# Synthesis of macrobicyclic tetrathiafulvalenophanes with three TTF bridges

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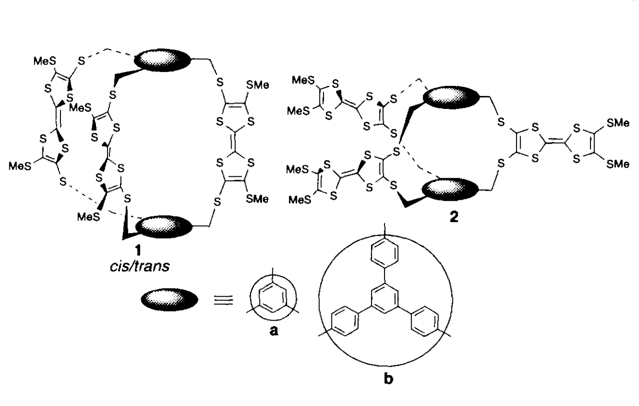
**Using a stepwise selective protection–deprotection of tetrathiafulvalene (TTF)-thiolates under high dilution conditions, the first three-dimensional macrobicyclic tetrathiafulvalenophanes are readily prepared.**

The molecular design of three-dimensionally bridged macropolycyclic compounds is currently a challenge in synthetic chemistry[1] and incorporation of redox-active groups into such molecules is of interest for the preparation of macropolycyclic receptor molecules[2] such as the Cram carcerand synthesis.[3a] A redox active three dimensional ferrocenyl cryptand must also be mentioned.[3b] Systems of this type can in principle be designed to signal electrochemically the binding of any charged or neutral guest. Tetrathiafulvalene (TTF) is a well known redox-active compound and a large number of TTF derivatives has been synthesised during the last two decades mainly with the aim of preparing organic conductors and superconductors.[4] The recent combination of TTF chemistry and supramolecular chemistry has led to the construction of new elaborated TTF systems[5] such as tetrathiafulvalenophanes[6] containing one or two TTF units. In the majority of the reports, the TTF core is prepared in the last step by a coupling reaction between two 1,3-dithiole moieties. Following this strategy, a bis-TTF-belt[7] and criss cross-overlapped tetrathiafulvalenophanes[8] have been prepared recently. However, the synthesis of more elaborated macropolycycles requires another synthetic strategy. We have recently developed a new strategy for the incorporation of preformed TTF groups into macrocyclic compounds.[9] Using this methodology, based on the facile protection–deprotection of TTF-thiolates and their subsequent *in situ* alkylation, we have prepared the first macrobicyclic cyclotetrathiafulvalenophanes **1** and **2** (Scheme 1) with three bridges, *via* tris-TTF intermediates **5** and **6**, respectively.[†]

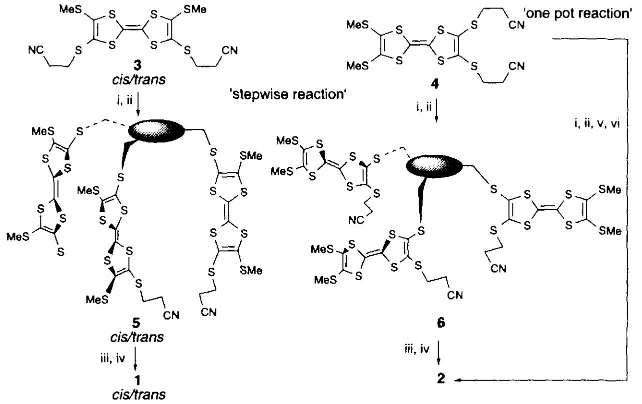
The title compounds were prepared either by a stepwise method or in a one-pot synthesis (Scheme 2). The first step in the reaction sequence involves the monodeprotection of a bisprotected TTF [either 2,7(6)-bis(2′-cyanoethylsulfanyl)-3,6(7)-bis(methylsulfanyl)-tetrathiafulvalene **3** as a mixture of *cis/trans* isomers[9b] or 2,3(2′-cyanoethylsulfanyl)-6,7-bis-(methylsulfanyl)-tetrathiafulvalene **4**[9a]]. Upon treatment of an DMF solution of TTF **3** or **4** (1 equiv.) with cesium hydroxide monohydrate (1.05 equiv.) in methanol, one cyanoethyl protecting group was selectively eliminated whereupon the resulting thiolate was alkylated with either 1,3,5-tris(bromomethyl)benzene[10] or 1,3,5-tris[4-(bromomethyl)phenyl]benzene[11] (0.33 equiv.) in DMF to give tris-TTF **5a** (27–30%), **5b** (34–37%), **6a** (74–77%) and **6b** (75%). The poor yields obtained for compounds **5** relative to the isomeric compounds **6** are explained by the lower selectivity of the thiolate monodeprotection of **3**, which additionally gives rise also to bisdeprotection. Note that compounds **5** are soluble; they show a single spot on TLC and they are obtained as an inseparable mixture of *cis/trans* isomers.

The tripod–tripod coupling for the construction of symmetrical cages **1** and **2** was achieved by simultaneous addition of a DMF–MeOH solution of fully deprotected TTF-thiolate **5** or **6** (1 equiv.) and an DMF solution of the appropriate tribromide (1 equiv.) under high dilution conditions using a perfusor pump. Macrobicycles **1a**, **1b**, **2a** and **2b** were isolated in 43, 39, 68 and 32% yield respectively as yellow or orange powders after purification by column chromatography on silica gel using $CH_2Cl_2$–light petroleum (1 : 1) as eluent. Owing to the presence of *cis/trans* isomers, it was difficult to assign the $^1H$ NMR spectra of **1**. However compounds **1** display three different multiplets for $SCH_3$, $SCH_2$ and aromatic protons. For **1a**, molecular modeling showed that the all-*trans* isomer was also possible due to the high flexibility of molecules of type **1**. The macrocycles **2** exhibited much simpler spectra, due to a more rigid structure and an overall $D_{3h}$ symmetry on the NMR timescale at room temperature in $CDCl_3$.

Because of the relatively high yields in the individual steps of the synthesis of the macrocycles **2a–b**, a one-pot reaction was possible. Treatment of an DMF solution of the diprotected TTF-dithiolate **4** with 1.05 equiv. of caesium hydroxide selectively generated the TTF-monothiolate, which on treatment with 0.33 equiv. of 1,3,5-tris(bromomethyl)benzene gave the tris-TTF **6a** in near quantitative yield, as evidenced by TLC. This compound was immediately thereafter treated (without isolation) with cesium hydroxide to cleave off the remaining protecting groups,



**Scheme 1**



**Scheme 2** *Reagents and conditions*: i, $CsOH{\cdot}H_2O$ (1.05 equiv.), MeOH, DMF, room temp., $N_2$; ii, tribromide (0.33 equiv.), DMF, room temp., $N_2$; iii, $CsOH{\cdot}H_2O$ (3.15–3.6 equiv.), MeOH, DMF, room temp. $N_2$; iv, tribromide (1 equiv.), DMF, high dilution, room temp., $N_2$; v, $CsOH{\cdot}H_2O$ (1.05 equiv.), MeOH, DMF, room temp., $N_2$; vi, tribromide (0.33 equiv.), DMF, room temp., $N_2$

and the resulting trithiolate was realkylated with another 0.33 equiv. of 1,3,5-tris(bromomethyl)benzene without high dilution conditions to give the macrocycle **2a** as the only product in 68% yield after purification by column chromatography. This reaction demonstrates the efficiency of each individual step in the synthesis, since a one-pot reaction of this type would never be possible if an incomplete synthetic step was involved. The synthesis of the macrocycle **2a** is an example of an assisted self-assembly reaction, since the individual components of the macrocycle appears to be pre-programmed for cyclisation due to their complementary geometry.

The redox behaviours of **1**, **2**, **5** and **6** were investigated by cyclic voltammetry (Table 1). Compounds **1b**, **2b**, **5b** and **6b** possessing large spacers between the TTF units exhibit two well-defined three-electron reversible redox waves corresponding to the simultaneous formation of three radical cations followed by three dications at higher potentials. On the contrary compounds **1a**, **2a**, **5a** and **6a** where the TTF groups are linked by the 1,3,5-trimethylenebenzene spacer, CVs show broader waves, shoulders or additional waves for the generation of the radical cation state. In particular compound **2a**, which is a rigid molecule with three TTF groups pointing out of the cavity, only a broad first redox wave is visible indicating weak interactions between the redox centres. On the other hand compound **1a** exhibits three redox waves for the generation of the radical cation state (Fig. 1). This type of electrochemical behaviour in **1a** is explained by the close proximity of the three redox moieties which allows stronger through-space Coulombic interactions.[12] However in the next step, a simultaneous loss of three electrons gives rise to the six-fold charged tris(dicationic) state, as commonly observed,[12b,13] although Coulombic interactions could also play a role.[12a]‡ Preliminary electrocrystallisation of **2a** in the presence of $PF_6^-$ gave a radical cation salt as black plates.

**Table 1** Cyclic voltammetry data: oxidation peak potentials[a]

| Compound[b] | $E_{ox}^1$/V | $E_{ox}^2$/V | $E_{ox}^3$/V | $E_{ox}^4$/V |
|---|---|---|---|---|
| TTF | 0.41 | | | 0.88 |
| **1a** | 0.43 | 0.53 | 0.62 | 0.89 |
| **1b**[c] | 0.53 | | | 0.86 |
| **2a**[c] | 0.58 (br)[d] | | | 0.86 |
| **2b** | 0.54 | | | 0.86 |
| **3** | 0.59 | | | 0.91 |
| **4** | 0.595 | | | 0.91 |
| **5a** | 0.51 (sh)[d] | 0.60 | | 0.875 |
| **5b** | 0.56 | | | 0.87 |
| **6a** | 0.52 (sh) | 0.61[d] | | 0.88 |
| **6b** | 0.58 | | | 0.88 |

[a] Reference electrode: Ag/AgCl; working and counter electrodes: platinum; sweep rate: 0.1 V s$^{-1}$; solvent: $CH_2Cl_2$–MeCN (3:1), supporting electrolyte: $Bu_4NPF_6$ 0.1 mol; [b] concentration of compound: 5 × 10$^4$ mol l$^{-1}$. [c] Concentration of compound <5 × 10$^{-4}$ mol dm$^{-3}$. [d] sh: shoulder, br: broad.

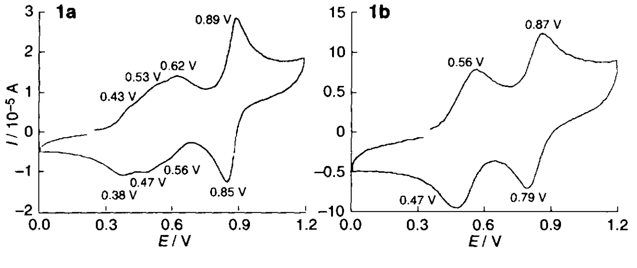


**Fig. 1** Cyclic voltammetry for compounds **1a** and **1b** showing the effect on the CV by the different spacers ($CH_2Cl_2$–MeCN 3:1, $TBAPF_6$ 0.1 mol dm$^{-3}$, Ag/AgCl, sweep rate 0.1 V s$^{-1}$).

## Footnotes

† All new compounds were characterised using NMR ($^1$H, 250 MHz; $^{13}$C 62.5 MHz), MS (EI, PDMS, FABMS), IR, CV and elemental analysis. For compounds **1b** and **5b** the last traces of solvent were impossible to remove, however satisfactory spectral data and isotopic pattern of the molecular ions determined by high resolution MS were obtained. *Spectroscopic data* for Compound **1a** mp 155–160 °C (dec). $^1$H NMR ($CDCl_3$) $\delta_H$ 2.38–2.49 (m, 18 H, $SCH_3$), 3.83–4.09 (m, 12 H, $SCH_2Ar$) and 6.99–7.23 (m, 6 H, arom H). $^{13}$C NMR ($CDCl_3$) $\delta_C$ 19.08, 19.15, 19.26, 19.33, 19.38, 39.74, 40.02, 40.08, 40.16, 40.30, 112.28, 112.39, 123.35, 129.22, 129.27, 129.48, 129.57, 136.79, 136.91, 137.39, 137.46 and 138.04. For Compound **2a** mp 240–243 °C (dec). $^1$H NMR ($CDCl_3$) $\delta_H$ 2.44 (s, 18 H, $SCH_3$), 3.84 (s, 12 H, $SCH_2Ar$)and 7.06 (s, 6 H, arom. H). $^{13}$C NMR 125 MHz ($CDCl_3$) $\delta_C$ 19.19, 40.27, 110.00, 111.83, 127.60, 128.12, 128.90 and 138.24.

‡ An estimate of the number of exchanged electrons in **1a** and **1b** in each redox process was tentatively obtained from the ratio between the area of the different redox waves: for **1a** ($E_{ox}^1 \mid E_{ox}^2 \mid E_{ox}^3)/E_{ox}^4 = 1.25$ and for **1b**, $E_{ox}^1/E_{ox}^2 = 0.98$. This preliminary result suggests that the number of exchanged electrons is the same in each step.

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*Received, 16th November 1995; Com. 5/07494K*