

A Pyrrolo-Tetrathiafulvalene Cage: Synthesis and X-ray Crystal Structure

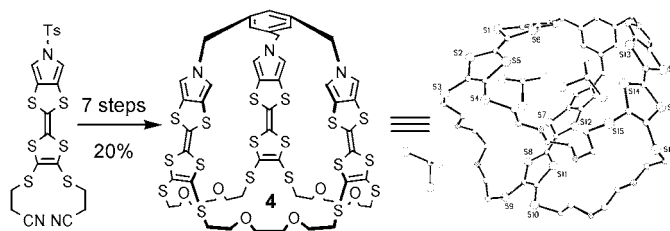
Kent A. Nielsen,[†] Jan O. Jeppesen,^{*,†} Eric Levillain,[‡] Niels Thorup,[§] and
Jan Becher^{*,†}

Department of Chemistry, University of Southern Denmark (Odense University),
Campusvej 55, DK-5230, Odense M, Denmark, Department Ingénierie Moléculaire et
Matériaux Organiques, CNRS UMR 6501, Université d'Angers, 2 Bd Lavoisier,
F-49045 Angers, France, and Department of Chemistry, The Technical University of
Denmark, DK-2800, Lyngby, Denmark

jbe@chem.sdu.dk

Received August 29, 2002

ABSTRACT



A novel type of tetrathiafulvalene-cage **4** containing three monopyrrolo-tetrathiafulvalene units has been prepared employing a general and efficient synthetic approach. X-ray crystal structure analysis revealed that the cage is able to accommodate solvent molecules within a cavity in the solid state.

Cyclophanes^{1,2} are fundamentally important compounds in many aspects of macrocyclic and supramolecular chemistry, and research in this field has expanded rapidly in recent years. Tetrathiafulvalene³ (TTF) and its derivatives have been intensively studied during the past two decades, because of their unique π -electron donor properties. They were origi-

nally prepared for the development of electrically conducting materials and have, as such, been synonymous with the development of molecular organic metals. However, during the past few years, the utility of TTF derivatives as building blocks in macrocyclic and supramolecular chemistry has revealed that the TTF moiety is useful^{3c–e,4} beyond the field of materials chemistry and it has been incorporated into elaborate molecular devices such as sensors,^{4b,c,h} shuttles,^{4d,f}

[†] University of Southern Denmark (Odense University).

[‡] Université d'Angers.

[§] The Technical University of Denmark.

(1) (a) Vögtle, F., Ed. *Cyclophanes I*. In *Topics in Current Chemistry*; Springer: Berlin, Germany, 1983; Vol. 113. (b) Vögtle, F., Ed. *Cyclophanes II*. In *Topics in Current Chemistry*; Springer: Berlin, Germany, 1983; Vol. 115. (c) Vögtle, F. *Cyclophane Chemistry*; Wiley: Chichester, UK, 1993.

(2) (a) Diederich, F. *Cyclophanes*. In *Monographs in Supramolecular Chemistry*; Fraser Stoddart, J., Ed.; The Royal Society of Chemistry: London, UK, 1991. (b) Vögtle, F.; Seel, C.; Windscheif, P.-M. *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Suslick, K. S., Eds.; Pergamon: New York, 1996; Vol. 2, Chapter 7, pp 211–265.

(3) (a) Garin, J. *Adv. Heterocycl. Chem.* **1995**, *62*, 249–304. (b) Schukat, G.; Fanghänel, E. *Sulfur Rep.* **1996**, *18*, 1–294. (c) Bryce, M. R. *J. Mater. Chem.* **2000**, *10*, 589–598. (d) Nielsen, M. B.; Lomholt, C.; Becher, J. *Chem. Soc. Rev.* **2000**, *29*, 153–164. (e) Segura, J. L.; Martín, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 1372–1409.

(4) (a) Jeppesen, J. O.; Perkins, J.; Becher, J.; Stoddart, J. F. *Org. Lett.* **2000**, *2*, 3547–3550. (b) Le Derf, F.; Levillain, E.; Trippé, G.; Gorgues, A.; Sallé, M.; Sebastian, R. M.; Caminade, A. M.; Majoral, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 224–227. (c) Le Derf, F.; Mazari, M.; Mercier, N.; Levillain, E.; Trippé, G.; Riou, A.; Richomme, P.; Becher, J.; Garin, J.; Orduna, J.; Gallego-Planas, N.; Gorgues, A.; Sallé, M. *Chem. Eur. J.* **2001**, *7*, 447–455. (d) Jeppesen, J. O.; Perkins, J.; Becher, J.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2001**, *40*, 1216–1221. (e) Collier, C. P.; Jeppesen, J. O.; Luo, Y.; Perkins, J.; Wong, E. W.; Heath, J. R.; Stoddart, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12632–12641. (f) Jeppesen, J. O.; Becher, J.; Stoddart, J. F. *Org. Lett.* **2002**, *4*, 557–560. (g) Luo, Y.; Collier, C. P.; Jeppesen, J. O.; Nielsen, K. A.; Delonno, E.; Ho, G.; Perkins, J.; Tseng, H.-R.; Yamamoto, T.; Stoddart, J. F.; Heath, J. R. *ChemPhysChem* **2002**, *3*, 519–525. (h) Trippé, G.; Levillain, E.; Le Derf, F.; Gorgues, G.; Sallé, M.; Jeppesen, J. O.; Nielsen, K.; Becher, J. *Org. Lett.* **2002**, *4*, 2461–2464.

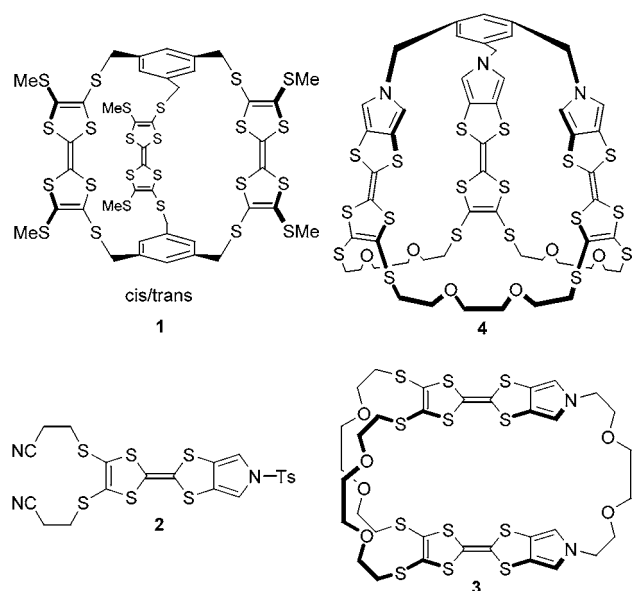


Figure 1.

and switches.^{4c,g} In addition, TTF has also been used for the preparation of macrocyclic compounds, such as TTF-belts,⁵ crisscross TTF-phanes,⁶ and TTF-cages.⁷ Conventional cyclophanes^{1,2} are a fundamentally important class of synthetic host molecules—thus, it is of interest to develop simple routes to TTF cyclophanes, which can act as hosts for electron-deficient guest molecules. Until now, and essentially for synthetic reasons, the TTF unit has mainly been introduced into macrocyclic systems as a tetrathio-TTF moiety.^{3–7} Since the TTF core has a D_{2h} symmetry with four identical potential attachment sites, incorporation of the tetrathio-TTF moiety into macrocyclic systems often results in the isolation of cis/trans isomeric mixtures, as in the case of the TTF-cage^{7b} **1** (Figure 1). This inherent cis/trans isomerism may alter the complexing ability of the host.⁸ This problem can be circumvented using the monopyrrolo-TTF building block⁹

(5) For TTF-belts, see: (a) Adam, M.; Enkelmann, V.; Räder, H.-J.; Röhrich, J.; Müllen, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 309–310. (b) Matsuo, K.; Takimiya, K.; Aso, Y.; Otsubo, T.; Ogura, F. *Chem. Lett.* **1995**, 523–524. (c) Otsubo, T.; Aso, Y.; Takimiya, K. *Adv. Mater.* **1996**, *8*, 203–211. (d) Simonsen, K. B.; Svenstrup, N.; Lau, J.; Thorup, N.; Becher, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1417–1420. (e) Spanggaard, H.; Prehn, J.; Nielsen, M. B.; Levillain, E.; Allain, M.; Becher, J. *J. Am. Chem. Soc.* **2000**, *122*, 9486–9494. (f) Nielsen, K.; Jeppesen, J. O.; Thorup, N.; Becher, J. *Org. Lett.* **2002**, *4*, 1327–1330.

(6) For crisscross-TTF molecules, see: (a) Tanabe, J.; Kudo, T.; Okamoto, M.; Kawada, Y.; Ono, G.; Izuoka, A.; Sugawara, T. *Chem. Lett.* **1995**, 579–580. (b) Takimiya, K.; Shibata, Y.; Imamura, K.; Kashiwara, A.; Aso, Y.; Otsubo, T.; Ogura, F. *Tetrahedron Lett.* **1995**, *36*, 5045–5048. (c) Tanabe, J.; Ono, G.; Izuoka, A.; Sugawara, T.; Kudo, T.; Saito, T.; Okamoto, M.; Kawada, Y. *Mol. Cryst. Liq. Cryst.* **1997**, *296*, 61–76. (d) Takimiya, K.; Imamura, K.; Shibata, Y.; Aso, Y.; Ogura, F.; Otsubo, T. *J. Org. Chem.* **1997**, *62*, 5567–5574. (e) Nielsen, M. B.; Thorup, N.; Becher, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1305–1308. (f) Jeppesen, J. O.; Takimiya, K.; Becher, J. *Org. Lett.* **2000**, *2*, 2471–2473. (g) Takimiya, K.; Thorup, N.; Becher, J. *Chem. Eur. J.* **2000**, *6*, 1947–1954.

(7) For TTF-cages, see: (a) Blanchard, P.; Svenstrup, N.; Becher, J. *Chem. Commun.* **1996**, 615–616. (b) Blanchard, P.; Svenstrup, N.; Rault-Berthelot, J.; Riou, A.; Becher, J. *Eur. J. Org. Chem.* **1998**, 1743–1757.

(8) For instance, it has been shown that only the cis-isomer of a TTF-crown is able to complex cations, see ref 4c.

2 (Figure 1)—which only possesses three attachment sites—and we have very recently succeeded in preparing a TTF-belt **3** (Figure 1) devoid of cis/trans problems. Although the neutral belt **3** has a cavity between the two TTF moieties it was not able to accommodate electron-deficient guest, such as 7,7,8,8-tetracyano-*p*-quinodimethane (TCNQ), within this molecular cavity.¹⁰ One solution to this problem might be to enlarge the cavity surrounded by TTF moieties and design cyclophanes containing more than two TTF moieties.

Here, we report such an accomplishment and describe a general and efficient method for the preparation of TTF-cages employing the monopyrrolo-TTF building block **2**, together with a crystal structure analysis of the TTF-cage **4**. Furthermore, we describe our preliminary complexation studies between the TTF-cage **4** and 1,3,5-trinitrobenzene, which have been carried out in solution using ¹H NMR and UV–vis spectroscopies.

The TTF-cage **4** was designed to participate in host–guest chemistry,¹¹ and a Cory–Pauling–Koltun (CPK) modeling suggests that our target, tris-TTF-cage **4**, has a rather larger and more flexible cavity that those of **1** and **3** thereby increasing the likelihood for **4** to act as a host molecule for electron-deficient guests such as 1,3,5-trinitrobenzene.¹² Retrosynthetic analyses of the TTF-cage **4** reveal a range of possible disconnections for this novel class of TTF-cage molecules. The approach that was eventually adopted allows the rim-spacers to be identically or varied individually, thus allowing functional groups, e.g., hydrogen-donor/acceptor or flexible/rigid, long/short, or other types of spacers, to be incorporated into the cage. The number of TTF moieties can also easily be changed from three to four, five, etc. Furthermore, it is possible to change the size and geometry of the top-spacer in the final step. The flexibility in design and straightforward synthesis of this novel class of TTF-cage molecules make them useful for studying their complexation properties with appropriate guest molecules. In the TTF-cage **4** presented in this Letter triethyleneglycol units were chosen as the rim-spacers and 1,3,5-trimethylbenzene as the top-spacer to balance out flexibility and rigidity.

The TTF cage **4** was synthesized as illustrated in Schemes 1 and 2. A THF solution of the cyanoethyl-protected monopyrrolo-TTF building block⁹ **2** was treated with 1.0 equiv of CsOH·H₂O. This procedure generated the TTF-monothiolate, which was alkylated with 1.0 equiv of 2-[2-(2-iodoethoxy)ethoxy]ethanol (**5**). Subsequently, deprotection/alkylation with 1.0 equiv of CsOH·H₂O and 1.0 equiv of **5**, respectively, gave (Scheme 1) the TTF derivative **6** in 88% yield. Mesylation (96%) of **6** in CH₂Cl₂ followed by treatment of **7** with NaI in Me₂CO gave (86%) the TTF

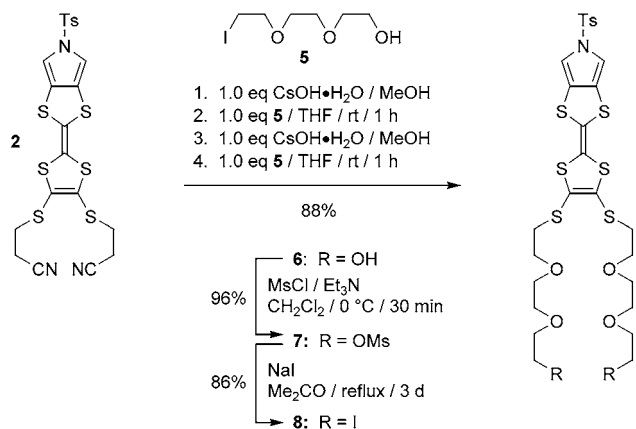
(9) (a) Jeppesen, J. O.; Takimiya, K.; Jensen, F.; Becher, J. *Org. Lett.* **1999**, *1*, 1291–1294. (b) Jeppesen, J. O.; Takimiya, K.; Jensen, F.; Brimert, T.; Nielsen, K.; Thorup, N.; Becher, J. *J. Org. Chem.* **2000**, *65*, 5794–5805.

(10) A solid-state X-ray crystal structure analysis of the charge transfer (CT) complex **3**·TCNQ revealed that TCNQ is associated outside (alongside) one of two TTF donors, see ref 5f.

(11) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, Germany, 1995.

(12) In contrast to previous synthesized TTF-cage structures, **4** has the π -electrons from the TTF-moieties pointing into the cavity and thereby increasing the possibility for complexation with electron-deficient guests.

Scheme 1. Synthesis of the TTF Derivative **8**, Starting from the Monopyrrolo-TTF Building Block **2**



derivative **8**. The TTF derivative **9** (Scheme 2) was prepared according to the literature procedure.^{5f} Macrocyclization of the 36-member-ring system **10** was performed using high-dilution conditions. A THF solution of **9** was treated with 2.0 equiv of CsOH·H₂O. This procedure generated the TTF-bisthiolate, which was transferred to a syringe. TTF **8** was at the same time dissolved in THF and transferred to a second syringe. By employing a perfuser pump the two solutions were simultaneously pumped to a reaction flask over a period of 6 h, affording (Scheme 2) the trisTTF-macrocycle **10** in extraordinary 81% yield. Removal of the tosyl protecting groups was carried out in 88% yield by refluxing **10** in a 1:1 mixture of THF-MeOH in the presence of an excess of NaOMe. Finally, the TTF-cage¹³ **4** was obtained in 45% yield following *N*-alkylation of the three pyrrole units in **11**¹⁴ with 1,3,5-tris(bromomethyl)benzene (**12**) in DMF containing NaH.

Scheme 2. Synthesis of the TTF-Cage **4**

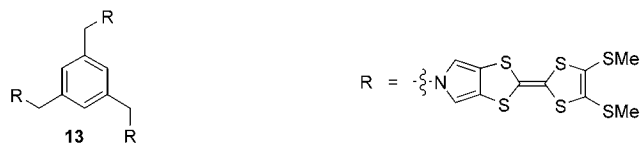
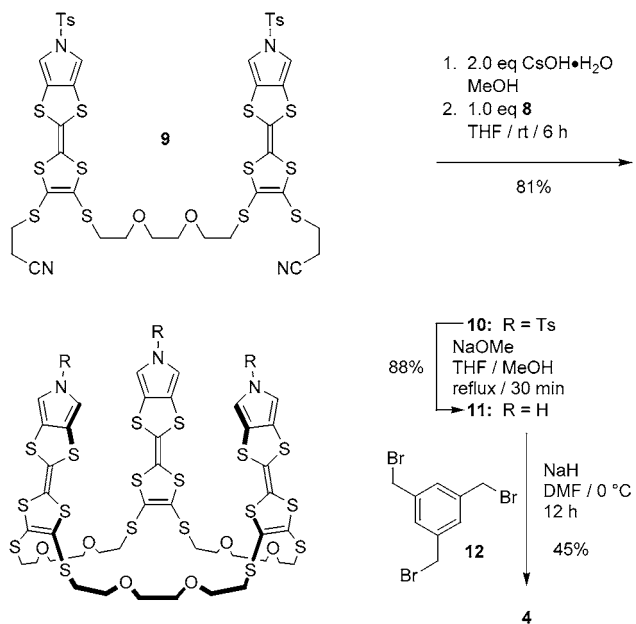


Figure 2. Structure of the model compound **13**.

A comparison of the ¹H NMR spectra (CDCl₃, 298 K) of the flexible macrocycle **11**, the model compound¹⁵ **13** (Figure 2), and the more rigid TTF-cage **4** revealed (Table 1)

Table 1. Selected ¹H NMR Spectroscopic Data (δ Values in ppm) for **4**, **11**, and **13** in CDCl₃ at 298 K

compd	SCH ₂	pyrrole-H	Ar-H
4	2.87–2.94 and 3.01–3.10	6.40	7.21
11	3.00	6.61	
13		6.43	6.75

significant changes in the chemical shift values. For the signal associated with the six pyrrole protons an upfield shift ($\Delta\delta = 0.21$ ppm) was observed between **4** and **11**. The signals associated with the twelve SCH₂ protons in **4** split up into two multiplets each integrating to six protons—presumably six of the SCH₂ protons are pointing into the cage and six out of the cage. In addition, a downfield shift ($\Delta\delta = 0.46$ ppm) was observed for the three aromatic protons, when comparing the ¹H NMR spectra of the flexible model compound **13** and the rigid cage **4**. These findings clearly indicate that a closure of the flexible macrocycle **11** to the somewhat more rigid TTF-cage **4** has taken place.

The redox behavior of the TTF-cage **4** was investigated in solution by cyclic voltammetry (CV). The CV¹⁶ of **4**, performed at 100 mV s⁻¹ at semi-infinite diffusion conditions in THF (Figure 3), exhibits two oxidation waves correspond-

(13) **Data for TTF-cage 4:** ¹H NMR (300 MHz, CDCl₃, 298 K) δ 2.87–2.94 (m, 6H), 3.01–3.10 (m, 6H), 3.63 (s, 12H), 3.63–3.67 (m, 12H), 4.86 (s, 6H), 6.40 (s, 6H), 7.21 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, 298 K) δ 35.1, 54.4, 70.1, 70.4, 109.8, 112.1, 120.1, 121.5, 127.6, 129.0, 138.3; MS-(FAB) *m/z* 1377 (M⁺, 88), 1378 (M⁺ + 1, 75), 1379 (M⁺ + 2, 100); 1380 (M⁺ + 3, 66), 1381 (M⁺ + 4, 53); mp 153–153.5 °C. Anal. Calcd for C₅₁H₅₁N₃O₆S₁₈·0.75CH₂Cl₂ (1379.2): C, 43.08; H, 3.67; N, 2.91. Found: C, 42.98; H, 3.75; N, 2.79.

(14) **Data for macrocycle 11:** ¹H NMR (300 MHz, CDCl₃, 298 K) δ 3.00 (t, *J* = 6.2 Hz, 12H), 3.62 (s, 12H), 3.67 (t, *J* = 6.2 Hz, 12H), 6.61 (d, *J* = 2.0 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃, 298 K) δ 35.0, 69.2, 69.6, 107.3, 110.6, 117.0, 121.6, 126.8; MS(FAB) *m/z* 1263 (M⁺, 98), 1264 (M⁺ + 1, 72), 1265 (M⁺ + 2, 100), 1266 (M⁺ + 3, 59), 1267 (M⁺ + 4, 46); mp 118–120 °C. Anal. Calcd for C₄₂H₄₅N₃O₆S₁₈ (1264.9): C, 39.88; H, 3.59; N, 3.32. Found: C, 40.21; H, 3.32; N, 3.34.

(15) **Data for 13:** ¹H NMR (300 MHz, CDCl₃, 298 K) δ 2.43 (s, 18H), 4.91 (s, 6H), 6.43 (s, 6H), 6.75 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, 298 K) δ 19.2, 53.8, 112.8, 112.9, 119.9, 124.9, 127.2, 139.0, one carbon is missing; MS(FAB) *m/z* 1119 (M⁺); mp 220–220.5 °C.

(16) CV was performed using a 0.43 mM solution of **4** in anhydrous THF with *n*-Bu₄NPF₆ (0.40 M) as supporting electrolyte and Ag/AgCl as reference electrode. Electrochemical experiments were carried out in a glovebox containing dry, oxygen-free (<1 ppm) argon, at room temperature. The number of electron processes were calculated by using dichloronaphthoquinone as internal reference.

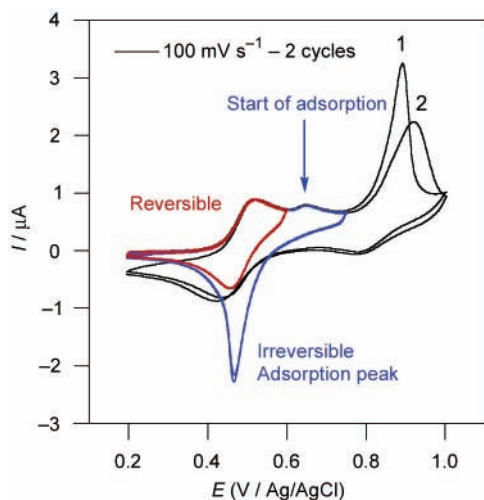


Figure 3. Cyclic voltammogram of **4** recorded in THF.

ing to the generation of the radical cation (TTF^{•+}) and the dication (TTF²⁺) respectively at ~ 0.48 and ~ 0.85 V vs Ag/AgCl. At 100 mV s^{-1} , the first wave is a classical reversible process. A weak broadening of this oxidation wave is observed. However, it is not significant enough to make any conclusion whether intra- or intermolecular interactions are taking place between the TTF moieties. The second wave reveals that a strong adsorption to the electrode is taking place, probably due to the insolubility of the dication in THF. Thin layer cyclic voltammetry (TLCV) showed that the first oxidation wave corresponds to three one-electron processes. The second wave is probably a similar process but the adsorption phenomenon observed does not allow any unequivocal conclusion to be made.

Single crystals of **4** suitable for X-ray diffraction analysis were obtained by crystallization¹⁷ from CDCl_3 and the molecular structure of **4** is illustrated in Figure 4. The unit cell contains two TTF-cage molecules and six CDCl_3 molecules, three per TTF-cage. Two of the CDCl_3 molecules reside inside the cavity of **4**, while the other is positioned outside the cage. None of the CDCl_3 molecules appears to be involved in any strong interactions with the TTF-cage. Somewhat surprisingly, no intra- or intermolecular stacking between the TTF moieties was observed, and only one shorter nonbonding $\text{S}\cdots\text{S}$ distance was observed. The fact that no intramolecular stacking is observed and that two CDCl_3 molecules reside inside the cavity of the solid-state structure of **4** give some promise that **4** may act as a host molecule for other guest molecules as well.

Preliminary complexation studies were carried out for 1:1 solutions¹⁸ of the TTF-cage **4** (host) and 1,3,5-trinitrobenzene (guest) using UV–vis and ^1H NMR spectroscopies. Addition of 1.0 equiv of 1,3,5-trinitrobenzene to a solution of **4** (5.0

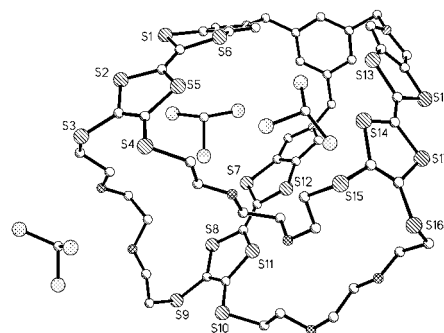


Figure 4. Crystal structure of the TTF-cage **4**· 3CDCl_3 . Hydrogen atoms are omitted for clarity.

$\times 10^{-4} \text{ M}$) resulted in an immediate color change from orange to light green and the appearance of a weak CT absorption band, centered on λ_{max} 646 nm, indicating that a complexation between host and guest is taking place. The ^1H NMR spectrum¹⁹ (250 MHz) recorded on a 1:1 mixture of **4** and 1,3,5-trinitrobenzene at 298 K in CDCl_3 revealed weak upfield shifts for the resonances associated with the three aromatic protons ($\Delta\delta = 0.09$ ppm) on the 1,3,5-trinitrobenzene unit and the six pyrrole protons ($\Delta\delta = 0.05$ ppm) on **4**, respectively. Downfield shifts were observed for the three aromatic protons ($\Delta\delta = 0.10$ ppm) on **4** and for one of the SCH_2 multiplets²⁰ (2.87 – 2.94 ppm, $\Delta\delta = 0.03$ ppm), respectively. The fact that only one of the SCH_2 multiplets is downfield shifted might indicate that 1,3,5-trinitrobenzene is complexed inside the cage.

In summary, an efficient and flexible synthetic strategy for the preparation of TTF-cages has been developed. From ^1H NMR and UV–vis spectroscopies it was shown that complexation between the TTF-cage **4** (host) and 1,3,5-trinitrobenzene (guest) took place in solution. However, these results do not provide any solid information regarding whether the complexation is taking place inside or outside the cavity of the host molecule **4**. To answer this question a solid-state structure determination of the complex is required. The synthetic strategy described allows us to make related TTF-cages in which the rim- and top-spacers—together with the number of TTF moieties—can be varied to fine-tune the complexation properties of the host with 1,3,5-trinitrobenzene or other guests.

Acknowledgment. We thank the University of Southern Denmark for a Ph.D. Scholarship to K.A.N. and Carlsberg-fondet for financial support to J.O.J.

Supporting Information Available: Crystallographic data for **4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL026816H

(17) Crystals of **4** utilized in the X-ray analysis crystallized out from a CDCl_3 solution of **4** used for NMR spectroscopy.

(18) A CPK model inspection revealed that only one 1,3,5-trinitrobenzene (guest) can be accommodated inside the cage (host).

(19) No line broadening indicating the radical character of the cage was observed.

(20) The resonance associated with the other SCH_2 multiplet (3.01 – 3.10 ppm) did not reveal any shift upon complexation.