S_5 chain.[11] Prior to this report, Barbier had described the use of sulfur dichloride to prepare sulfide- and disulfide-linked indole derivatives.[12] Similar strategies, involving the use of SCl_2, rather than S_2Cl_2, have been employed to prepare various open chain, single atom bridged pyrrole sulfides.[13] This precedent, although limited, led us to consider that sulfur dichloride, if it could be used to link α,α′-free pyrrolic precursors, might provide a general entry into a new class of oligopyrrole macrocycles containing multiple bridging sulfur atoms. To the best of our knowledge, such systems have not yet been reported in the literature.

The synthesis of target compounds **4–6** is summarized in Scheme 1. Briefly, reaction of α,α′-free pyrroles **1–3** under argon at −78 °C with a solution of S_2Cl_2 in tetrahydrofuran furnishes, after



Scheme 1 Synthesis of sulfur bridged macrocycles **4**, **5**, and **6**. Unless otherwise indicated, the reaction conditions were: −78 °C, THF, S_2Cl_2.

---

*sessler@mail.utexas.edu

purification by chromatography over silica gel, macrocycles **4**, **5** and **6** as yellow solids. The isolated yields were 21, 34, and 27% in the case of **4**, **5a**, and **6**, respectively.†

The new macrocycles showed reasonable chemical stability when stored at or below room temperature in the absence of air and light. However, they were found to decompose rapidly when heated, when treated with acid, or when subject to extensive column chromatography over silica gel. All three systems were soluble in tetrahydrofuran and could be purified by recrystallization under evaporative conditions. In the case of **4** and **5a**, slow evaporation from hexanes and DMSO, respectively, provided diffraction grade crystals and allowed for characterization by X-ray diffraction analysis.

The structures of compounds **4** and **5a** are shown in Fig. 1. As can be seen from this figure, compound **4** bears little structural resemblance to a porphyrin. On the other hand, the bowl-like features are reminiscent of the cone conformation of calix[4]-pyrroles and related non-aromatic oligopyrrolic macrocycles.[14] A major difference, however, is that the inner periphery of compound **4** is much smaller than that present in most of these other well-characterized systems. Also, most obviously, a set of three linked sulfur atoms define the bridging elements, rather than $C(CH_3)_2$–pyrrole–$C(CH_3)_2$ subunits as is true in, *e.g.*, the case of calix[4]pyrroles.

In contrast to **4**, compound **5a** bears a structural resemblance to a well-known porphyrinoid, namely the ethylidine-linked porphycene system introduced by Vogel.[15] However, a greater deviation from planarity is seen in the case of the disulfide bridged system **5a** as compared to the corresponding porphycene bearing the same β-pyrrolic substituents.[15]

While no structural information is currently available for compound **6**, on the basis of the above findings it is expected that it will bear considerable resemblance to an "expanded calixpyrrole" containing two 1,3-bis(pyrrolyl)benzene subunits whose synthesis and structure was recently reported.[16] To the extent this assumption holds true, compound **6** is expected to display a folded, wing-like conformation in the solid sate.

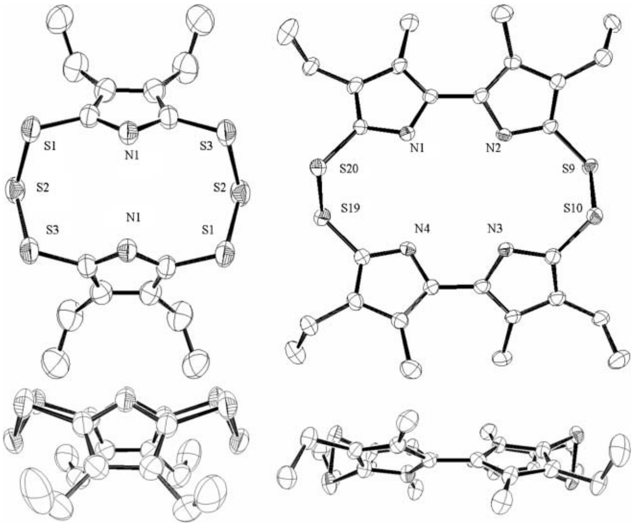


Fig. 1 X-Ray crystal structures of compounds **4** (left) and **5a** (right) showing top and side views.

Currently, the mechanism of formation of macrocycles **4**–**6** is not known. However, it is noteworthy that the same reagent, S_2Cl_2, and identical reaction conditions leads to the formation of products containing a different number of bridging sulfur atoms depending on the choice of the starting material. Thus, in the case of **4**, the starting pyrrole, 3,4-diethylpyrrole, is linked by two sets of three sulfur atoms, while in the case of oligopyrroles **2** and **3** the bridges in the resulting products (**5** and **6**) have only two sulfur atoms. On the other hand, the crude reaction mixtures from which **5** and **6** are obtained are seen to contain a range of other minor products, including ones containing three sulfur atom bridges, as inferred from mass spectrometric analysis.‡ In addition, purified samples of **5** and **6** if warmed gently or allowed to sit under ambient conditions for extended periods of time, give rise to product distributions that resemble those seen initially. This leads us to propose that the sulfur dichloride serves as a source of electrophilic, catenated sulfur atoms and that the specific product(s) obtained are those that are most stable in a thermodynamic, rather than kinetic, sense under the reactions conditions. Consistent with this supposition are the findings that *i*) treatment of bipyrrole **2b** with purified SCl_2 (as opposed to S_2Cl_2) also gives rise to macrocycle **5b** and that *ii*) the use of dichloromethane–THF mixtures, as opposed to pure THF, led to an increased yield of the putative bis(S_3)-linked analogue of **5b**.

To conclude, we describe here a method that allows sulfur bridged oligopyrrolic macrocycles to be synthesized readily and in one step from appropriate α,α′-free pyrrolic precursors. The three test systems isolated to date, **4**, **5**, and **6**, bear important analogy to known carbon-linked oligopyrrole macrocycles, leading us to suggest that they or their putative congeners could have a role to play as ligands for cation complexation or as receptors for anion recognition. In accord with this latter suggestion is the finding that the addition of tetrabutylammonium chloride to $CDCl_3$ solutions of **6** led to a broadening and downfield shift in the pyrrolic NH signal in the ^1H NMR spectrum, as is seen in the case of both calix[4]pyrroles and their larger 1,3-bis(pyrrolyl)benzene derived analogues.[14,16] Current efforts are thus devoted to understanding in greater detail the chemical properties of macrocycles **4**–**6** and the other systems now in hand and to exploring further the S_2Cl_2 coupling procedure from both the mechanistic and preparative perspectives.§¶

David Sanchez-Garcia, Thomas Köhler, Daniel Seidel, Vincent Lynch and Jonathan L. Sessler*
Department of Chemistry and Biochemistry and Institute for Cellular and Molecular Biology, 1 University Station-A5300, The University of Texas, Austin, Texas, 78712-0165, USA.
E-mail: sessler@mail.utexas.edu; Fax: +1 512 471 7550;
Tel: +1 512 471 5009

Notes and references

† **General procedure for the synthesis of the macrocycles**: S_2Cl_2 (0.5 mL, 0.5 mmol, 1 M solution in tetrahydrofuran) was added dropwise to a solution of pyrrole (0.5 mmol) in tetrahydrofuran (40 mL) at −78 °C under argon. The resulting mixture was stirred for 1 h at −78 °C and then allowed to warm up to room temperature. The solvent was removed *in vacuo* at 23 °C. The residue was purified *via* column chromatography on silica gel (hexanes–ethyl acetate 2:3).

‡ MS (CI^+) data for presumed bis(S_3)- and mono(S_3)-linked analogues of **5b** and **6**: $M^+ = 677$, 645 and $M^+ = 604$, 572, respectively.

§ Selected characterization data for **4**: yellow powder (22 mg, 21%). δ_H (400 MHz, tetrahydrofuran-d_8): 1.01 (t, J = 7.2 Hz, 12H), 2.52 (q, J =

7.2 Hz, 8H), 11.20 (s, br, 2H); δ_C (400 MHz, tetrahydrofuran-d_8): 15.9, 18.3, 121.5, 132.6. HRMS (CI): calc. for $C_{16}H_{22}N_2S_6$ (M^+), 434.0107. Found 434.0102.

For **5a**: yellow powder (47 mg, 34%). δ_H (300 MHz, DMSO-d_6): 1.08 (t, J = 6.3 Hz, 12H), 1.89 (s, 12H), 2.52 (q, J = 6.3 Hz, 8H), 11.12 (s, 4H); δ_C (400 MHz, tetrahydrofuran-d_8): 9.9, 15.8, 18.2, 116.0, 118.1, 125.9, 131.9. HRMS (CI): calc. for $C_{28}H_{36}N_4S_4$ (M^+), 556.1823. Found 556.1803.

For **6**: yellow powder (36 mg, 27%). δ_H (400 MHz, tetrahydrofuran-d_8): 6.35 (m, 4H), 6.6 (m, 4H), 7.34 (t, J = 7.6 Hz, 2H), 7.54 (d, J = 7.6 Hz, 4H), 7.97 (s, 2H), 11.94 (s, br, 4H); δ_C (400 MHz, tetrahydrofuran-d_8): 108.2, 120.2, 120.8, 122.3, 122.5, 129.4, 133.0, 137.2. HRMS (FAB): calc. for $C_{28}H_{19}N_4S_4$ (M − H), 539.0493. Found 539.0502.

¶ Crystallographic summary for **4**·THF: well formed orange prisms were grown by slow evaporation from hexanes. $C_{16}H_{22}N_2S_6\cdot(C_4H_80)$, M = 510.12, monoclinic, $C2/c$ (No. 15), Z = 4 in a cell of dimensions: a = 18.6529(3), b = 8.898(1), c = 15.4412(3) Å, β = 96.589(1)°, V = 2545.9(3) Å^3, ρ_{calc} = 1.32 g cm^{-3}, μ = 0.552 mm^{-1}, $F(000)$ = 1072. A total of 4743 reflections were measured, 2921 unique (R_{int} = 0.020), on a Nonus Kappa CCD using graphite monochromatized Mo Kα radiation (λ = 0.71073 Å) at 153 K. The structure was refined on F^2 to an R_w = 0.0841, with a conventional R = 0.0363 (2016 reflections with $F_o > 4[\sigma(F_o)]$), and a goodness of fit = 1.03 for 155 refined parameters. CCDC 260322.

Crystallographic summary for **5a**·(DMSO)$_4$: well formed orange prisms were grown by slow evaporation from DMSO. $C_{28}H_{36}N_4S_4\cdot(C_2H_6S0)_4$, M = 873.8, monoclinic, $P2_1/n$ (No. 14), Z = 4 in a cell of dimensions: a = 15.9670(3), b = 19.1060(5), c = 16.5190(4) Å, β = 119.053(1)°, V = 4405.3(2) Å^3, ρ_{calc} = 1.31 g cm^{-3}, μ = 0.446 mm^{-1}, $F(000)$ = 1856. A total of 17043 reflections were measured, 9859 unique (R_{int} = 0.072), on a Nonus Kappa CCD using graphite monochromatized Mo Kα radiation (λ = 0.71073 Å) at 153 K. The structure was refined on F^2 to an R_w = 0.184, with a conventional R = 0.101 (5806 reflections with $F_o > 4[\sigma(F_o)]$), and a goodness of fit = 1.29 for 405 refined parameters. CCDC 260321.

See http://www.rsc.org/suppdata/cc/b5/b500735f/ for crystallographic data in .cif or other electronic format.

1 L. R. Milgrom, *The Colours of Life. An Introduction to the Chemistry of Porphyrins and Related Compounds*, Oxford University Press, Oxford, 1997.

2 *Expanded Contracted and Isomeric Porphyrins*, ed. J. L. Sessler and S. J. Weghorn, Elsevier, Oxford, 1997, pp. 520.

3 J. L. Sessler, A. Gebauer and S. J. Weghorn, "Expanded Porphyrins" in *The Porphyrin Handbook*, ed. K. M. Kadish, K. M. Smith and R. Guilard, Academic Press, San Diego, CA, 2000, vol. 2, ch. 9.

4 J. L. Sessler, A. Gebauer and E. Vogel, "Porphyrin Isomers" in *The Porphyrin Handbook*, ed. K. M. Kadish, K. M. Smith and R. Guilard, Academic Press, San Diego, CA, 2000, vol. 2, ch. 8.

5 J. L. Sessler and D. Seidel, *Angew. Chem. Int. Ed.*, 2003, **42**, 5134.

6 W. B. Callaway, J. Veauthier and J. L. Sessler, *J. Porphyrins Phthalocyanines*, 2004, **8**, 1.

7 A noteworthy example is provided by verdoheme, a green iron porphyrin with an oxygen atom in place of one of the bridging methine units (*meso* carbons). See for instance: K. T. Nguyen, S. P. Rath, L. Latos-Grazynski, M. M. Olmstead and A. L. Balch, *J. Am. Chem. Soc.*, 2004, **126**, 6210; S. Saito and H. A. Itano, *J. Chem. Soc., Perkin. Trans 1*, 1986, 1.

8 For interesting examples of heteroporphyrinoids bridged by phosphorus atoms, see: G. Märkl, J. Amrhein, T. Toiber, U. Stieble and P. Kreitmeier, *Tetrahedron*, 2000, **58**, 2251.

9 M. J. Broadhurst, R. Grigg and A. W. Johnson, *J. Chem. Soc. D*, 1970, **13**, 807; M. J. Broadhurst, R. Grigg and A. W. Johnson, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1124.

10 Corrole by S extrusion: *cf.* ref. 9 and: R. L. N. Harris, *Tetrahedron Lett.*, 1969, **42**, 3689; J. L. Sessler and S. J. Weghorn, *Expanded Contracted and Isomeric Porphyrins*, Elsevier, Oxford; 1997, ch. 2, pp. 520.

11 L. S. Konstantinova, O. A. Rakitin and C. W. Rees, *Chem. Commun.*, 2002, 1204.

12 M. Barbier and M. Devys, *J. Heterocycl. Chem.*, 1989, **26**, 1, 265.

13 Various mono-S linked open chain pyrroles: B. Ghosh and D. A. Lightner, *J. Heterocycl. Chem.*, 2003, **40**, 6, 1113; Q. Chen and D. Dolphin, *Synthesis*, 2001, **1**, 40; A. K. Tipton, D. A. Lightner and A. F. McDonagh, *J. Org. Chem.*, 2001, **66**, 1832; M. Devys and M. Barbier, *Synthesis*, 1990, **3**, 214; H. Falk and H. Floedl, *Monatsh. Chem.*, 1987, **120**, 45.

14 P. A. Gale, J. L. Sessler, V. Kral and V. Lynch, *J. Am. Chem. Soc.*, 1996, **118**, 5140; P. A. Gale, P. Anzenbacher, Jr. and J. L. Sessler, *Coord. Chem. Rev.*, 2000, **222**, 57.

15 E. Vogel, M. Koecher, H. Schmickler and J. Lex, *Angew. Chem.*, 1986, **98**, 262; E. Vogel, P. Koch, X.-L. Hou, J. Lex and M. Lausmann, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1600–4.

16 J. L. Sessler, D. An, W.-S. Cho, V. Lynch and M. Marquez, *Chem. Eur. J.*, 2005, DOI: 10.1002/chem.200400894.