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Substituent Effects on Monopyrrolo-Tetrathiafulvalenes in Calixaren-Based Molecular Receptors

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Herein we report the first synthesis of a monpoyrrolo-tetrathiafulvalene (MPTTF) with two alkyl substituents, performed using a triphenylphosphine-mediated coupling reaction. An Ullmann-type *N*-arylation reaction was used to prepare a calixarene-based *bis*-MPTTF receptor, as well as an arylated *mono*-MPTTF derivative. Complexation studies with electron-deficient compounds showed strongly enhanced affinity of the alkyl-substituted MPTTF derivatives in comparison with the non-substituted MPTTF analogues.

Tetrathiafulvalene[1] (TTF) and its derivatives are redox active heterocyclic compounds that first found use in the field of organic electronics[2] because of their ability to form various types of electrically conductive solid phases. Due to the fact that the strong electron donating properties of TTFs can be turned off by reversible oxidation,[3] TTF subunits have been exploited as in a number of supramolecular systems with redox control, such as organogels,[4] molecular sensors,[5] functional materials,[6] and interlocked supramolecular systems, e.g. catenanes and rotaxanes.[7] In the latter TTF-containing interlocked molecular architectures,[7] a single TTF moiety was reversibly bound inside a cyclobis(paraquat-p-phenylene) macrocyle, being sandwiched between two electron-deficient 4,4'-bipyridyl moieties.

Examples of the reversed design of molecular receptors, which comprise several TTF groups serving as a molecular recognition centre for single electron deficient guests, are much less common. TTF-calix[4]pyrrole receptors developed in a collaboration between the *Sessler* and *Jeppensen* groups contain four monopyrollo-tetrathiafulvalene[8] (MPTTF) units, which form a molecular recognition center.[9] The possibility of switching the calix[4]pyrrole cores between the *alternate* and *cone* conformations allowed to employ these electron-rich receptors for the binding of two different substrate classes: either planar electron-deficient aromatic molecules, or spacious spherical fullerenes. These receptors were employed for investigation of fundamental processes, such as electron transfer in supramolecular systems.[10] Additionally, this class of receptors was used to create supramolecular polymers[11] and molecular sensors for nitro aromatics,[12] pointing out a path towards practical applications. Glycoluril-based *bis*-TTF molecular architectures designed in the groups of *Chiu*[13] and *Hudhomme*[14] constitute two additional rare examples of molecular tweezers with TTF arms.

In our previous work, we employed MPTTF derivatives for the synthesis of molecular receptors with a molecular tweezers architecture. The basal subunit of such a receptor consists of a calix[4]arene[15] or a 1,3,5-substituted 2,4,6-triethylbenzene scaffold[16] to which two or three TTF units are attached *via* the apex *N*-atoms of the pyrrolo groups. The MPTTF units make up the tongues of the tweezers, between which an electron-deficient guest molecule can be bound. *Bis*-MPTTF-calix[4]arene molecular tweezers displayed a high binding affinity towards electron-deficient substances. As an added benefit, these molecular receptors are rich in sites that might allow for further synthetic modifications.

In this communication we report the first synthesis and characterization of *bis*-methyl-substituted monopyrrolo-tetrathiafulvalene **1**, its application in Cu(I)-catalyzed *N*-arylation reactions, and investigations into the binding properties of its *mono*- and *bis*-derivatives with electron-deficient substrates. Additionally, we report the formation of a previously unknown side product in the phosphite-mediated ketone-thione cross-coupling reaction.

The synthesis of *bis*-methyl substituted MPTTF derivative **1** is shown in Scheme 1. First, *N*-tosylated MPTTF derivative **2** was prepared using a standard phosphite-mediated cross-coupling reaction between dithiole-ketone **3** and dithiole-thione **4** by heating in neat triethylphosphite. Analysis of the reaction mixture revealed the presence of a second colourless product **5** in addition to *N*-tosylated MPTTF derivative **2**, with a very

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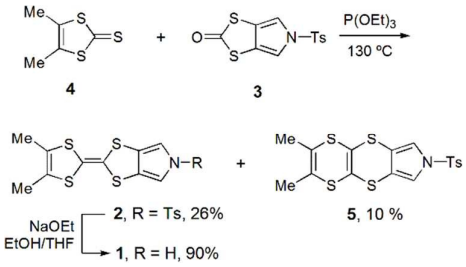
† Electronic Supplementary Information (ESI) available: Experimental details, ^{1}H NMR, ^{13}C NMR, UV/vis spectra, details on electrochemical characterization and determination of the binding constants, X-ray crystal data of **5** (CCDC 1415145) and **8b** (CCDC 1415146). See DOI: 10.1039/x0xx00000x

similar R_f value, identical molecular mass and almost indistinguishable ^{1}H and ^{13}C NMR spectra (ESI†).



Scheme 1 Synthesis of monopyrrolo-tetrathiafulvalene **1**.

Differences in solubilities allowed us to separate **2** and **5**. X-ray structure determination† revealed that compound **5** has a tricyclic backbone with two annealed six-membered dithiine type rings (Fig. 1). Both rings are folded along the S—S vectors, rendering the chair-like conformation to the annealed ring system. Structurally similar bicyclic 1,4,5,8-tetrathianaphthalene had been reported to rearrange into a tetrathiafulvalene after treatment with a large excess of a strong base, such as LDA or ^{t}BuOK, in THF,[17] but no examples of the reverse reaction have been reported to date. Heating of **5** for prolonged periods of time (up to 4 h) in hot $P(OEt)_3$ did not lead to its rearrangement into **2**, indicating that **5** forms *via* an unreported side branch of the commonly accepted mechanism of tetrathiafulvalene formation.[18]

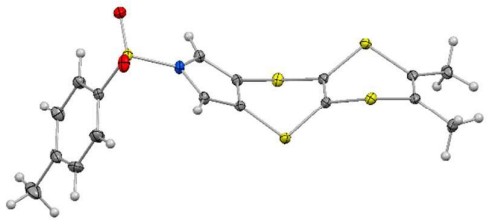
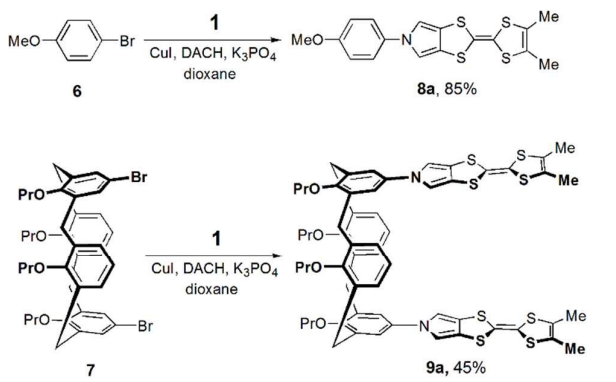


Fig. 1 X-Ray structure of byproduct **5**. Thermal ellipsoids are shown at the 50% probability level.

Treatment of the tosylated derivative **2** with sodium methanoate solution afforded the target compound **1** as a yellow crystalline powder. The reactivity of MPTTF **1** towards Cu(I) catalyzed *N*-arylation was tested by reaction with bromoanisole **6** and with bis-brominated calix[4]arene derivative **7** (Scheme 2). Both reactions afforded the desired *mono*- and *bis*-MPTTF derivatives **8a** and **9a**, respectively, as bright yellow crystalline powders stable under ambient conditions. Compound **9a** features a molecular tweezers architecture that can serve as a potential host for electron-deficient molecular guests.



Scheme 2 Copper catalyzed *N*-arylation reaction using MPTTF **1**. DACH = *trans*-1,2-diaminocyclohexane.

The crystal structure of **8a**† unambiguously confirmed the constitution of the dimethyl-substituted MPTTF scaffold (Fig. 2). In the crystal, the MPTTF moiety of **8** features an almost planar arrangement, with a maximum deviation of fitted atoms from the least-square plane, defined by heavy atoms of the MPTTF backbone, of 0.139 Å. The molecule as a whole is twisted, with an angle of 36.18° between the two least-square planes of the pyrrole and benzene rings, defined by their heavy atoms.

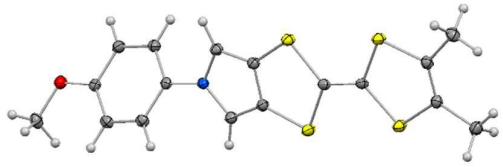


Fig. 2 X-Ray structure of arylated MPTTF derivative **8a**. Thermal ellipsoids are shown at the 50% probability level.

New MPTTF derivatives **1**, **8a**, and **9a** were investigated using cyclic voltammetry in CH_2Cl_2. Compound **1** displays only one quasi-reversible oxidation at a potential of 0.18 V, whereas the second oxidation wave is irreversible. Both *N*-arylated derivatives **8a** and **9a** show the common tetrathiafulvalene behaviour with two TTF-centred oxidation potentials, the first leading to formation of the radical-cation, and at the second potential the dication is formed (Fig. 3). *Bis*-MPTTF derivative **9a** displays a prominent splitting of the first oxidation wave, which had been occasionally observed for tetrathiafulvalene derivatives with two or more spatially proximal TTF groups.[19] This effect was explained by the formation of mixed-valence tetrathiafulvalene dimers $(TTF_2)^{+\bullet}$, stabilized by intramolecular charge-transfer interactions between TTF and $TTF^{+\bullet}$ moieties.[20] The splitting observed in the case of **9a** is much stronger when compared to cyclic voltammograms of similar calixarene-based *bis*-MPTTF molecular tweezers with less electron-donating substituents (SPr or H-atoms) at the TTF group.[15]

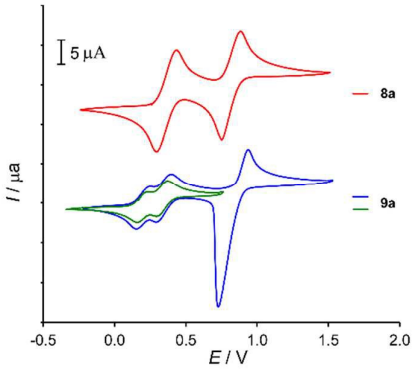


Fig. 3 Cyclic voltammograms of compounds **8a** (red) and **9a** (blue). For **9a**, the green curve shows a CV scan centered on only the first two oxidation potentials of the TTF moieties. (Plotted *vs.* SCE; CH_2Cl_2/0.1 M Bu_4NClO_4).

Table 1 Electrochemical data of new pyrrolo-TTF derivatives.[a]

Compound	$E_{1/2}^{ox1.1}$ (V)	$E_{1/2}^{ox1.2}$ (V)	$E_{1/2}^{ox2}$ (V)
1	0.18	-	-
8a	0.41	-	0.84
9a	0.17	0.33	0.80

[a] Data were obtained using a one-compartment cell in CH_2Cl_2/0.1 M Bu_4NClO_4, Pt as the working and counter electrodes and a non-aqueous Ag/Ag+ reference electrode; scan rate 100 mV/s. Values given at room temperature *vs.* SCE; the Fc/Fc^+ couple (0.480 V *vs.* SCE) was used as a reference.[21]

Binding studies† were performed to evaluate the electron-donation properties of the alkyl-substituted MPTTF derivatives **8a** and **9a** in comparison with their non-substituted counterparts[15] **8b** and **9b** (Fig. 4). Tetracyanoquinodimethane **10** (TCNQ) was used as the guest for molecular tweezers **9a**,**b**, whereas cyclobis(paraquat-p-phenylene) macrocycle **11**[22] ($CBPQT^{4+}$) was used as molecular host for MPTTFs **8a**,**b** (Fig. 5). Pairwise mixing of host-guest solutions leads to formation of deeply-coloured charge-transfer complexes, easily visible to the naked eye and showing intense charge-transfer bands in their UV/vis spectra above 600 nm. TCNQ gives an intense green colour with molecular tweezers **9a**,**b**, whereas mixing of compounds **8a**,**b** with $CBPQT^{4+}$ leads to formation of green-yellowish-coloured solutions.

Neither the MPTTF derivatives, nor any of the acceptors show absorption bands in the wavelength range of 500 to 1100 nm, which allowed determination of binding constants using UV/vis spectroscopy in dichloromethane (for **9a**,**b**) or Me_2CO (for **8a**,**b**). Initial qualitative experiments gave evidence of a very high binding affinity for the **9a**/TCNQ host-guest pair, prompting us to use the dilution method,[23] which is well suited for the determination of very high binding constants.

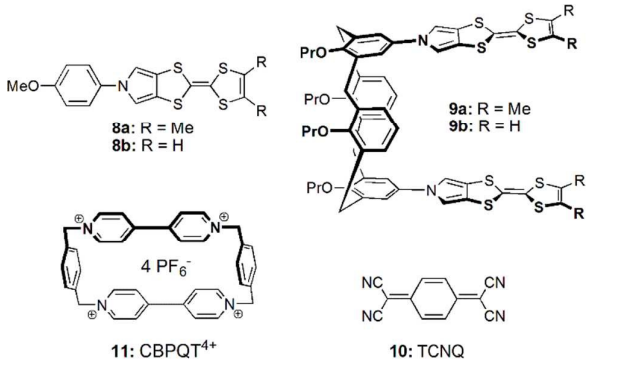


Fig. 4 Structures of the donor-type (**8a**,**b** and **9a**,**b**) and acceptor-type (**10** and **11**) molecular guests/hosts.

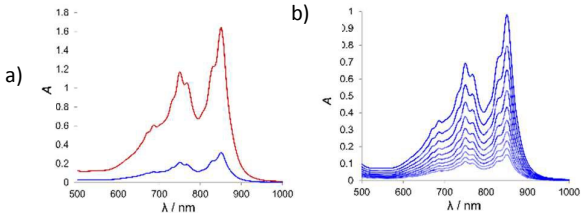


Fig. 5 a) Comparison between the charge-transfer bands of molecular complexes of receptors **9a** (red) and **9b** (blue) with TCNQ (CH_2Cl_2, [**9**] = [TCNQ] = 2×10^{-4} M); b) UV/Vis spectra of dilution of 1:1 receptor **9a** / TCNQ mixture (CH_2Cl_2, [**9a**] = [TCNQ] = 1.25×10^{-4} – 2.42×10^{-5} M).

Molecular tweezers **9a** exhibits a remarkably high affinity towards TCNQ with a binding constant of K_a = 250 000 M^{-1} and a very strong extinction coefficient for the complex ε = 9200 $M^{-1}cm^{-1}$ (**Error! Reference source not found.**). Receptor **9b** shows a lower binding constant of 90 000 M^{-1} and an almost five-fold decrease of the complex extinction coefficient. Comparison of MPTTF derivatives **8a** and **8b** in binding experiments with $CBPQT^{4+}$ also showed increased binding affinity of the methyl-substituted MPTTF **8a** in comparison with its non-substituted counterpart **8b** (Table 2).

The differences in binding affinity between the non-substituted and methylated MPTTF derivatives can be attributed to the electron-donating effect of the Me-groups, affording an increase in electron density on the TTF units. Combined with good chemical stability, this increase in donor ability renders Me-substituted MPTTF a highly promising building block for the construction of electron-rich redox-active molecular architectures.

Table 2 Binding properties of MPTTF derivatives **8a**,**b** and **9a**,**b**.[a]

Compound	K_a, M^{-1} (ε, $M^{-1}cm^{-1}$) with **10**[b]	K_a, M^{-1} (ε, $M^{-1}cm^{-1}$) with **11**[c]
9a	2.5×10^5 (9200)	-
9b	9.5×10^4 (1900)	-
8a	-	6200 (2600)
8b	-	4200 (1900)

[a] Data were obtained in CH_2Cl_2 (**9a**,**b**) or Me_2CO (**8a**,**b**) solns. using UV/Vis dilution method at room temperature.

[b] Absorption maximum for CT complexes of **10** with receptors **9a**,**b** lies at 850 nm.

[b] Absorption maxima for CT complexes of **11** with receptors **8a**,**b** lie at 876 nm

and 854 nm, respectively.

In conclusion, we have performed the first synthesis of novel alkyl-substituted monopyrrolotetrathiafulvalene **1** and successfully employed it in a copper-catalyzed arylation reaction. New MPTTF derivatives displayed good chemical stability combined with low oxidation potentials and exceptional electron-donating properties. Calix[4]arene-based molecular tweezers **9a** shows an extremely high affinity for TCNQ, forming stable charge-transfer complexes with very high extinction coefficients. Such molecular architecture should serve as a headstone for the development of efficient hosts for other classes of electron-deficient guests. Formation of an unexpected byproduct **5** in the phosphite-mediated coupling between **3** and **4** requires a deeper look into the mechanism of this reaction.

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