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Calix[4]arenesulfonylamidines. Synthesis, structure and influence on Mg^{2+}, ATP-dependent calcium pumps

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Abstract—Calix[4]arenes, functionalized at the wide rim with two or four N^2-sulfonylamidine groups were prepared. In the crystalline state, the bowl shaped calix[4]arene-bis-*N*-sulfonyltrifluoromethylacetamidine **3b** is associated through intermolecular hydrogen bonds, NH···O=S, while the phenyl rings of the Ph–SO_2-fragments are hosted in the cavities of the nearby molecules of **3b**. Calixarene **4b** influences Ca^{2+} transport in Mg^{2+}, ATP-dependent calcium pumps.
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Intramolecular cavities of calixarenes, formed by the phenolic rings, can host complementary cations,[1] anions[2] and neutral molecules[3] especially when several binding sites are preorganized at the wide or narrow rim of the macrocycle. Preorganization of several hydrogen bonding functional groups (amide, carbamide, peptide, etc.) at the wide rim of calixarenes affords self-assembling molecular capsules,[4] boxes,[5] cyclic aggregates[6] and results in affinities to proteins.[7] Highly selective extractants,[8] supramolecular catalysts,[9] sensors[10] and bioactive compounds[11] have been obtained from calixarenes.

Calix[4]arenes functionalized by pharmacophore peptide groups at the wide rim of the macrocycle are receptors and blockers of enzymes and co-enzymes (chymotrypsin, alkali phosphatase and cytochrome C).[12] Peptidocalix[4]arenes can selectively bind specific proteins and disturb their functions, thus showing antibacterial action.[13] Calixarenes can also influence bio-membranes. They can disturb transmembrane potentials due to the formation of channels for Na and K cations.[14] Other calixarene derivatives block chloride anion channels.[15]

We report here the synthesis, structure and hydrogen bonding of calix[4]arenes functionalized at the wide rim of the macrocycle with pharmacophore sulfonylamidine groups and their influence on Mg^{2+}, ATP-dependent calcium pumps. Calcium ions are considered as universal second messengers that play an important role in electrical and pharmacological coupling in smooth muscles. Electrical or pharmacological stimulation of smooth muscles during the excitation/contraction cycle changes the concentration of Ca^{2+} in myocytes, which is regulated by systems of energy-independent (passive) and energy-dependent (active) transport of these cations. The latter involves the Mg^{2+}, ATP-dependent calcium pumps of the sarcoplasmic reticulum, plasma membrane and mitochondrial Ca^{2+}-accumulating system.

The acylation of aminocalixarenes **1** and **2** by *N*-sulfonylimidoyl chlorides in the presence of Et_3N as a base afforded bis- and tetrasulfonylamidines **3** and **4**, respectively, in 11–80% yields (Scheme 1).

The ^1H NMR spectra of compounds **3** and **4** measured in $CDCl_3$ at 295 K contain two AB doublets with $^2J_{HH} = 10$–13 Hz, which correspond to the methylene

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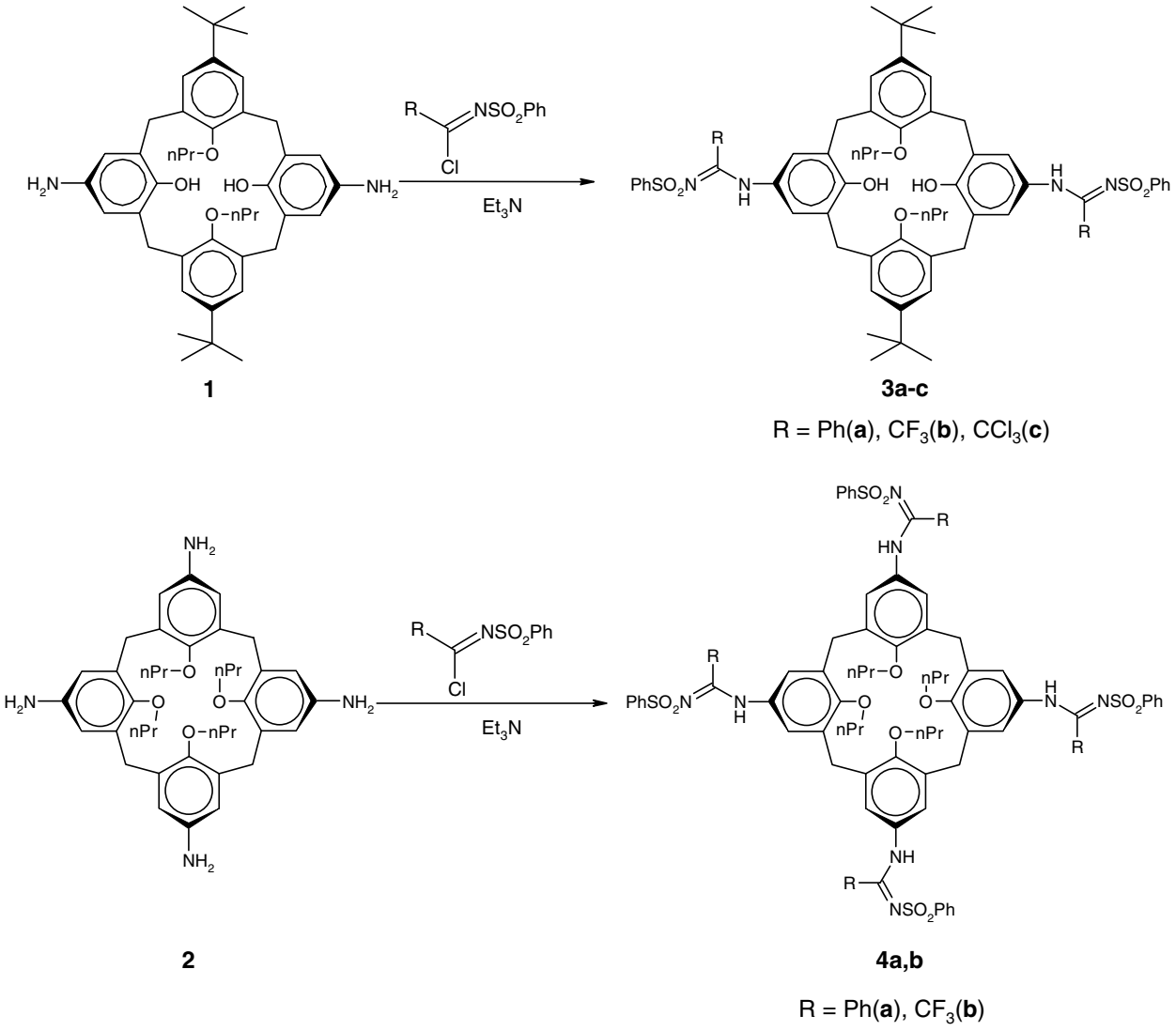

Scheme 1. Synthesis of compounds **3** and **4**.

protons of the bridges. This pattern is characteristic of the cone conformation in which all the aromatic rings are pointing in one direction.[16] It seems plausible that the cone conformation of compounds **3** may be stabilized by two intramolecular hydrogen bonds, $OH\cdots OC_3H_7$, at the narrow rim of the macrocycle.[17] Indeed, the IR spectra of **3** in $CHCl_3$ contains a stretching band for the O–H bond at 3290–3310 cm^{-1}, which does not change its shape and position within the concentration range 0.05–0.005 M.

Diffraction quality crystals of **3b** were obtained by slow crystallization from toluene. The molecule of **3b** adopts a somewhat distorted (pinched) cone conformation (Fig. 1). The dihedral angle between the rings bearing the *tert*-butyl groups is 39.52(8)° while the rings with the sulfonylamidine fragments attached forms an angle of 97.04(8)°.[18] Two intermolecular hydrogen bonds are formed between the hydroxy groups and propoxy fragments at the narrow rim because the distances O(1B)–O(1C) and O(1A)–O(1D) equal 2.740(3) Å and 2.677(2) Å, respectively. One C–CF_3 bond is pointing towards and the other outwards from the plane of the macrocycle. Such a geometry completely excludes the intramolecular hydrogen bonding involving N–$H\cdots O_2S$, so that intermolecular hydrogen bonds are formed (N–O distances −2.852(3) to 2.877(3) Å), which result in 12-membered hydrogen bonded rings. In this way molecules of **3b** form hydrogen bonded chains (Fig. 2). The phenyl rings of the sulfonylamidine fragments of **3b** are accommodated in the nearby calixarene cavities. Apparently, this self-inclusion is caused by the requirements of dense packing for the crystal. The shortest distances between carbon atoms of the included phenyl residues and the hydrogen atoms of the phenyl residues are 3.742 Å and indicate weak CH–π interactions.

The sulfonylamidine groups of **3b** also form hydrogen bonds in non-polar solvents. The IR spectrum of **3b** measured in $CHCl_3$ contains a broad band between 3275 and 3300 cm^{-1} characteristic of the hydrogen bonds, N–$H\cdots O{=}S$. The independence of the shape and position of this band on concentration indicates

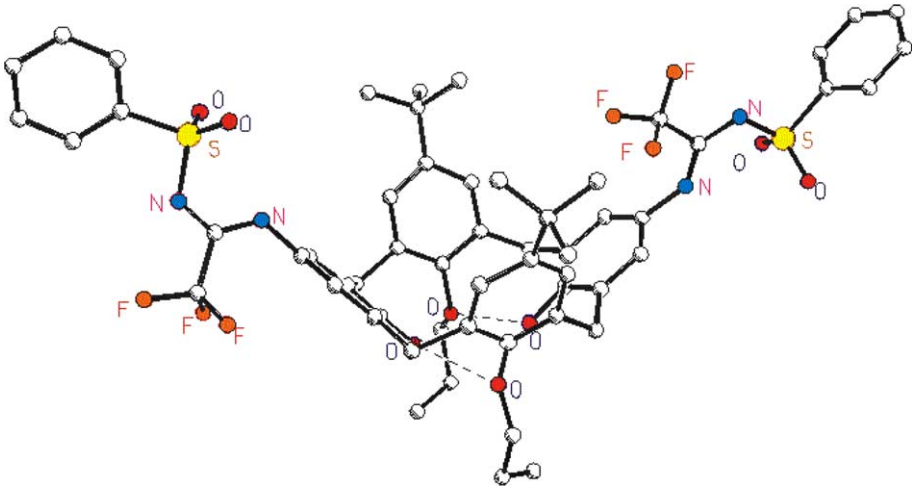

Figure 1. Molecular structure of **3b**.

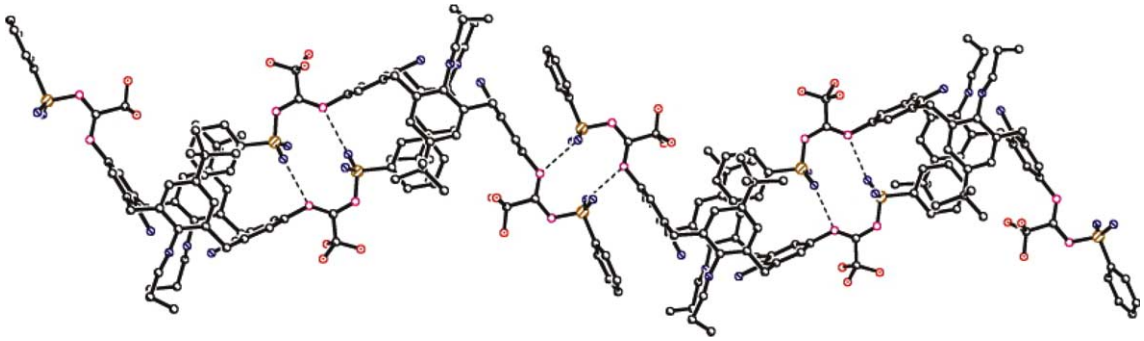

Figure 2. Crystal packing of **3b**. Hydrogen bonds are shown by dashed lines.

that the hydrogen bonds are intramolecular. Accordingly, the ^{1}H NMR spectrum of **3b** in $CDCl_3$ contains a broad singlet at δ 9.73 ppm for the NH amidine protons—which shows rather strong hydrogen bonding. As expected the position of this signal is independent of the concentration.

The energy minimized structure of the model N^1-methanesulfonyl-N^2-phenyltrifluoroacetamidine **5** is shown in Figure 3. The SO_2 and the NH groups form intramolecular hydrogen bonds, which results in a six-membered cyclic hydrogen bonded array. It seems plausible that two such arrangements could be formed at the wide rim of **3b** in $CHCl_3$. The fact that in the crystalline state the intermolecular hydrogen bonds are preferred implies a relative weakness of the intermolecular hydrogen bonding in solution.

The ability of the calix[4]arenesulfonylamidines to form intermolecular hydrogen bonds as well as 'host–guest' inclusion complexes indicates their affinity to protein surfaces[7c,12a] or bio-membrane compartments.[14a,15]

We examined the effect of calixarene **4b** on the activity of the sarcoplasmic reticulum and plasma membrane calcium pumps, Ca^{2+} accumulation in mitochondria and the catalytic activity of the plasma membrane

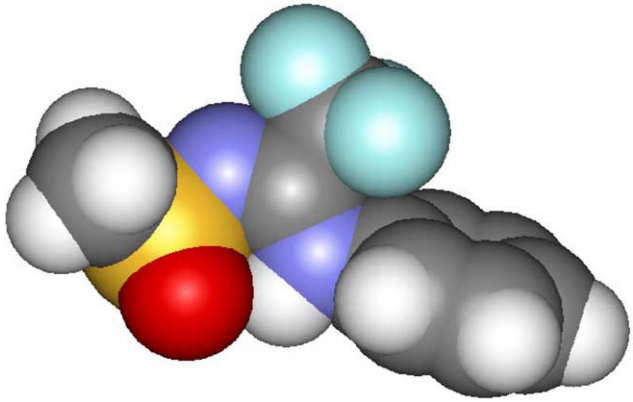

Figure 3. Energy minimized structure of N^1-methanesulfonyl-N^2-phenyltrifluoroacetamidine **5** (ab initio, 6-31G*).

Ca^{2+}-independent Mg^{2+}-ATPase and ouabaine-suppressed Na^+, K^+-ATPase of myometrium.[19]

The effect of calixarene **4b** (100 μM) on the ruthenium red insensitive, oxalate-stimulated and thapsigargin-suppressed Mg^{2+}, ATP-dependent Ca^{2+} accumulation (Mg^{2+}, ATP-dependent calcium pump) in the myometrial sarcoplasmic reticulum was studied. In this case Ca^{2+} transport was decreased by 75%. A similar result

was obtained with the Ca^{2+}, Mg^{2+}-ATPase (Mg^{2+}, ATP-dependent calcium pump) purified from the plasma membrane (the value of the inhibitory effect is 70%). On the other hand calixarene **4b** did not affect the ruthenium red sensitive and thapsigargin-insensitive Ca^{2+}-transport in mitochondria and the catalytic activity of the plasma membrane Ca^{2+}-independent Mg^{2+}-ATPase and ouabaine-suppressed Na^{+}, K^{+}-ATPase.

In conclusion, the effect of calixarene **4b** on Ca^{2+} exchange in the smooth muscle might be useful for identification of the role of the Mg^{2+}, ATP-dependent Ca^{2+} pumps of the sarcoplasmic reticulum and plasma membrane in regulation of free Ca^{2+} concentration in cells.

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Supplementary data

Information available: Experimental procedures and characterization for **1**, **3** and **4**, crystal data for **3b**. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.07.069.

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