PAPER

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A calixarene–amide–tetrathiafulvalene assembly for the electrochemical detection of anions†

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The synthesis of a calix[4]arene derivative bearing pendant tetrathiafulvalene (TTF) units is described. Two electroactive TTF units are linked to the calix[4]arene platform through amide functions for the binding of anions. An X-ray structure of a calixarene–amide–TTF assembly existing in a cone conformation is provided. The binding ability of this receptor for $H_2PO_4^-$ is shown by ^{1}H-NMR and electrochemical studies (cyclic voltammetry).

Introduction

Considering the particular importance of anions in biological systems, intense efforts have been recently been devoted to the synthesis of receptors able to bind and to electrochemically detect anionic guests. In this context, amide-functionalized systems, which most often involve a metallocene moiety as the electroactive part, have been designed: (i) as anion receptors (taking profit from hydrogen-bond formation) and also (ii) as electrochemical sensors (resulting from electrostatic interactions between the bound anion and the redox-active metallocene unit).[1] In particular, some are built around the calixarene platform.[1a,b,2]

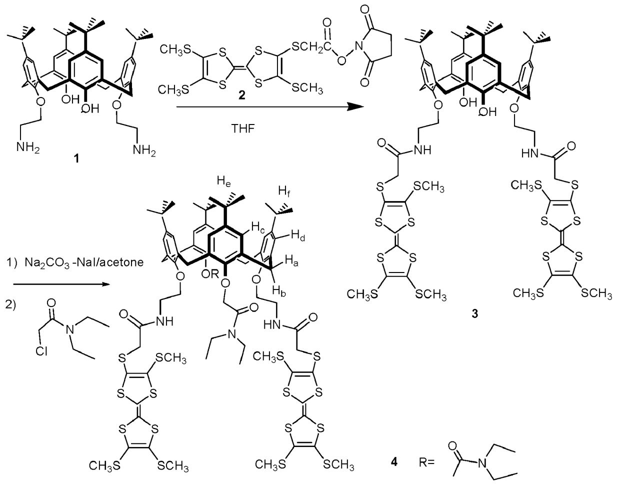
In the course of our studies related to the use of the tetrathiafulvalene (TTF) unit in electrochemical sensing[3a] or binding control of cations,[3b] we have developed a wide variety of redox-responsive ligands by covalent association between a binding block (*e.g.* a crown or a podand fragment) and the electroactive TTF framework.[3c] Also, the first examples of TTF-based macrocyclic ligands for recognition of halide anions (F^-, Cl^-, Br^-) have been described very recently,[4] which prompt us to report herein the synthesis of the first calix[4]arene–amide–TTF assembly designed for anion recognition,[5] a corresponding X-ray structure, as well as the anion-recognition properties determined by ^{1}H-NMR and electrochemical studies.

Results and discussion

Synthesis of the 1,3-distally substituted calix[4]arene diamine **1** was carried out in two steps from the corresponding *p-tert*-butylcalix[4]arene.[6] Generation of calix-diTTF **3** through formation of two amide bonds (Scheme 1) was made possible (76% yield) thanks to the synthesis of the succinimidyl activated TTF ester **2**.[7] The two residual phenolic groups of **3** were then reacted with *N*,*N*-diethyl α-chloroacetamide in the presence of a Na_2CO_3/NaI mixture, to produce the target tetrasubstituted calix[4]arene **4** (55%) after silicagel chromatography (methylene chloride-acetone).

Interestingly enough, crystals of the calix-diTTF system **3** could be obtained (Fig. 1), which allow establishment of the main crystallographic features of this assembly (see Experimental). The calixarene skeleton displays a slightly distorted flattened cone conformation, and accepts one molecule of methylenechloride inside the cavity. Dihedral angles between the least squares plane defined by the methylene bridges and the phenyl groups bearing the TTF units on the one hand, and unsubstituted phenol rings on the other hand, are approximately of 61° and 49° leading to a significantly opened conformation on the upper rim. This certainly results from O–H···O hydrogen-bonding interactions between adjacent phenolic rings (d(O···O) = 2.67(4) and 2.99(3) Å) on the lower rim and, to a lesser extent, from transannular N–H···O–H interactions between NH and adjacent OH phenolic groups (d(N···O) = 2.91(4) and 3.03(3) Å).[2a,8] On the other hand, both TTF units lie along the polyaromatic scaffold, and adopt a concave conformation which accommodates the conical shape of the polyaromatic system, as already observed for complexes between TTF and spherical C_{60}.[9]

^{1}H-NMR spectra of receptors **3** and **4** present the expected AB splitting pattern corresponding to the bridging diastereo-



Scheme 1 Synthesis of calixarene–TTF assemblies **3** and **4**.

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† Electronic supplementary information (ESI) available: ^{1}H-NMR binding isotherm of calixarene derivative **4** in the presence of bromide. See http://dx.doi.org/10.1039/b504339e

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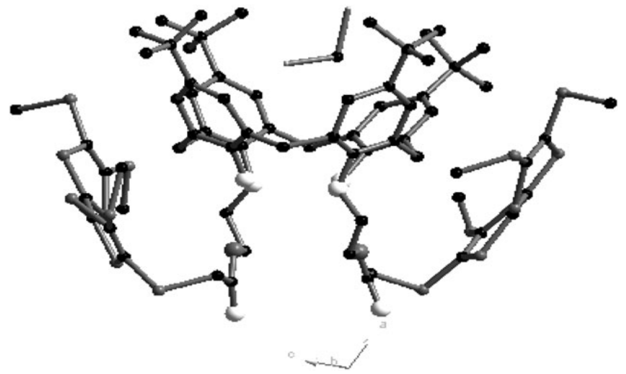

Fig. 1 X-ray crystal structure of $3 \cdot CH_2Cl_2 \cdot H_2O$ (water molecule omitted).

topic methylene protons ($ArCH_aH_bAr$), with a pair of doublets ($J = 13$ Hz) and a $\Delta\delta(H_b - H_a)$ value of 0.87 ppm for both **3** and **4**, characteristic of cone conformation.[10] This is also confirmed by ^{13}C-NMR for which the methylene carbon appears at δ 32.17 and 31.37 for **3** and **4**, respectively.[10c,10d] Furthermore, the cone appears essentially symmetrical in both cases, as indicated by the very low $\Delta\delta(H_d - H_c)$ observed between the two different types of aromatic protons (0.08 and 0.21 ppm for **3** and **4** respectively), which indicates that the introduction of two additional amide substituent in **4** does not alter significantly the cavity shape compared to **3**. In agreement with the above solid state observations, intramolecular NH$\cdots$OH hydrogen-bonds are observed in **3**, as shown by the δ value of NH (8.50 ppm) which is significantly deshielded relative to the same signal in the tetrasubstituted **4** (7.97 ppm).

No clear ^{1}H-NMR evidence of anion binding was found for **3** upon observation of the signals of the calixarene platform, presumably because of intramolecular hydrogen-bonds which prevent any interaction occurring with the anion.[11] Compound **4**, on the contrary, exhibits the expected anion complexation ability. In the case of ($X^- =$) dihydrogenophosphate, benzoate or acetate anion, the binding affinity is manifested by the concomitant appearance of a new set of signals on the ^{1}H-NMR spectrum and disappearance of those of **4**, which corresponds to the complex in slow equilibrium with the free ligand on the NMR time scale (Fig. 2, Table 1). It is noteworthy that the complex exists alone (no more free **4**) after the addition of two equivalents of Bu_4NX per unit of **4**, indicating the cooperative participation of amide functionalities in the formation of a 1 : 2 stoichiometric complex ($4 \cdot (X^-)_2$). Considering the chemical shifts of H_{a-f} relative to those of free **4**, the complex $4 \cdot (X^-)_2$ presents a pinched cone conformation in the three cases ($X^- = H_2PO_4^-$, $C_6H_5CO_2^-$, $CH_3CO_2^-$). It is also noted that the N–H signal appears at lower fields in the complex (8.44 ppm *vs.* 7.97 ppm in **4**), as expected from its participation in the process of binding the anion. Significant variations of δ are also observed at the proximity of the amide functions for the three anions (OCH_2CO: −0.22; NCH_2CH_2O: +0.19; NCH_2CH_2O: +0.13 ppm), confirming the anion location. Finally, it should be stressed that the ^{1}H-NMR spectra of the $4 \cdot (X^-)_2$ complexes, show a better resolution than that of free **4**, which undoubtedly results from a higher rigidity promoted by anion binding in the complex.

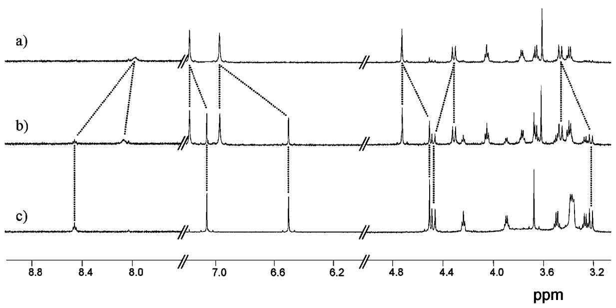

Fig. 2 ^{1}H-NMR spectra of **4** ($CDCl_3$), in presence of $TBAH_2PO_4$, for $[H_2PO_4^-]/[\mathbf{4}]$ equal to: (a) 0, (b) 1, (c) 2.

A different behaviour is observed in the case of the spherical anion Br^-, since in this case the complexation does not alter the signals corresponding to the calixarene cavity, nor the functionalities located on the lower rim, but is simply characterized by a progressive downfield shift of the amide proton ($\Delta\delta$(N–H) = +0.12 ppm), until 2 equivalents of Br^- per unit of **4** have been added after which no additional variation is observed (see ESI†). Such data can probably be explained by the mismatched structure of the calix-TTF receptor **4** for spherical anions.

A cyclic voltammetry study shows that the calixarene–amide–TTF assembly **4** presents the expected two redox system behaviour (at E^1_{ox} and E^2_{ox}), corresponding to the two step one electron oxidation of the two TTF units which behave independently. The electrochemical sensing properties of **4** towards anions were evaluated from the changes in the electrochemical response of E^1_{ox} (cyclic voltammetry, CV) upon progressive addition of X^- (TBAX) into the electrolytic solution ($TBAPF_6$).[12] The electrochemical signature of the binding is somewhat complicated in the cases of $X^- = C_6H_5CO_2^-$, $CH_3CO_2^-$ by the flattening of the reduction waves, typical of an electrochemical mechanistic response, as often observed with other redox-active receptors upon titration of anions.[2,13] Such behaviour indicates that the anion strongly interacts with the oxidized TTF moiety, therefore inhibiting the electron-transfer back to the TTF. In the case of $X^- = H_2PO_4^-$, the host–guest interaction is manifested by a two-wave behaviour with the appearance of a distinct voltammetric curve growing at more negative potential ($\Delta E^1_{ox} = -0.10$ V) which corresponds to the complex, at the expense of that from free **4** (Fig. 3). As previously noted with several amide–ferrocene receptors, the bound anion stabilizes the positively charged TTF moiety, facilitating oxidation redox process (lowering of E^1_{ox}). As far as we know, this is the first example of such a two-wave response for a TTF-based ligand upon anion titration. It can be also noted that the CV of the parent $TTF(SMe)_4$ remains unchanged under the same conditions in the presence of $H_2PO_4^-$, which illustrates the critical contribution of $X^-\cdots$H–N hydrogen-bonding promoted by the amide functionalities of **4** in synergy with electrostatic ion-pairing interactions. The selectivity of this process is also illustrated by the fact that these experiments were led in presence of a $[PF_6^-]/[H_2PO_4^-]$ ratio ranging from *ca.* 3600 (dashed line). A progressive loss of the electrochemical reversibility is observed for higher $H_2PO_4^-$ concentrations, presumably because of passivation of the

Table 1 ^{1}H-NMR chemical shifts (δ/ppm, $CDCl_3$) of compound **4** ($C = 2.24$ mM) in the presence of various anions (X^-) (n-Bu_4NX, $([X^-]/[\mathbf{4}]) = 3$)

X^-	δH_a	δH_b	$\Delta\delta(H_b - H_a)$	δH_c	δH_d	$\Delta\delta(H_d - H_c)$	δH_e	δH_f	$\Delta\delta(H_f - H_e)$
Free **4**	3.42	4.29	0.87	6.97	7.18	0.21	1.03	1.21	0.18
$H_2PO_4^-$	3.16	4.45	1.26	6.50	7.06	0.56	0.83	1.30	0.47
$C_6H_5CO_2^-$	3.16	4.45	1.29	6.50	7.05	0.55	0.83	1.30	0.47
$CH_3CO_2^-$	3.11	4.41	1.29	6.46	7.01	0.55	0.78	1.26	0.47
Br^-	3.37	4.25	0.88	6.93	7.13	0.20	1.00	1.16	0.16

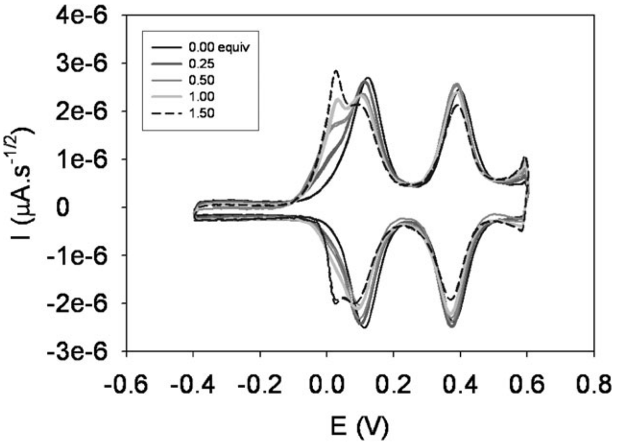

Fig. 3 Deconvoluted CV of **4** (0.279 mM) in CH_3CN–CH_2Cl_2, $TBAPF_6$ (0.25 M), in presence of increasing amounts of $TBAH_2PO_4$: $[H_2PO_4^-]/[\mathbf{4}] = 0.00, 0.25, 0.50, 1.00, 1.50$; Pt, diam = 1.6 mm; $v = 100$ mV s^{-1}, *vs.* Fec$^+$/Fec.

electrode surface. Finally, no potential shift is observed for the second redox system of the TTF probe (E^2_{ox}) which could signify a lack of anion-binding for the fully oxidized **4**$^{4+}$ state. Such an observation may be attributed to conformational changes which certainly arise upon oxidation to **4**$^{4+}$, and which result from repulsive interactions between both dicationic TTF units, leading to the disappearance of any synergy between amide functions on the binding of an anion.

In conclusion, a novel class of calixarene–amide–TTF assemblies has been designed which electrochemically recognize $H_2PO_4^-$. The potential of the calixarene scaffold to organize a 3-D environment for multifunctional systems appears very promising and extension of this concept to other types of calixarene–TTF based receptors is underway.

Experimental

Syntheses

Calixarene–amide–TTF assembly 3. TTF derivative **2** (0.5 g, 0.95 mmol) was dissolved in dry THF (20 mL) and degassed with N_2 for 10 min. A solution of the calix[4]arene **1** (0.28 g, 0.38 mmol) in 10 mL dry THF was then added, and the reaction mixture stirred overnight. The solvent was removed in vacuum, and the resulting solid was dissolved in CH_2Cl_2, washed with water, dried with $MgSO_4$ and purified by silica column (CH_2Cl_2 : ethyl acetate (9 : 1)) to give **3** as an orange powder (76% yield). ^{1}H-NMR ($CDCl_3$): δ 8.50 (t, CONH, 2H), 8.37 (s, OH, 2H), 7.05 (s, ArH, 4H), 6.97 (s, ArH, 4H), 4.26 (d, J = 13.5 Hz, $ArCH_2Ar$, 4H), 4.14 (t, J = 5 Hz, OCH_2, 4H), 3.96 (m, NCH_2, 4H), 3.58 (s, SCH_2, 4H), 3.39 (d, J = 13.5 Hz, $ArCH_2Ar$, 4H), 2.42 (s, SCH_3, 6H), 2.35 (s, SCH_3, 6H), 2.33 (s, SCH_3, 6H), 1.25 (s, $C(CH_3)_3$, 18H), 1.09 (s, $C(CH_3)_3$, 18H); ^{13}C-NMR ($CDCl_3$): δ 171.12, 167.75, 149.32, 148.58, 148.16, 142.95, 133.10, 133.02, 127.75, 127.62, 127.44, 126.08, 125.72, 123.01, 110.96, 75.45, 60.38, 39.97, 39.71, 39.55, 34.18, 33.90, 32.17, 31.59, 31.58, 31.07, 19.24, 19.21; FT-IR ν/cm^{-1} (KBr-pellet): 3317.9 (OH), 1656.9 (C=O); ESI-MS: m/z 1587.2 [M + Na$^+$, 100]; 1562 [M, 87]; HR-ESI$^+$: $C_{70}H_{86}N_2O_6S_{16}$, calcd: 1562.2017; found : 1562.2018.

Calixarene–amide–TTF assembly 4. A solution of calix[4]arene **3** (0.125 g, 0.08 mmol) in dry acetone (10 ml) was stirred under N_2 in presence of Na_2CO_3 (0.170 g, 1.6 mmol) and NaI (0.240 g, 1.6 mmol). The solution was refluxed for 30 min. Then the *N*,*N*-diethyl-α (0.024 g, 0.022 ml, 0.16 mmol) was added. After 6 days, the reaction mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was dissolved in 20 ml of CH_2Cl_2 and washed with 10% HCl (10 mL × 3). The organic layer was separated and dried over $MgSO_4$. The solution was concentrated in vacuum. The purification was carried out by column chromatography on silicagel (CH_2Cl_2 : acetone (4 : 1)) to produce **4** as an orange powder (79 mg, 55% yield). ^{1}H-NMR ($CDCl_3$): δ 7.97 (broad s, CONH, 2H), 7.18 (s, ArH, 4H), 6.97 (s, ArH, 4H), 4.71 (s, OCH_2CO, 4H), 4.29 (d, J = 12.5 Hz, $ArCH_2Ar$, 4H), 4.02 (t, J = 6.5 Hz, OCH_2, 4H), 3.73 (m, CH_2N, 4H), 3.62 (q, J = 7.0 Hz, NCH_2CH_3, 4H), 3.57 (s, SCH_2CO, 4H), 3.42 (d, J = 12.5 Hz, $ArCH_2Ar$, 4H), 3.35 (q, J = 7.0 Hz, NCH_2CH_3, 4H), 2.42 (s, SCH_3, 6H), 2.40 (s, SCH_3, 6H), 2.39 (s, SCH_3, 6H), 1.33 (t, J = 7.0 Hz, CH_3CH_2N, 6H), 1.27 (t, J = 7.0 Hz, CH_3CH_2N, 6H), 1.21 (s, $C(CH_3)_3$, 18H), 1.03 (s, $C(CH_3)_3$, 18H); ^{13}C-NMR ($CDCl_3$): δ 167.99, 167.51, 149.01, 148.81, 148.56, 147.52, 134.56, 133.82, 131.59, 127.53, 125.98, 123.45, 111.60, 110.69, 75.51, 73.93, 41.89, 41.46, 39.60, 39.16, 34.24, 34.01, 31.37, 31.11, 31.42, 31.07, 19.28, 14.39, 13.22; FT-IR ν/cm^{-1} (KBr-pellet): 1656, 1648; MS (Maldi tof): m/z 1812.88 [M + Na$^+$]; HR-ESI$^+$: $C_{82}H_{108}O_8N_4S_{16}Na$ calcd: 1813.3599; found: 1813.3499.

X-Ray crystallography

Crystal data for **3**$\cdot CH_2Cl_2 \cdot H_2O$. $C_{71}H_{86}Cl_2N_2O_7S_{16}$, M = 1663.28, monoclinic, a = 23.106(3) Å, b = 12.387(1) Å, c = 31.118(4) Å, β = 108.95(1)°, V = 8423(2) Å^3, space group $P2_1/c$, Z = 4, calculated density = 1.312 g cm^{-3}, crystal dimensions/mm^3: 0.8 × 0.3 × 0.1, T = 120 K, STOE-IPDS diffractometer, graphite-monochromated MoKα radiation (λ = 0.71073 Å), μ = 0.523 mm^{-1}, $2\theta_{max}$ = 42°, 15875 measured reflections of which 6357 were unique ($R_{(int)}$ = 0.085) and 4208 had $I/\sigma(I) > 2$. The hydrogen atoms were treated with a riding model. The refinements of positions of non-H atoms, and anisotropic thermal motion parameters of sulfur atoms, converge to $R(F)$ = 0.23 (4208 reflections, 474 parameters), $wR_2(F^2)$ = 0.49 (all data), GOF on F^2 1.09, $\Delta\rho_{max}$ = 1.56 e Å^{-3}. In spite of bad reliability factors correlated to poor crystal quality, all atoms belonging to the calixarene–tetrathiafulvalene molecule were unambiguously located, bond distances and bond angles being in good agreement with the expected values. The structure also incorporates two solvent molecules (CH_2Cl_2, H_2O). CCDC reference numbers 263773. See http://dx.doi.org/10.1039/b504339e for crystallographic data in CIF or other electronic format.

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