An electron-rich three dimensional receptor based on a calixarene-tetrathiafulvalene assembly

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ABSTRACT

The synthesis of a calix[4]arene scaffold persubstituted with four redox-active tetrathiafulvalene (TTF) moieties at the lower rim is described. This assembly strongly binds sodium cation, and the binding process is accompanied by a conformational change of the receptor, as shown from NMR titration and by an X-ray diffraction led on the complex. This dynamic behavior remarkably results in a modification of the electrochemical response of TTF probes, which behave independently after sodium complexation.

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Efforts are continuously produced for molecular systems capable of sensing charged or neutral substrates. An important class of receptors is based on redox-responsive ligands built from the association of a binding subunit with a redox-active moiety.[1–5] Many recent examples incorporate the electroactive tetrathiafulvalene (TTF) unit.[6–17] Indeed, TTF derivatives display a remarkable electrochemical behavior, supported by a high π-donating ability, and a good reversibility of the two successive one electron redox processes. In such responsive ligands, complexation of a guest leads to an electrochemical detection generally occurring through electrostatic interaction between the bound ion and the redox probe. Besides, rare examples of TTF-based receptors allow a recognition process based on a conformational change, and in those cases, the receptors present conformationally flexible structures built for example around a biphenyl relay[18] or a vinylogous TTF skeleton.[19] On the other hand, p-tert-butylcalix[4]arene tetraesters are known for their ability to bind alkaline cations.[20] In particular, it appears that p-tert-butylcalix[4]arene tetraethyl esters in cone conformation 1a, strongly bind sodium cation through contribution of the four O-phenolate atoms and the four carbonyl groups (Scheme 1). Consequently, whereas free ligand 1a presents a distorted cone conformation in the crystal,[21] X-ray structure of the corresponding 1a–Na+ complex exhibits a highly symmetrical locked structure, promoted by the octa-coordinated metal cation.[22]

On this ground, we were interested in evaluating how replacement of ethyl fragments in 1a by redox-active TTF units (compound 1b), could be translated in an electrochemical response upon sodium cation binding. Several examples associating a calixarene platform to redox-active ferrocene units have already been described, and have been used for anion sensing.[23–28] From this point of view, a TTF-based receptor would also be interesting, given the peculiar electronic properties of this moiety. In addition, though electron-rich receptors incorporating polyaromatic platforms and TTF units have been the subject of intense interest in the recent years,[29–36] no example of calixarene persubstituted with TTF units has been described so far. We propose herein the synthesis of receptor 1b, as well as a study of Na+ binding over the conformational and electrochemical behaviors of this electron-rich receptor, including the solid state characterization of the sodium complex.
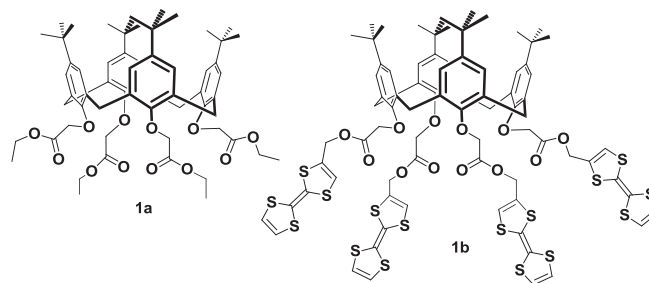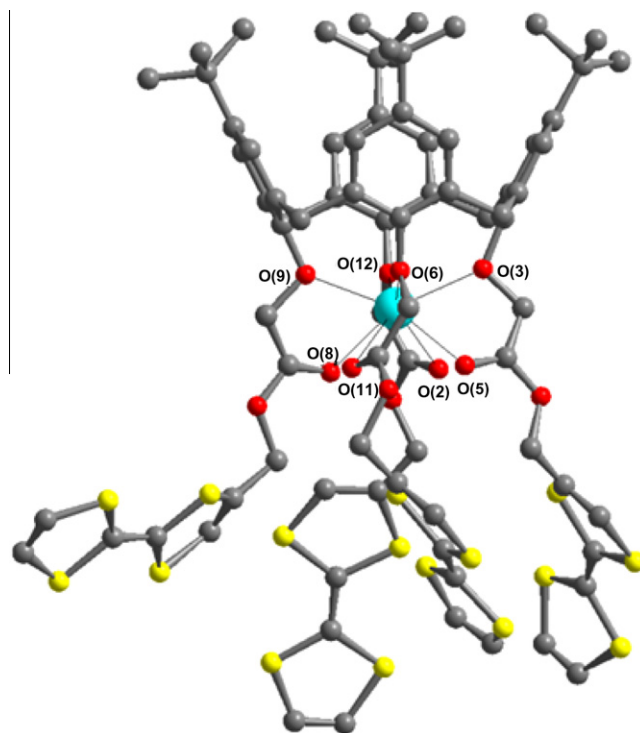

Scheme 1. Target system 1b.

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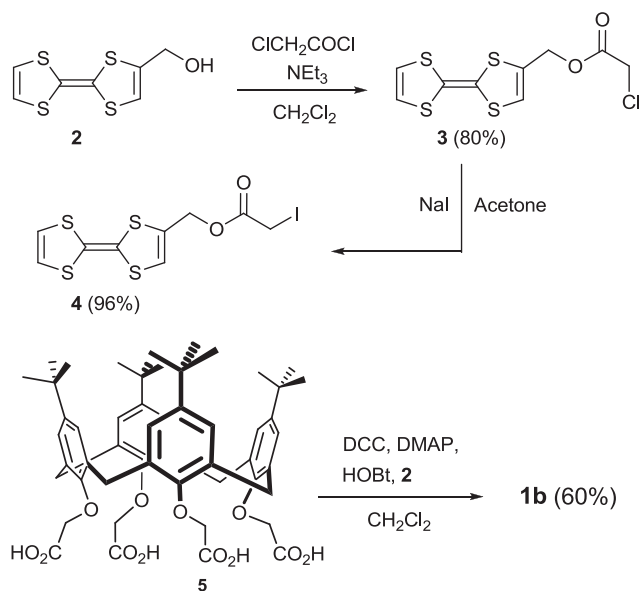
Scheme 2. Synthetic access to 1b.

Figure 2. X-ray structure of 1b–NaPF$_6$(CH$_2$Cl$_2$)$_{1.5}$ (solvent and anion omitted).

Two synthetic routes were explored to reach the target calixarene derivative 1b (Scheme 2). Hydroxymethyl-TTF 2[37,38] was successively converted to the corresponding chloroacetate derivative 3 by reaction with 2-chloroacetyl chloride in presence of an excess of triethylamine (80% yield), and to the iodoacetate analog 4 by refluxing with NaI (acetone). Various attempts to couple this building block to p-tert-butylcalix[4]arene failed, either using sodium hydride or potassium carbonate as a base and/or heating the mixture. Whatever the conditions, ester 4 was systematically hydrolyzed regenerating the starting hydroxymethyl-TTF 2. We therefore synthesized tetraacid calixarene derivative 5, according to the described procedure.[20] Tetraesterification to 1b could then be successively carried out with hydroxymethyl-TTF 2, in presence of dicyclohexylcarbodiimide (DCC), 4-(N, N-dimethylamino)pyridine and hydroxybenzotriazole (HOBt). Under these conditions, the target compound 1b, which associates four TTF units with the calixarene platform, was isolated as a yellow solid in a 60% yield.

NMR signals of 1b could be fully assigned on the basis of HMQC and HMBC studies. This compound exists in a cone conformation which is characterized by a pair of doublets for diastereotopic

ArCH$_2$Ar (H$_f$ protons) (Fig. 1). In addition, only one kind of aromatic (H$_{h,g}$) and tert-butylic protons is found, which agrees with a symmetric C_{4v} cone conformation. The cone appears significantly closed since $\Delta[(\delta_{f1}) - \Delta(\delta_{f2})] = 4.71 - 3.21 = 1.50$ ppm.[39]

The conformational modification of this system upon binding of an alkaline cation could be monitored by ^{1}H NMR. The progressive introduction of NaClO$_4$ aliquots onto 1b (CD$_3$CN–CD$_2$Cl$_2$) results in the appearance of a new set of signals and the concomitant disappearance of those of free 1b. This observation is assigned to the progressive formation of a complex in slow exchange with free ligand 1b at the NMR time scale. Such observation constitutes a first evidence of the high affinity of receptor 1 for Na$^+$. Noteworthy, no additional change is observed for NMR spectra carried out with an excess of NaClO$_4$ related to 1b, in agreement with a 1/1 stoichiometry ((1b)$_1$(NaClO$_4$)$_1$). Moreover, the most affected protons upon Na$^+$ binding, are those belonging to calixarene ring (H$_{h,g}$, H$_{f1,f2}$),
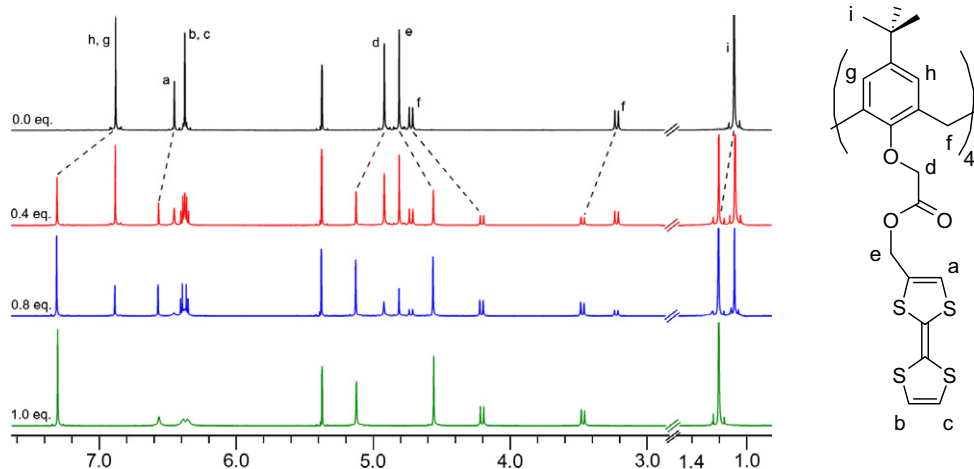

Figure 1. ^{1}H NMR spectrum of compound 1b (C = 9.1 × 10^{-3} mol/L, CD$_3$CN–CD$_2$Cl$_2$, 1:1) in presence of increasing amounts of NaClO$_4$.

Table 1
Na–O distances in **1b**–NaPF$_6$ complex

O(02)–Na	2.44(1)
O(03)–Na	2.45(1)
O(05)–Na	2.85(1)
O(06)–Na	2.45(1)
O(08)–Na	2.45(1)
O(09)–Na	2.43(1)
O(11)–Na	2.83(1)
O(12)–Na	2.50(1)

and at a lower extent, those belonging to appended ester arms (H$_d$, H$_e$). On the other hand, TTF protons are mostly unaffected. These observations suggest a binding process through oxygen atoms which results in a more rigid cone, as promoted by Na$^+$ octa-coordination. A significant decrease of $\Delta(\delta_{f1}-\delta_{f2})$ is observed upon sodium complexation (0.74 ppm) compared to 1.50 ppm for the free ligand **1b**, which is indicative of a more opened cone cavity.[39] Therefore, the cone shape persists (two doublets for ArCH$_{f1}$H$_{f2}$Ar), but the volume of the binding cavity has increased in order to receive the sodium cation. Finally, receptor C$_{4v}$ symmetry is maintained in the complex, as shown by occurrence of only one set of signals for aromatic (H$_{h,g}$) and *tert*-butyl protons.

Yellow single crystals of the corresponding sodium complex, could be obtained by slow diffusion of a dichloromethane–acetonitrile solution of ligand **1b** into a methanol solution containing sodium hexafluorophosphate. The complex crystallizes in the $P\bar{2}_1/c$ space group with 1.5 molecules of CH$_2$Cl$_2$, and four molecules of **1b** are found per unit (**1b**–NaPF$_6$(CH$_2$Cl$_2$)$_{1.5}$) (Fig. 2). The calixarene part clearly adopts a symmetrical cone conformation in the solid state, in accordance with solution NMR data. The cone characteristics are very similar to the ones observed for the previously described Na$^+$ complexes of *p-tert*-butylcalix[4]arene tetraethyl ester **1a**,[8] which indicates that the introduction of four bulky TTFCH$_2$ units does not perturb the binding process of Na$^+$. The sodium cation occupies the center of the cavity formed by the four

pendant Ar–O–CH$_2$–C(O)–X groups, and is octa-coordinated according to an antiprism mode, by the four oxygen atoms from the phenate rings and the four oxygen atoms from the carbonyl groups (see Na–O distances in Table 1). Six Na–O distances are comprised between 2.43 and 2.50 Å, and the other two, involving carbonyl groups, are higher (2.83–2.85 Å). Two TTF planes are nearly parallel within the molecule, with S···S inter-TTF distances in the range of 3.95 Å (Fig. 3). The corresponding TTF dimer stacks with another dimer from the next calix-TTF system, with S···S inter-TTF distances of 3.76 Å, thus giving rise to a TTF stack along the *c* axis. Finally, the two residual TTF units of the receptor are engaged in short S···S intermolecular distances (3.56 Å), a value which is significantly lower than the sum of the sulfur van der Waals radius (3.70 Å). Altogether, this combination of interactions leads to a crystallographic organization where slabs of sulfur rich (TTF) units are alternated with slabs of calixarene units along the *b* axis. The anion and solvent molecules are localized near ester-appended residues, between calixarene and TTF units.

Receptor **1b** bears four electroactive TTF units whose electrochemical signature can be characterized by cyclic voltammetry and which can be potentially affected upon sodium binding. The parent TTF unit is known to be reversibly oxidized according to two successive one electron redox processes, giving rise to stable cation-radical and dication species. The cyclic voltammogram of **1b** shows the presence of two quasi-reversible electrochemical processes. The first redox process appears split in two waves (Fig. 4a), which is even more evident from the deconvoluted CV (Fig. 4b). As already described for several covalent poly-TTF systems,[30,32,35,40–44] the first oxidation to the poly(radical-cation) state is broadened or split because of intramolecular interactions between pendant TTF units. This originates from an electronic stabilization of the first formed radical cation by a neighboring TTF unit. On the contrary, the second redox process (E$_{ox}^2$ = 0.73 V) presents an expected electrochemical feature for independent TTF units and corresponds to a full oxidation to **1b**$^{8+}$. This indicates that TTF units are at a larger distance and no longer in electronic
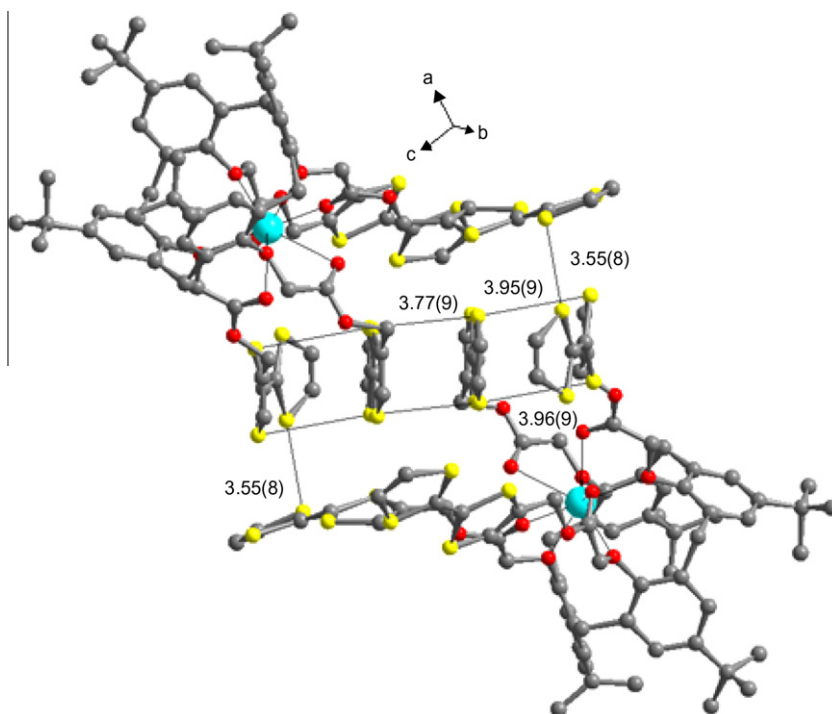

Figure 3. X-ray structure of **1b**–NaPF$_6$(CH$_2$Cl$_2$)$_{1.5}$, showing intermolecular S···S distances (anion and solvent not presented for clarity) and illustrating alternation between S-rich and calixarene slabs.
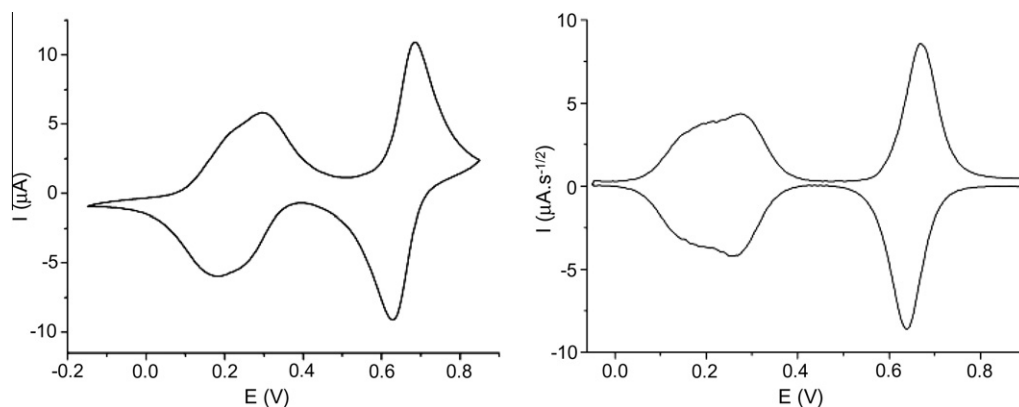
Figure 4. (a) Cyclic voltammogram (CV) of **1b**; (b) deconvoluted CV of **1b**; [**1b**] = 5×10^{-4} mol/L, TBAPF$_6$ 0.1 M, v = 100 mV/s versus Ag/AgCl, acetonitrile/CH$_2$Cl$_2$ (1:1), Pt, $\varnothing$ = 1.6 mm.
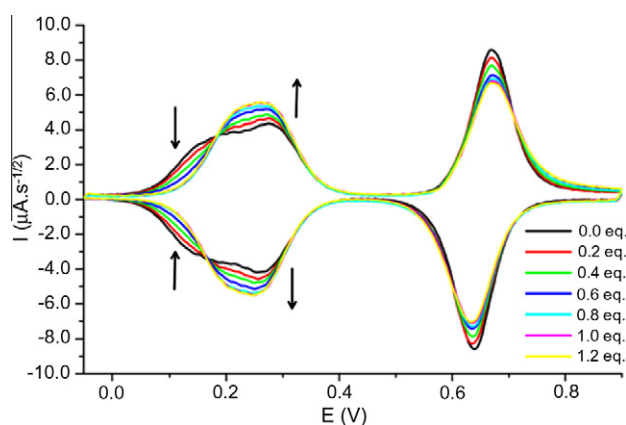

Figure 5. Deconvoluted CV of **1b** in presence of increasing amounts of sodium perchlorate; [**1b**] = 5×10^{-4} mol/L, TBAPF$_6$ 0.1 M, v = 100 mV/s versus Ag/AgCl, acetonitrile/CH$_2$Cl$_2$ (1:1), Pt, $\varnothing$ = 1.6 mm. Acetonitrile/CH$_2$Cl$_2$ (1:1). Pt, $\varnothing$ = 1.6 mm.

communication. Such behavior has already been depicted with various poly-TTF systems, and is supported by conformational changes resulting from electrostatic repulsive interactions between TTF^{2+} units. In a way, our system behaves as a flower which is closed (TTF units in interactions around the calixarene ring), and whose petals (TTF units) spread away upon a stimulus (oxidation to the **1b**$^{8+}$ state). This behavior is confirmed by geometry optimization (*MM+*, Hyperchem 7.5) led on the neutral compound **1** (*closed flower*) and **1**$^{8+}$ (*opened flower*) (Supplementary data).

Introduction of aliquots of MClO$_4$ (M = Li, Na) results in a narrowing of the first redox process, whereas no change is observed on the second system (Fig. 5 and Supplementary data). The thinner shape of the first redox wave for the sodium complex relative to free receptor **1**, is assigned to the conformational reorganization which occurs upon cation binding, as anticipated from the above NMR data. The rigidity gained by the system does not authorize—or at least decrease—interactions between TTF units, which now are close to behave as independent redox units. Therefore, the electrochemical response to cation binding does not result in this case from electronic effects but rather from a conformational change induced by cation complexation.

In summary, we have presented a synthetic access to a calix[4]-arene platform persubstituted with four redox-active TTF units. This system strongly binds one sodium cation as shown by NMR studies. This complexation rigidifies the calixarene moiety in a symmetrical conformation whose X-ray structure could be solved.

The conformational change can be followed by a modification of the electrochemical response of appended TTF redox-active units.

Acknowledgment

Supplementary data

Supplementary data (experimental procedures and NMR spectra for compounds **1b**, **3**, **4**; X-ray data for **1b**–NaPF$_6$; CV titration studies of **1b** in presence of LiClO$_4$. Geometry optimization of **1** and **1**$^{8+}$) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.112.

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