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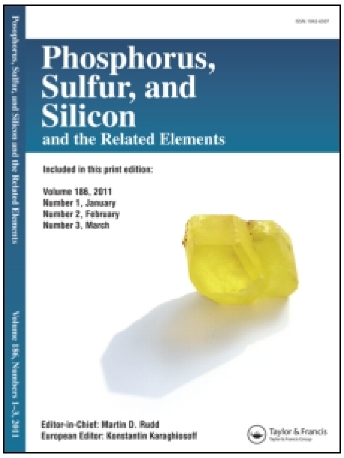

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Tetrathiafulvalenes: Versatile Building Blocks in Macrocyclic and Supramolecular Chemistry

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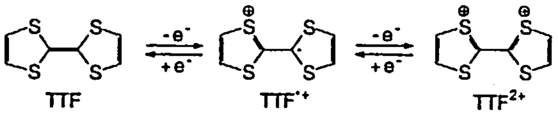
A complete set of tetrathiafulvalene (TTF) based building blocks have been developed, allowing easy construction and preparation of complex molecular assemblies. The facile deprotection of the 2-cyanoethyl group, a versatile protecting group for 1,3-dithiolium-2-thione-4,5-dithiolates as well as TTF-thiolates, is an excellent method for the incorporation of TTF units into macrocyclic and supramolecular compounds. This selective and stepwise protection-deprotection methodology have been used extensively by our group for the preparation of two and three dimensional macrocyclic (mono-, bis- and tricyclic) as well as TTF-based supramolecular systems. Recent examples described here are: Dendrimeric and oligo-TTF's, three dimensional tetrathiafulvalenophanes, TTF-containing catenanes and donor acceptor systems based on TTF as the donating group.

Keywords: Tetrathiafulvalenes; macrocycles; catenanes; dendrimers; cyclophanes

INTRODUCTION

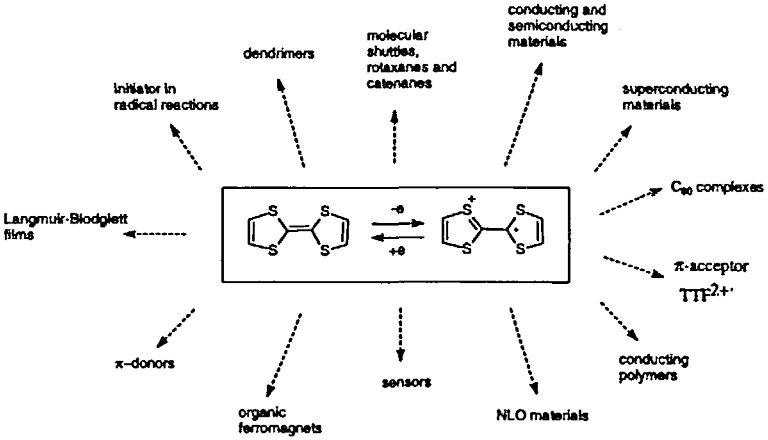
Tetrathiafulvalene (TTF) is a reversible, stable two electron donor (Scheme 1) which has been a subject of high interest for more than two decades[1].



Thus, a large number of TTF derivatives have been synthesized with the aim of preparing organic conductors and superconductors. However, due to the combination of chemical stability and suitable π-donor properties the utility of TTF derivatives in the field of supramolecular chemistry has led to new elaborate TTF systems[2]. Macrocycles and cyclophanes are still fundamental structures in the majority of supramolecular systems and properties of the TTF group makes it a prime candidate for the incorporation into macrocyclic and supramolecular systems. There are two main research areas where the TTF-type π-donors are of special interest; *i:* the application of TTF-derivatives as π-donors in supramolecular chemistry and *i:* the more "classical" topic of molecular conductors and superconductors.

New materials based on TTF-containing molecular systems may show usefull properties because the TTF-group has a unique combination of properties: 1) oxidation to the cation radical and the dication species occurs sequentially and reversibly; 2) the oxidation potentials are dependent on the substituents on the TTF-ring and can therefore be varied; 3) TTF-cation radicals are thermodynamically very stable; 4) oxidized TTF-units (radical cation, TTF^{2+}) have a high propensity to form dimers or higher aggreates with high internal electron mobility. Finally; as already mentioned 5) the neutral TTF-group is an excellent π-donor, whereas on the other hand the TTF-dication may also act as an acceptor, it is therefore obvious to use these properties in the design and synthesis of for example self-assembling molecular systems in combination with complementary acceptors and donors.

The electronic properties of conductors based on radical ion salts are extremely dependent on the stabilisation of a multidimensional chalcogen-chalcogen network in the solid state. It is almost impossible to predict and control crystal packing at the molecular level[3]. The rationale behind the idea of covalent linking of the TTF-groups in oligo-TTFs is that this may increase the dimensionality in the solid state. It is evident that the degree of conformational freedom of a bis-TTF-system will decrease by changing the connection from one to two linkers at the 2,3- or 2,7-positions of the TTF. For oligomeric TTFs with more than two TTF-units many more combinations are possible, both 2- and 3-dimensional.



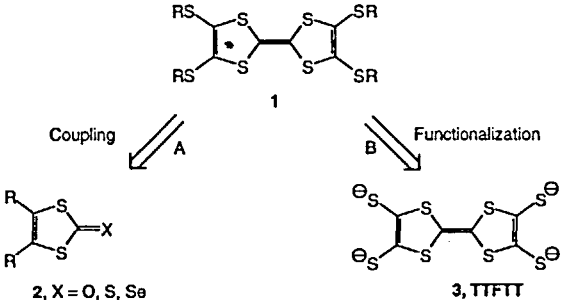
Examples of applications where π-donors derived from TTFs have been used.

Prior to our work, a simple and practical method for incorporation of the TTF-group in larger structures was unknown. We therefore decided to improve this situation and in the last eight years we have been interested n the incorporation of TTF into macrocyclic and supramolecular compounds.

THE BUILDING BLOCKS

TTF starting materials, protection and deprotection

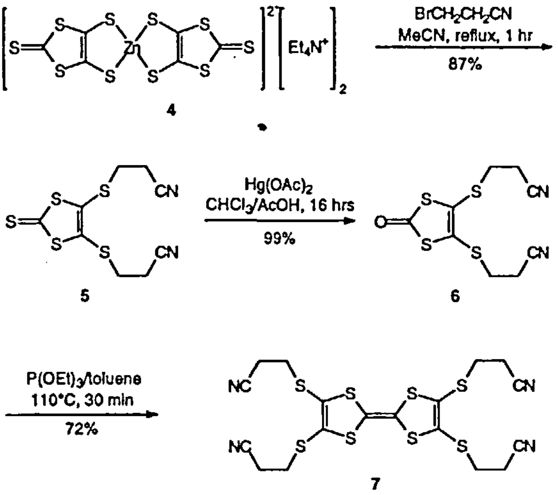
There are two standard synthetic strategies for the preparation of structurally modified tetraalkylthio TTF's (**1**):



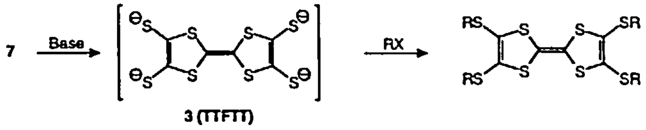
i: disconnection A; the coupling method and *ii:* disconnection B; functionalization of a preformed tetrathiafulvalene tetrathiolate (**3**, TTFTT).

In many cases the usual synthetic methods (disconnection A) tends to give intramolecular coupled products rather than larger oligomers when starting from bis-1,3-dithiole-2-thiones. Further, a number of substituted 1,3-dithioles are unable to survive the reaction conditions in the coupling step, especially systems containing ester-, thioester-, urethane-, alcohol or carbonyl functionalities.

Early on we realized that the most successful route to macrocyclic and oligomeric TTF's should be based on a preformed tetrathia-TTF moiety and hence would require a stable and versatile protecting group for the thiolate function, later allowing us to take advantage of the high nucleophilicity of the thiolate sulfur. The 2-cyanoethyl group turned out to be an almost ideal protection group for 1,3-dithiole-4,5-dithiolate and TTF thiolates[4].



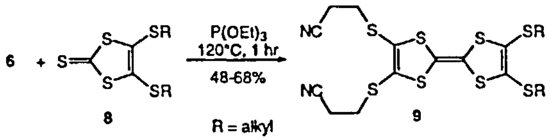
2,3,6,7-Tetrakis(2-cyano-ethylthio)TTF (7) is an excellent precursor for TTFTT 3. Generation of TTFTT is achieved in quantitative yield, as evidenced by the yields in the subsequent alkylation step. Treatment with the appropriate electrophile gave the well known compounds such as for example bisethylenedithio tetrathiafulvalene (BEDT-TTF) in almost quantitatively yields[4].



Several methods are effective for the deprotection of 7. Of these methods, the deprotection using a methanolic solution of caesium hydroxide in dimethylformamide is routinely used in our laboratory. Because TTF-thiolates are sensitive to oxidation all reactions must be carried out under an inert atmosphere.

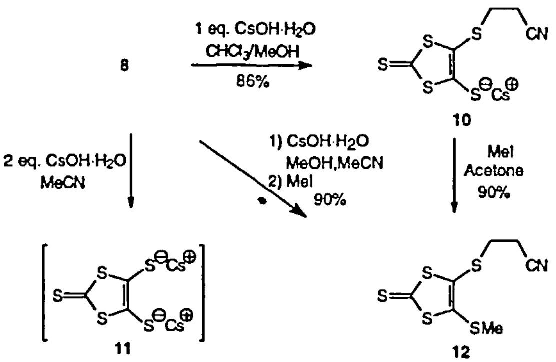
Bases used for deprotection	solvent	time
NaOEt	EtOH	4 h
NaH	DMF	1 h
Bu_4NOH, MeLi or LDA	THF	5 min
CsOH in MeOH	THF or DMF	5 min

This methodology has been succesfully employed in the preparation of a range of the bis-cyanoethyl protected TTF's **9**. Thus reaction of an equimolar mixture of 4,5-bis(alkylthio)-1,3-dithiole-2-thiones **8** and 4,5-bis(2-cyanoethylthio)-1,3-dithiole-2-one **6** in neat triethyl phosphite at 120°C gave the unsymmetrical (cross coupled) TTF's in satisfying yields (48-68%)[5].



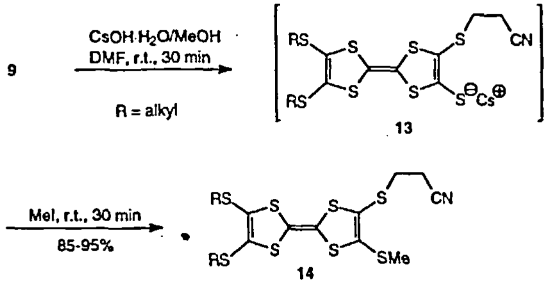
The cyanoethyl protected TTFs are soluble in standard solvents and hence easy to isolate by chromatography, usually the compounds are stable and well crystalline.

Monodeprotection

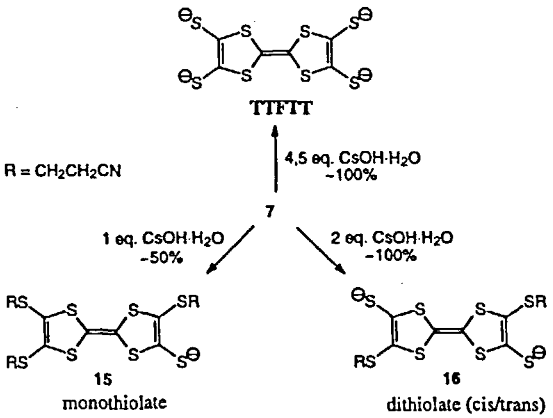


Treatment of a chloroform solution of thione **8** ($R=COOC_6H_5$) with one equivalent of caesium hydroxide monohydrate in methanol selectively generated the mono caesium salt **10**, which precipitated from the reaction mixture in excellent yield[5, 6].

We had already noted the enhanced stability of the DMIT caesium thiolates compared to their sodium and potassium analogues[7]. Since fortunately the caesium mono thiolate **10** is considerably more stable than the corresponding dicaesium salt **11** (prepared by using two eq. base in acetonitrile, it can be stored in the air for several months), and provides an excellent precursor to unsymmetrally substituted 1,3-dithiole-2-thiones. This facile monodeprotection was then extended to the unsymmetrically TTF series **9**. Thus, when a dimethylformamide solution of the appropriate TTF **9** was treated dropwise with a methanol solution of caesium hydroxide monohydrate (one equivalent), the TTF-monothiolate **13** was generated selectively. Subsequent quenching without isolation of the thiolate with iodomethane (or another lectrophile) gave the methylthio substituted TTF's **14** in near quantitative yields.

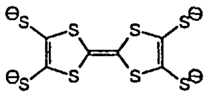


Using the key starting material 2,3,6,7-tetrakis(2-cyanoethylthio)TTF **7** and the appropriate amount of caesium hydroxide gives access to TTFTT **3**, as well as the monothiolate **15** and bisthiolate **16**.

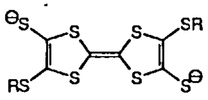


Normally the TTF-thiolates are not isolated and instead they are directly realkylated with electrophiles. Note that thiolates such as **14**contain a latent thiolate function which can be liberated in a later reaction-sequence by subsequent deprotection and realkylation.

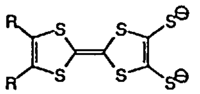
Complete set of TTF building blocks



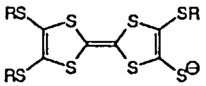
TTFTT



2,6(7)-dithiolate



2,3-dithiolate



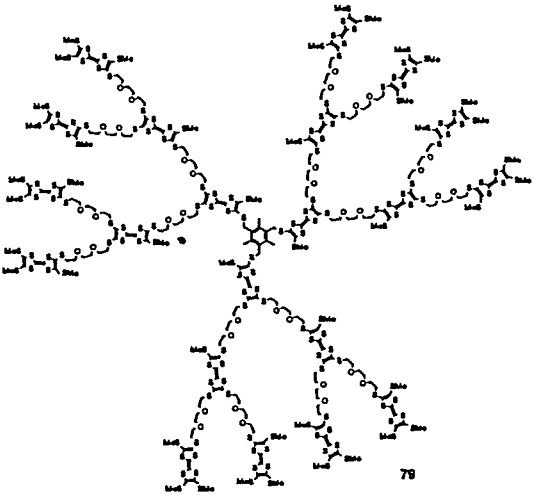
monothiolate

These building blocks either alone or in combinations will allow construction of more elaborate oligo-TTF systems, not forgetting further possibilities using the relative effective intramolecular phosphite coupling of bis-1,3-dithiole-2-thiones or -ones. In the last section we will focus on the versatility of the building blocks for the incorporation of TTF into macrocyclic and supramolecular assemblies using selective monodeprotection/alkylation[8].

MACROCYCLIC AND SUPRAMOLECULAR TTF-SYSTEMS

Dendrimeric TTFs

Redox active dendrimers are of interest for a number of reasons[9], thus using the building blocks outlined above a number of TTF based dendrimers have been obtained via a stepvise convergent synthesis[10], for example:



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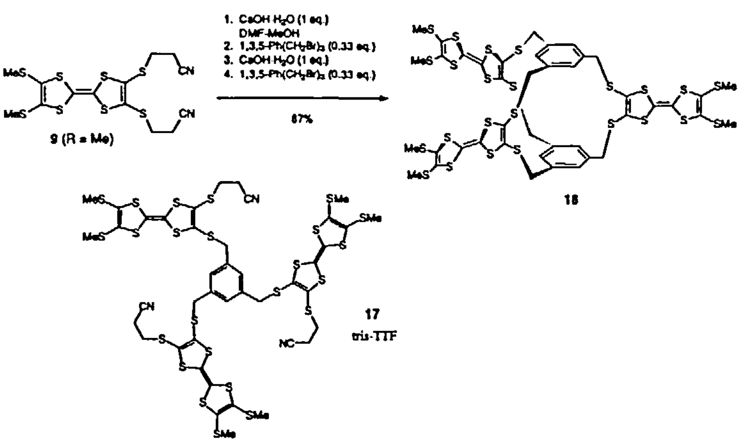
In this example the $(TTF)_{21}$ dendrimer was cleanly oxidised to the 21+ and hence 42+ cation upon electrochemical oxidation, moreover spectroelectrochemistry of the species formed upon partial oxidation revealed intra- or interdendrimer π-π interactions of the TTF-radical cations. To a certain extend different linking groups will control the inter- or intramoleculer interactions and by careful design it may therefore be possible to control the properties of such redox active dendrimers with regards to, rigidity, solubility, shape etc.

TTF-macrocycles and Cage molecules

The molecular design of three-dimensionally bridged macropolycyclic compounds is a challenge for the synthetic chemist[11] and incorporation of redox-active units into such molecules is of interest for the preparation of macropolycyclic receptor molecules[12]. Therefore the introduction of TTF into macrocycles[2] could lead to interesting applications. Apart from the design of new three dimensional organic conducting materials, such topological complex molecules may act as receptor for electron poor compound (acceptors), and the resulting electroactive recognition could be investigated and confirmed electrochemically.

The cyanoethyl deprotection methodology is well suited for the preparation of macrobicyclic cyclotetrathiafulvalenophanes containing three TTF-bridges, either by a stepwise method or in a one-pot synthesis, the example depicted below illustrates this strategy[13].



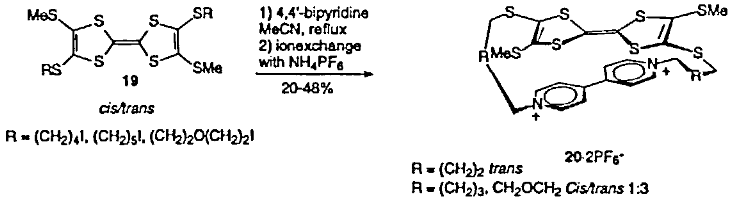
The appropriate tris-thiolate **17**, generated *in situ*, by alkylation with 1/3 equiv. of either 1,3,5-tris(bromomethyl)benzene or 1,3,5-tris[4-(bromomethyl)-phenyl]benzene in DMF. The tripod-tripod coupling for the construction of the cages was achieved by simultaneous addition of a DMF solution of the deprotected tris TTF thiolates such as **17** and a DMF solution of the appropriate tribromide under high dilution conditions. The resulting macrocycles **18** were isolated in excellent yields (32-68%) after chromatographic separation.

Interestingly it was also possible to prepare compound **18** by a direct one-pot reaction as depicted in the scheme. Instead of isolating tris-TTF intermediate **17**, the solution containing this intermediate was treated *in situ* with caesium hydroxide (3 eq.) to cleave off the remaining protecting groups. The resulting trithiolate was realkylated with another 1/3 eq. of the required tribromide without high dilution conditions to give the macrocycle **18** as the sole product in 68% yield. The synthesis of this cage molecule is an example of an assisted self-assembly reaction, since the individual components are pre-programmed due to their complementary geometry.

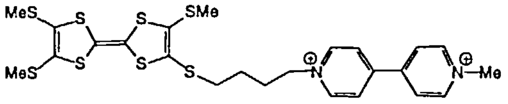
Donor-acceptor cyclophanes

Numerous bis- and oligo-TTF's have been prepared and investigated electrochemically, since Wudl *et al.*[14] suggested that molecules containing two electron donors might allow formation of charge transfer complexes of higher dimensionality. In these examples, the right geometry and connection of the donor portions are essential for intramolecular interactions. With the exception of the prominent work performed by Staab *et al.*[15] on donor and acceptor cyclophanes, there are relative few reports on systems containing macrocyclic donor/acceptor units which are covalently attached.

In order to obtain more insight into the structural conditions necessary for π-interactions between two different electroactive systems, we investigated systems in which the donor (TTF) and the acceptor (4,4'-bipyridinium unit) were connected *via* a chain either in a rigid conformation, *e.g.* a macrocycle, or in a open conformation where the two systems are linked together by a bridge. The direct synthesis to the donor acceptor systems was achieved by using the suitable TTF-thiolates. The alkylation of the appropriate bis-thiolate TTF, generated *in situ* from **16**, with various α-bromo-ω-chloro reagents, followed by halogen exchange using sodium iodide in acetone gave the starting bis-iodo TTF **19** in near quantitatively yields. The donor acceptor macrocycles were prepared simply by refluxing compound **19** with 4,4'-bipyridine for several days and purified by chromatography and anion exchange with ammonium hexa-fluorophosphate to give **20**·$2PF_6^-$ as dark green crystals[16].



The length and flexibility of the linker connecting the two redox active units have a great influence upon the conformation of the product. In the case of the short tetramethylene chain, the product was isolated in 48% yield only as the *trans* isomer (confirmed by X-ray). In the case of the pentamethylene and diethyl glycol linkers, the macrocycles were isolated as a mixture of *cis* and *trans* isomers.



21·$2PF_6^-$

The macrocycles give rise to a charge transfer band in the UV-VIS, situated around 650 nm. This indicates that an internal charge transfer interaction takes place between the TTF and the bipyridinium unit.

Interestingly compound **21** give rise to much weaker CT interactions, suggesting an open conformation in solution. We are currently trying to determine the scope and limitations of this type of reactions for the preparation of more complex donor acceptor systems. The surprisingly good yields observed in some cases, using the right linker, may be a result of self assembly during the formation of the donor-acceptor pair.

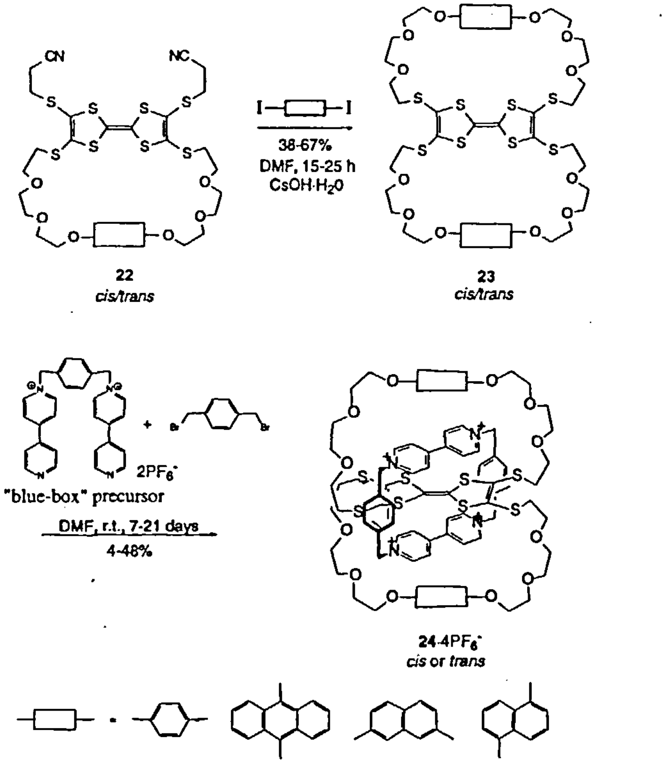
TTF-based Catenanes

The formation of interlocking molecular systems, such as rotaxanes and catenanes, has been a great challenge for the synthetic chemist during the last decade. Especially self-assembly have stimulated the development of several new synthetic methods for the preparation of such topologically complex structures. The extensive research performed by Stoddart *et al.*[17] using the ability of bis(benzyl)-4-4'-bipyridinium dication to self assemble with a variety of electron rich systems clearly illustrate the strong effect of noncovalent interaction in this type of synthesis. In particular, the π–π interaction and the stacking between the donor and acceptor systems (donor-acceptor interactions) have made it possible to design and construct a variety of mechanically interlocked systems, such as catenanes and rotaxanes. Although, some TTF-based catenanes and rotaxanes already have been synthesized the lack of a late common intermediate has prevented further exploration of such systems.

Use of the TTF-building blocks described in the previous sections has allowed the preparation of supramolecular systems such as for example catenanes.

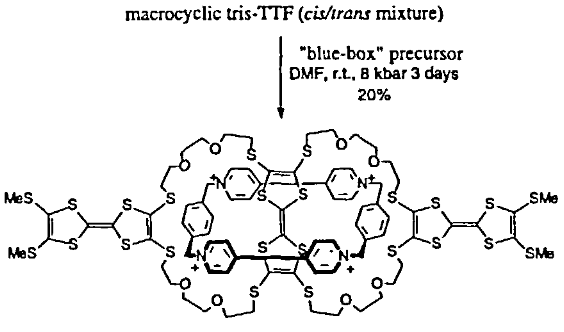
By a two step cyclisation reactions under high dilution conditions the dimacrocycles such as **23** were prepared from the appropriate bisalkylating reagents *via* the monocycle **22** as intermediate[18].

The [3]catenanes 24·$4PF_6^-$ were obtained by reacting the bis-macrocycles 23 with the "blue-box" precursor and 1,4-bis(bromomethyl)-benzene in dimethylformamide from three days to three weeks[18]. Depending upon the nature of the linker these novel assemblies were isolated either as pure *cis* or *trans* isomers after chromatography and anion exchange, although the starting bismacrocycles were an inseparable mixture of *cis* and *trans* isomers.



Interestingly no *cis/trans* isomerisation took place when a solution of [3]catenanes was treated with trifluoroacetic acid. Hence the fixation of the TTF by the tetracationic macrocycle effectively prevent protonation of the fulvene bond.

Starting from a bisprotected TTF (an analogoue of **19**) and the appropriate ethylene glycol linker followed by a two step macro cyclization on TTFTT **9** under high dilution condition afforded the required bis macrocyclic tris-TTF starting material. When this bismacrocycle was treated with the dication the "blue-box" precursor and 1,4-bis(bromomethyl)benzene in dimethylformamide at ultra high pressure (8 kbar) the *cis*-catenane $\mathbf{25}\cdot 4PF_6^-$ was obtained as the *cis* isomer after three days. As expected, **25** did not isomerize in solution in the presence of trifluoroacetic acid[19].



$\mathbf{25}\cdot 4PF_6^-$
cis

The catenanes were characterized by electrospray mass spectrometry (ESMS) and the various isomers were identified by their difference in the chemical shifts of the pyridinium protons. Variation of the linkers connecting the TTF units in these mono and bis-macrocycles, in order to change the geometry of these novel assemblies, are currently studied in our laboratory.

Conclusion and Outlook

We to have shown in this overview that the cyanoethyl group is a versatile protecting group for TTF thiolates. The complete set of π-donor building blocks enables us to design and construct a variety of topological complex TTF assemblies by use of the simple deprotection-realkylation methodology. The fact that several research groups already have adopted these synthons clearly shows the viability of the strategy: for example Fabre *et al.*[20] have synthesized the selenolate analogues using the cyanoethyl protecting group, Underhill *et al.*[21] have used the cross coupled TTF's to prepare nickel complexes of TTF dithiolates which show relative high conductivity, while Otsubo *et al.*[22] is using the corresponding alkoxycarbonylethyl protecting group in the synthesis of TTF-cyclophanes.

Our aim was from the beginning to develop the TTF functionality as a useful building block for macrocyclic and supramolecular systems rather than the preparation of simple TTF-derivatives for organic metals. However it later turned out that parts of our methodology also gave usefull results and methods for the preparation of new starting materials for organic metals.

The synthetic methods and developed building blocks have increased the possibilities for the creation of rather elaborate TTF systems and the new TTF thiolates serve as excellent building blocks for the incorporation of TTF into many different molecular structures. Because the synthetic operations involved are simple and give consistent high yields, we hope that chemists specialized outside the field of TTF chemistry will begin to explore the TTF moiety as a general electron donor.

TTF macrocycles may find applications into many different areas of chemistry, especially in host-guest chemistry. We have already mentioned the ability of such macrocycles to act as hosts for electron poor compounds, but actually this situation can be reversed. Thus, by generation of the dication, TTF^{2+}, an excellent host for electron donating guests is obtained[23]. TTF macrocycles may also be applied in materials chemistry, for example in the construction of electroactive materials and sensors. Electrocrystallization may afford unique molecular arrangements by including ligands and metal cations that might show electrical conductivity perhaps leading to new electroactive materials. Finally, it should be mentioned that use of TTF as a trigger for sequential radical translocation and functionalization reactions reported by Murphy *et al.*[24] may be extended to TTF macrocycles and cages.

We thank all the members of our laboratory who took part in the work outlined here and whose names appear in the references.

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