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Tetrathiafulvalene-functionalized Cavitands as Building Blocks for Redox Active Hemicarcerands

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Two new cavitands bearing four upper-rim tetrathiafulvalene (TTF) units were synthesized. One of these cavitands was used to prepare a redox-active hemicarcerand containing four TTF subunits covalently appended to its equatorial region. Preliminary electrochemical characterization data show that the four TTF residues in all these compounds behave as independent, non-interacting groups in their heterogeneous electron transfer reactions.

Keywords: Cavitand; Hemicarcerand; Electrochemistry; Tetrathiafulvalene

The design and preparation of receptors containing electroactive components have not only allowed the study of molecular recognition phenomena by electrochemical techniques but also opened the possibility of investigating redox processes coupled to other chemical events, such as inclusion complexation [1–3]. The availability of new synthetic procedures for tetrathiafulvalene (TTF) derivatization [4–6] has led to the preparation of a considerable number of supramolecular structures containing one or more TTF units [7–14]. The incorporation of TTF units into supramolecular systems gives rise to the following properties: (*i*) electrochemical activity resulting from the sequential and reversible oxidation of the TTF units to their radical monocation and dication forms; (*ii*) these oxidation processes take place at very accessible potentials that can be tuned by the attachment of suitable substituents; and (*iii*) the resulting TTF mono radical cations are highly stable. Despite the extensive use of TTF as a redox active subunit in supramolecular systems, to the best of our knowledge no examples of TTF-appended cavitands have been described. The incorporation of suitable TTF units in cavitands will lead to bowl-shaped, redox active molecules that can potentially engage in molecular recognition events. TTF-containing cavitands can also be used to synthesize more complicated structures such as redox-active carcerands and hemicarcerands [15–19]. Here we describe the synthesis and characterization of the first TTF-cavitands and a TTF-hemicarcerand.

The TTF-cavitands **4** and **5** were synthesized as outlined in Scheme 1. The tetramethylchloride cavitand **3** and the cyanoethylated TTF derivatives **1** and **2** were prepared according to published methods [20,21]. Assembly of the TTF-cavitand **4** was achieved by deprotecting **1** in DMF solution, using cesium hydroxide monohydrate dissolved in methanol, and mixing the resulting thiolate with cavitand **3**. After column chromatography on silica gel, using dichloromethane–hexane as eluent, **4** was obtained as an orange solid in 74% yield.[†] A similar

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[†] Synthesis *of tetrakis 3,6,7-trimethylthiotetrathiafulvalene cavitand with phenylethyl "feet"* (**4**). To a solution of **1** (165 mg, 0.38 mmol) in anhydrous degassed DMF (20 mL) was added, in one portion, a solution of $CsOH{\cdot}H_2O$ (67.4 mg, 0.40 mmol) in MeOH (2 mL). After stirring at room temperature under nitrogen for 2 h, cavitand **3** (100 mg, 0.08 mmol) was added in one portion and the mixture was stirred at room temperature for an additional 1 h. Then the mixture was stirred overnight at 50°C to afford a precipitate. The reaction mixture was evaporated *in vacuo* and water (10 mL) was added to the residue. The brown–yellow solid was filtered and washed with 10 mL of EtOH. The solid was preadsorbed on silica gel with CH_2Cl_2 and, after column chromatography (silica, eluent: dichloromethane–hexane, 1:1), compound **4** was obtained (157 mg, 74%) as a yellow–brown solid, mp 153–155°C. IR (KBr): $\nu = 1635, 1472, 975, 700\ \mathrm{cm}^{-1}$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.4 (br, 12H), 2.38 (s, 24H), 2.42–2.66 (m, 16H), 3.96 (s, 8H) 4.72 (d, $J = 7$ Hz, 4H), 4.92 (t, $J = 8$ Hz, 4H), 6.07 (d, $J = 7$ Hz, 4H), 7.10–7.26 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$): δ18.2, 19.2, 30.5, 32.5, 34.5, 37.1, 100.5, 110.6, 119.5, 124.4, 124.6, 126.1, 127.2, 128.3, 128.4, 128.6, 134.8, 138.0, 141.5, 153.8. MS (MALDI-TOF) m/z 2498 (M + calc. 2499).

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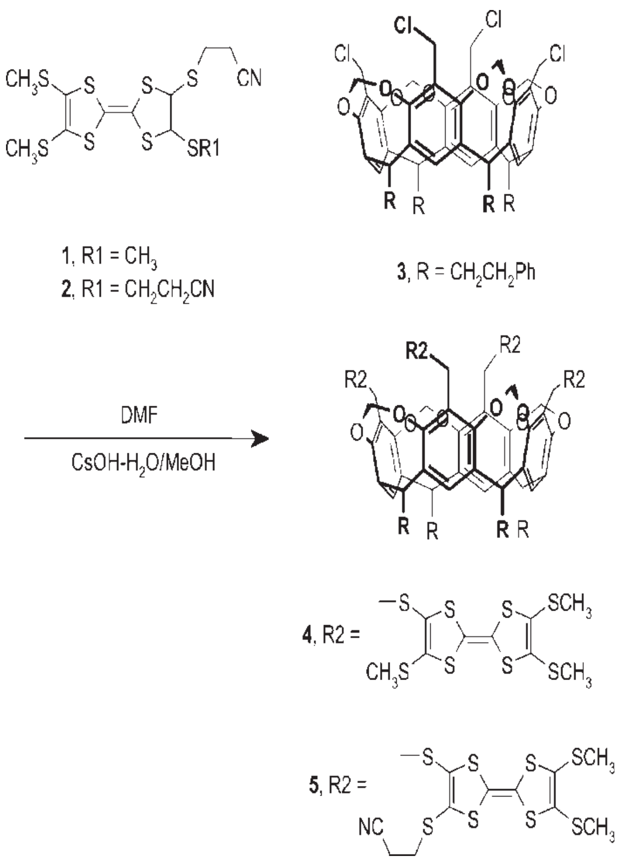

SCHEME 1 Synthesis of TTF-cavitands 4 and 5.

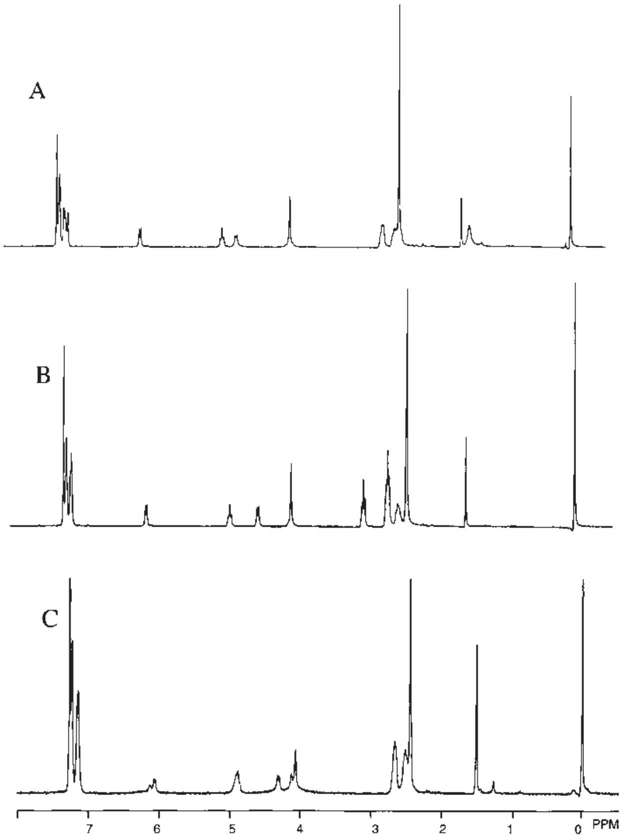

FIGURE 1 ^{1}H NMR spectra (300 MHz, CDCl$_3$) of (A) **4**, (B) **5** and (C) **6**.

synthetic protocol with compounds **2** and **3** led to the assembly of TTF-cavitand **5**, which was isolated as a yellow-brown solid in a 61% yield.[‡]

The structures of the new two cavitands **4** and **5**, with the TTF residues attached to their wider rims, have been established on the basis of ^{1}H and ^{13}C NMR and mass spectrometries. Figures 1A and 1B show the ^{1}H NMR spectra for the TTF-cavitands **4** and **5**. Both spectra combine the signals assigned to the framework of cavitand **3** with the pattern of resonances characteristic of the TTF derivatives **1** and **2**, respectively. Evidence of the substitution reaction was provided in the ^{1}H NMR spectrum by the upfield displacement (from 4.55 to 3.96 ppm) of the resonance corresponding to the methylene groups attached directly to chloro atoms in cavitand **3**, and in the case of TTF-cavitand **4** by the total absence of the triplets characteristic of the cyanoethyl protecting group of TTF derivative **1**.

To prepare hemicarcerand **6**, TTF-cavitand **5** was used, after appropriate deprotection, as the reactive wedge for the shell-closure reaction (see Scheme 2). The TTF-cavitand 5 was deprotected in DMF solution, using cesium hydroxide monohydrate dissolved in methanol, to generate the tetrakis (thiolate-TTF) cavitand, which was reacted *in situ* with cavitand **3** in a 1:1 ratio under high dilution conditions. The reaction mixture was stirred for 3 days at 50°C and, after solvent removal, the residue was washed with water. The residue was purified by column chromatography on silica using dichloromethane–hexane as eluent to furnish a brown–yellow

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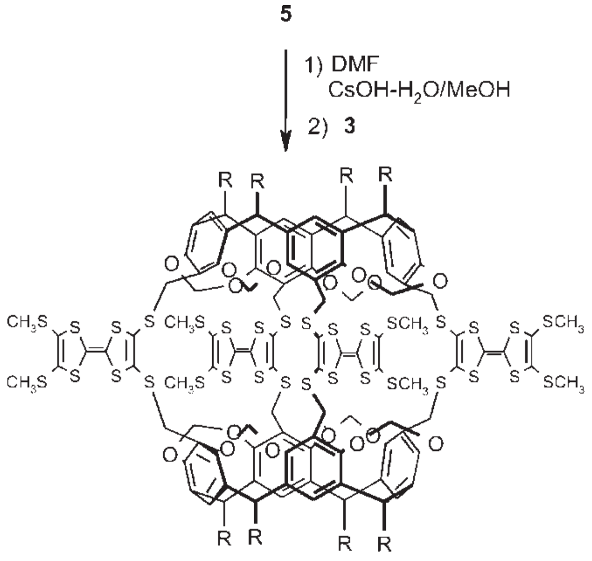
[‡] Analytical data for *tetrakis 3-(2-cyanoethylthio)6,7-bis(methylthio)tetrathiafulvalene cavitand with phenylethyl "feet"* (**5**). Yellow–brown solid (242 mg, 61%), mp 164–166°C. IR (KBr): $\nu = 2850, 1636, 1472, 1429, 975, 700\ \mathrm{cm}^{-1}$. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.38 (s, 24H), 2.46-2.51 (m, 16H), 2.65 (t, $J = 7$ Hz, 8H), 2.99 (t, $J = 7$ Hz, 8H), 4.02 (s, 8H), 4.49 (d, $J = 7$ Hz, 4H), 4.89 (t, $J = 7.6$ Hz, 4H), 6.08 (d, $J = 7$ Hz, 4H), 7.10–7.26 (m, 24H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 18.7, 19.1, 19.2, 30.9, 31.3, 32.7, 34.6, 37.1, 100.5, 108.7, 112.4, 117.6, 119.9, 122.6, 126.1, 126.9, 127.5, 127.6, 128.4, 128.6, 131.1, 137.9, 141.6, 153.9. MS (MALDI-TOF) m/z 2654 (M + calc. 2656).



6, R=CH_2CH_2Ph

SCHEME 2 Synthesis of hemicarcerand **6**.

solid in 23% yield.[¶] The presence of one singlet corresponding to the methylthio groups of the TTF moiety (2.46 ppm) and the absence of the triplets ascribed to the cyanoethyl protecting groups (2.65 and 2.99 ppm) in the ^{1}H NMR spectrum (Fig. 1C) indicate that the condensation of the TTF and cavitand units took place. The presence of two resonances for the protons of the CH_2SCH_2 portals (4.02 and 4.12 ppm) and for the outward-pointing Hs of the OCH_2O bridges (6.07 and 6.13 ppm) suggests that the hemicarcerand was isolated as a mixture of conformers. The inclusion of solvent molecules was not observed. Further confirmation of the structure was obtained from MALDI-TOF mass spectrometric data, which showed the molecular ion at m/z 3439.

The electrochemical properties of compounds **1** and **2** and TTF-cavitands **4** and **5** were investigated using cyclic voltammetry (CV) in dichloromethane solution, while those of hemicarcerand **6** were studied in DMF solution.[§] As shown in Fig. 2, the electrochemical behavior of all the compounds under study (the response of **6** is not shown) is characterized by two well-defined redox couples whose half-wave potentials are separated by more than 300 mV.

CV experiments at variable scan rates[§] with compounds **1**, **2** and **4** also showed a peak potential dependence that clearly indicated the quasi-reversible character of the redox processes for all the compounds under study. At a scan rate of $250\,\mathrm{mV\,s^{-1}}$, for instance, the differences between the anodic and cathodic peak potentials for compounds **1**, **2** and **4** were similar for the two redox waves and showed values of approximately 99, 92 and 157 mV, respectively. The two redox couples for the control compounds **1** and **2** are typical of the two consecutive one-electron oxidations of TTF systems, and the attachment of an extra cyanoethyl group to the TTF subunit in **2** produces an increase in its oxidation potentials, as compared to those of **1**, probably due to the electron-withdrawing properties of the cyanoethyl moiety. Analysis of the data[§] for compounds **1** and **2** at different scan rates (see Table I) revealed that the diffusion coefficients (D), the charge transfer coefficients (α values) and the electron transfer rate constants for each redox process (k^0) are, as expected, very similar for the two parent compounds.

As can be seen in Figs. 2C and 2D, TTF-cavitands **4** and **5** also exhibit two clearly defined redox waves, in analogy with their TTF precursors **1** and **2**. The first redox wave corresponds to the first oxidation of the TTF units to form the tetracationic species and the second one is related to the second oxidation of the TTF residues to yield a species bearing eight positive charges. The fact that only two redox waves were observed for the TTF-cavitands (see Fig. 2) indicates that the TTF units in these

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[¶] *Synthesis of 6,7-bis(methylthio)tetrathiafulvalene hemicarcerand with phenylethyl "feet"* (**6**). To a solution of **5** (150 mg, 0.056 mmol) in anhydrous degassed DMF (30 mL) was added a solution of CsOH·H_2O (62 mg, 0.37 mmol) in MeOH (3 mL) over a period of 0.5 h. After stirring at room temperature under nitrogen for 12 h, cavitand **3** (64.17 mg, 0.056 mmol) was added in one portion and the mixture was stirred at room temperature for an additional 1 h. Then the mixture was stirred for 3 days at 50°C to afford a precipitate. The reaction mixture was evaporated *in vacuo* and water (10 mL) was added to the residue. The brown–yellow solid was filtered and washed with 10 mL of EtOH. The solid was preadsorbed on silica gel and column chromatography (silica, eluent: dichloromethane–hexane, 7:3) yielded compound **6** (44.3 mg, 23%) as a yellow–brown solid, mp > 240°C. IR (KBr): $\nu = 2924, 1471, 1259, 1147, 1064, 1015, 978, 700\,\mathrm{cm^{-1}}$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 24H), 2.52-2.68 (m, 32H), 4.02 (s, 14H), 4.12 (s, 4H), 4.32 (d, $J = 7$ Hz, 8H), 4.88 (t, $J = 7$ Hz, 8H), 6.07 (d, $J = 7$ Hz, 6H), 6.13 (br, 2H), 7.10–7.23 (m, 48H). MS (MALDI-TOF) m/z 3439 (M + calc. 3444).

[§] CV experiments were carried out at 298 K in a conventional three-electrode cell in which a glassy carbon, an Ag/AgCl and a Pt wire were properly fitted as working, reference and counter electrodes, respectively. CV experiments were carried out using standard and ultramicroelectrodes. The electrolytic medium was a deoxygenated $TBAPF_6$ solution in the relevant solvent with a small concentration (see table footnote) of the electroactive compound surveyed. CV responses with standard minielectrodes and ultramicroelectrodes for all the compounds under study were obtained at different scan rates in the $20–1000\,\mathrm{mV\,s^{-1}}$ range and a rough calculation of thermodynamic and kinetic information was obtained from the analysis of the data using the method of Nicholson [22], the method reported by Zoski [23] and the method reported by Mirkin and Bard [24]. With these values as starting parameters, digital simulations (DigiSim v.3.03, BAS, West Layafette, IN, USA) of the experimental responses were carried out to improve the quality of the parameters presented in Table I. The diffusion coefficients were computed directly from the limiting currents obtained in voltammetric experiments with disk ultramicroelectrodes.

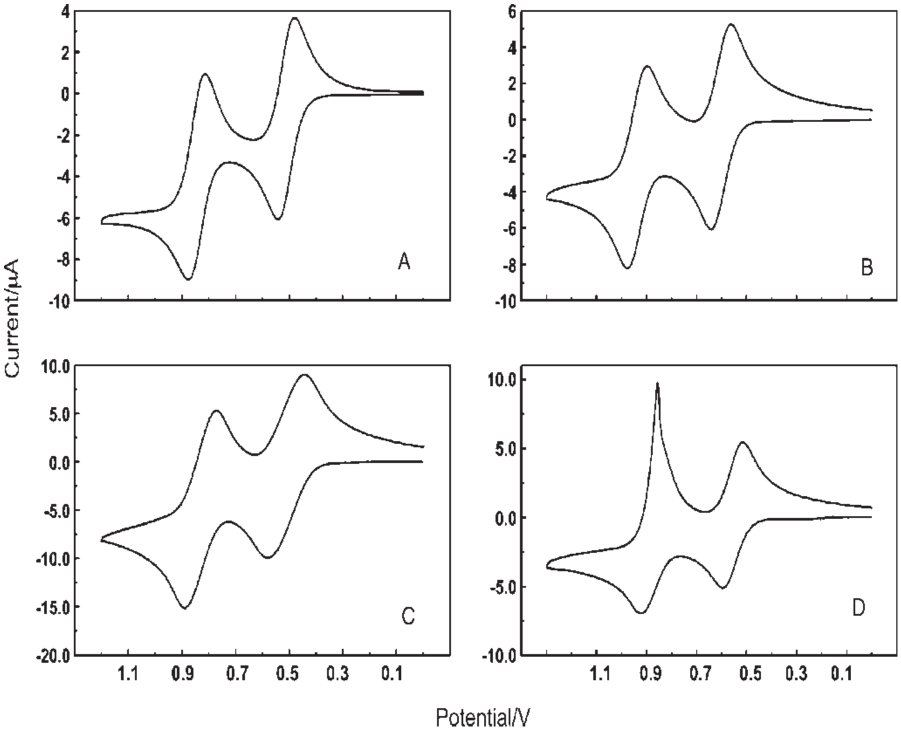

FIGURE 2 Cyclic voltammograms on a glassy carbon electrode (0.75 mm radius, Ag/AgCl reference electrode) of 1.0 mM solutions of (A) **1**, (B) **2**, (C) **4** and a 0.25 mM solution of (D) **5** in CH_2Cl_2/0.15 M $TBAPF_6$ at $0.1\,V\,s^{-1}$.

compounds behave as essentially independent redox centers [25]. Inspection of the voltammograms presented in Fig. 2 clearly shows that the electrochemical behavior of **5** is different from that of the other compounds surveyed. The shape of the most anodic wave, for instance, suggests that the removal of the second set of four electrons from **5** generates a non-soluble polycationic species that precipitates on the electrode surface, giving rise to the sharp peak observed during the corresponding reverse scan.

The data presented in Table I also show that the half-wave potentials for compounds **4** and **5** are lower than the corresponding potentials for their precursors **1** and **2**. This was rationalized by the same argument used previously to explain the differences observed between the half-wave potential values of **1** and **2**. In other words, the observed potential shifts are caused by the removal of the electron-withdrawing cyanoethyl groups upon attachment of the TTF unit to the relevant cavitand. The electron transfer rate constants for **4** and **5**, however, could not be obtained from the simulation of the voltammetric data because of the complexity involved in the multiple electron transfer events that characterize each redox wave for these species. As mentioned previously, however, the dependence of the peak potentials on the scan rate suggests that the heterogeneous electron transfer rate constants for **4** and **5** are also in the quasi-reversible kinetic regime. In terms of the diffusion coefficients for **4** and **5**, Table I shows that, as expected, the two values are similar and substantially smaller than those for **1** and **2**. This finding clearly reveals the larger size of these molecules compared to the parent compounds.

To the best of our knowledge, compound **6** is the first reported electroactive hemicarcerand.[||] Unfortunately, it was not soluble in dichloromethane and the electrochemical experiments had to be performed in DMF solution. The half-wave potential values were obtained at a scan rate of $6\,V\,s^{-1}$ and are also presented in Table I. It is important to note, however, that as observed for compound **5**, hemicarcerand **6** experienced an important change in solubility upon two-electron oxidation of each of the TTF units. Evidence of this effect was noted again in cyclic voltammetric experiments in which the shape of the peaks could be ascribed to an electrochemically induced deposition of material on the electrode surface. This finding is not surprising considering the extensive aromatic character of the hemicarcerand surface.

In conclusion, the new compounds described in this work present novel architectures with controlled placement of the TTF groups and the key property

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[||] We have previously reported the electrochemical properties of an electroactive guest, ferrocene, encapsulated inside an electroinactive hemicarcerand: [26].

TABLE I Electrochemical parameters for TTF-containing compounds **1**–**6** obtained from the voltammetric data [10]

Compound	$E^{1}_{1/2}$ (mV)	α_1	k^{0}_{1} (cm s^{-1})	$E^{2}_{1/2}$ (mV)	α_2	k^{0}_{2} (cm s^{-1})	D (cm^2 s^{-1})
1*	510	0.5	0.013	847	0.5	0.013	2.2×10^{-5}
2*	600	0.5	0.016	936	0.5	0.016	1.9×10^{-5}
4*	497			830			4.3×10^{-6}
5†	543			890			5.9×10^{-6}
6‡	560			880			

Experimental conditions: glassy carbon working electrode, Ag/AgCl reference electrode, Pt counter electrode, 25°C, TBAPF$_6$ (0.15 M) in *CH$_2$Cl$_2$, 0.1 V s^{-1}, [compound] = 1 mM; †CH$_2$Cl$_2$, 0.1 V s^{-1}, [compound] = 0.25 mM; the half-wave potentials for compound **5** were measured by normal pulse voltammetry; ‡DMF, 6 V s^{-1}, [compound] = 0.25 mM.

of multi-electron redox activity. The preliminary electrochemical data presented in this work provide the first step towards the understanding of the electron transfer reactions of these novel electroactive molecules. Further electrochemical characterization and the investigation of their complexation properties are in progress.

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