JOC Article

Ipso-Chlorosulfonylation of Calixarenes: A Powerful Tool for the Selective Functionalization of the Large Rim

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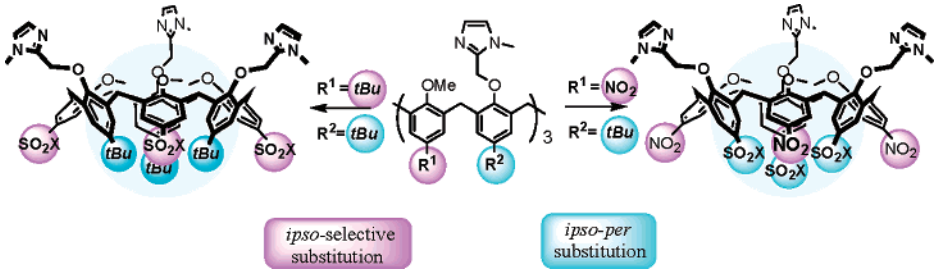

In our quest for the elaboration of supramolecular models of metallo-enzyme active sites, we became interested in developing new methodologies for the selective functionalization of the large rim of calix[6]arenes. Here, we describe a novel reaction, i.e. the *ipso*-chlorosulfonylation of calixarene derivatives. The process has been found to be highly efficient, selective and versatile. The regioselectivity is controlled by the nature of the *O*-substituents at the small rim. Indeed, when *O*-alkylated by a protonable imidazole group, the aromatic rings are deactivated toward an electrophilic attack and the anisol units can be selectively *ipso*-chlorosulfonylated under mild conditions (rt). Performing the reaction at a higher temperature allowed the *per*-chlorosulfonylation to take place. Hence, the synthesis of various sulfonate and sulfonamide derivatives is reported. Finally, a combination of *ipso*-nitration and chlorosulfonylation allows the *per*-functionalization of the aromatic units at the large rim in selective alternate positions. Overall, this novel methodology opens new routes to a variety of calixarenes, allowing the tuning of their physical properties without drastically altering their hydrophobic conic cavities.

Introduction

Over the past few years, we have been developing a novel supramolecular model of metallo-enzyme active sites. The system is based on a calix[6]arene functionalized at the small rim by three imidazolyl arms (**2**) that mimic the coordination core encountered in enzymes. Upon binding a transition-metal ion, the calix[6]arene-based ligand is constrained to a cone conformation, thereby mimicking the enzyme funnel that controls the access to the metal center (Figure 1).[1] An additional challenge is the water-solubilization of this hydrophobic model system. Indeed, important and fundamental information is expected from the comparison of the chemical properties, in an organic solvent and in aqueous solution, of the metal ion embedded in these hydrophobic pockets within the same first and second coordination sphere. Our strategy consists of the modification of the organic structure through the introduction of hydrophilic groups at the large rim of the calixarene in place of the *t*Bu substituents (R^1, R^2, Figure 1).

Classically, *ipso*-substitution for sulfonate groups is implemented for obtaining water-soluble calixarenes.[2] We have made use of this reaction for the design of water-soluble *tris*(imid-

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(1) Sénèque, O.; Campion, M.; Giorgi, M.; Le Mest, Y.; Reinaud, O. *Eur. J. Inorg. Chem.* **2004**, *9*, 1817−1826. Sénèque, O.; Giorgi, M.; Reinaud, O. *Supramol. Chem.* **2003**, *15*, 573−580. Rondelez, Y.; Rager, M.-N.; Duprat, A.; Reinaud, O. *J. Am. Chem. Soc.* **2002**, *124*, 1334−1340. Sénèque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2001**, *123*, 8442−8443. Seneque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2000**, *122*, 6183−6189.

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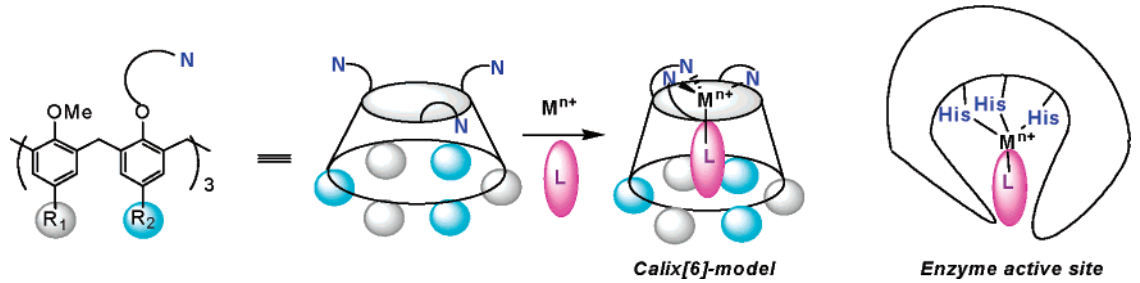
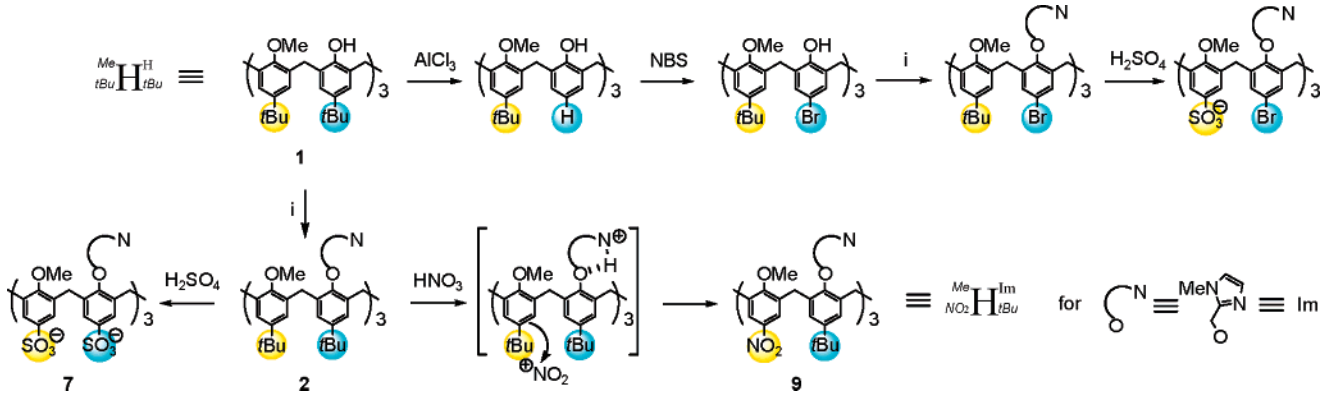


FIGURE 1. Calix[6]arene-based supramolecular modeling of metallo-enzyme active sites. $R^1 = R^2 = t$Bu: organo-soluble system; $R^1 = SO_3^-$, $R^2 =$ Br: water-soluble system.

SCHEME 1. Various Strategies for the Introduction of Hydrophilic Substituents at the Large Rim of Calix[6]arene N_3-Ligands[6]



azole) ligands. However, when direct sulfonation was carried out on the *tris*(imidazole) ligand, *per*-sulfonation occurred (Scheme 1), leading to the formation of a *hexa*-anion (**7**) that could not be constrained in the desired cone conformation due to excess anionic repulsion at the large rim. Hence, a good ligand design requires sulfonation of only three out of the six phenol units. This lead us to follow a de-tert-butylation−protection sequence on alternate aromatic units in order to prevent the *hexa*-sulfonate derivative to form at the final step. First, the *t*Bu substituents of the three phenol units were selectively removed with $AlCl_3$, and then the corresponding free *para*-positions were protected by bromine substituents (Scheme 1). Starting from the C_{3v} symmetrical *tris*-OMe *t*Bu-calix[6]arene (**1**), we selectively obtained within four steps a *tris*-imidazole ligand with only three sulfonate substituents in alternate positions.[3] Wanting to develop new methodologies for the selective functionalization at the large rim of calixarenes, we began to explore various *ipso*-reactions. Interestingly, we discovered the possibility of performing selective *ipso*-nitration on *per*-*O*-alkylated calixarenes (**9**).[4] The regioselectivity of the process is correlated to the presence of a protonable site on the *O*-substituent. The corresponding protonated heteroatom (N for the amines, O for the amides and the carboxylic acid), situated in γ-position of the phenoxyl moieties, deactivates the corresponding aromatic ring by removing electron density through intramolecular hydrogen bonding. Unfortunately, attempts to perform selective *ipso*-sulfonation with sulfuric acid under various conditions remained unsuccessful, invariably leading to a nonselective process[5] (Scheme 1).

In strong contrast, however, reaction with sulfonyl chloride turned out to be extremely efficient and selective, leading to the chlorosulfonyl derivatives (**3**). These electrophilic intermediates could be subsequently either hydrolyzed into sulfonate derivatives, or reacted with amines to provide sulfonamide derivatives. This reaction has been developed for the *tris*(imidazole) calix[6]arene ligand (**2**), opening new synthetic pathways for the selective functionalization at the large rim and the water-solubilization of such hydrophobic edifices.

Results

Tris(imidazole) calix[6]arene $^{Me}_{tBu}H^{Im}_{tBu}$ (**2**) was obtained by alkylation of the residual phenol units of the symmetrically 1,3,5-*tris*-*O*-methylated calix[6]arene $^{Me}_{tBu}H^{H}_{tBu}$ (**1**) with 2-chloromethyl-1-methyl-1*H*-imidazole, according to the previously reported procedure (85% yield, Scheme 1).[6,7]

Selective *Ipso*-Chlorosulfonylation and Related Calix[6]arene Derivatives. When $^{Me}_{tBu}H^{Im}_{tBu}$ (**2**) was reacted with chlorosulfonyl acid (150 equiv) in dry dichloromethane, first at 0 °C for a few minutes, then at room temperature for 1 h, the tris(chlorosulfonyl) derivative $^{Me}_{SO_2Cl}H^{ImH+}_{tBu}$ (**3**) was selectively produced. The ^{1}H NMR spectrum of the crude product displayed a profile that is characteristic of a major C_{3v}-symmetrical compound. The remaining *t*Bu substituents presented a single

(2) Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, *108*, 2409−2416. Shinkai, S.; Mori, S.; Tsubaki, T.; Sone, T.; Manabe, O. *Tetrahedron Lett.* **1984**, *25*, 5315−5318.

(3) Rondelez, Y.; Bertho, G.; Reinaud, O. *Angew. Chem., Int. Ed.* **2002**, *41*, 1044−1046.

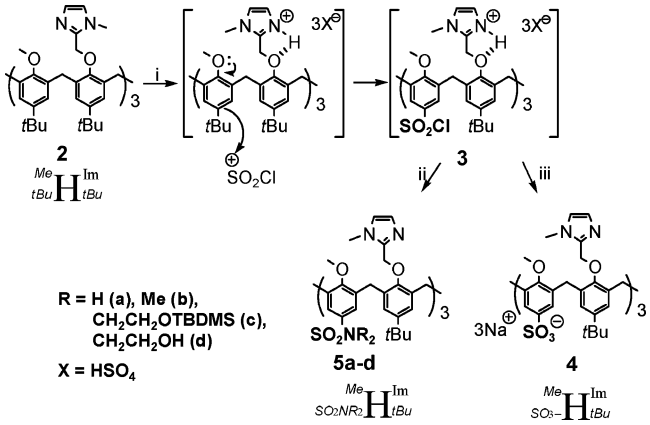
(4) Redon, S.; Li, Y.; Reinaud, O. *J. Org. Chem.* **2003**, *68*, 7004−7008.

(5) Rondelez, Y. Ph.D. Thesis, defended Sep 25, 2002.

(6) In our notation, the C_{3v} symmetrical calixarene core is symbolized by H and the small and large rim substituents are depicted by exponents and indexes, respectively.

(7) Sénèque, O.; Rager, M. N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2000**, *122*, 6183−6189.

SCHEME 2. Selective *Ipso*-Chlorosulfonylation of Tris-imidazole Calix[6]arene $^{Me}_{tBu}H^{Im}_{tBu}$ (2) and Subsequent Hydrolysis or Aminolysis[a]



[a] Reagents and conditions: (i) HSO_3Cl, CH_2Cl_2, 0 °C then rt; (ii) HNR_2, base, CH_2Cl_2, rt; (iii) base, DMSO/H_2O, 80 °C.

resonance at 0.8 ppm, integrating for 27 protons. Whereas one aromatic resonance was almost unchanged compared to the starting compound, the other was high-field shifted by 0.6 ppm, indicating *para*-substitution of three aromatic units by an electron-withdrawing group (SO_2Cl). All of this information indicates that calix[6]arene $^{Me}_{tBu}H^{Im}_{tBu}$ (**2**) has been selectively *ipso*-chlorosulfonylated on alternate positions. However, the broadness of its ^1H NMR resonances, probably due to a flexibility increase of the calixarene core, did not allow us to determine, by C−H correlation experiments, which *t*Bu groups had been removed.[8] Hence, the product was hydrolyzed in a DMSO/H_2O mixture in the presence of a base and subsequent acidification allowed the isolation of the crystalline *tris*-zwitterion $^{Me}_{SO_3^-}H^{ImH+}_{tBu}$. ^1H NMR analysis in D_2O at room temperature in the presence of NaOD allowed its unambiguous identification. Indeed, an HMQC experiment conducted on $^{Me}_{SO_3^-}H^{Im}_{tBu}\cdot 3Na^+$ (**4**) showed the presence of OMe substituents on the aromatic units shifted high-field, which indicates that the anisole units have been substituted for sulfonate groups. From these analyses, we could deduce that chlorosulfonation selectively proceeded in the *para* position of the anisole cores (Scheme 2) as in the case of *ipso*-nitration (Scheme 1) and yielded $^{Me}_{SO_2Cl}H^{ImH+}_{tBu}$ (**3**). Such a selectivity can be explained by the deactivation of three out of the six aromatic rings toward an electrophilic attack due to the removal of electron density by the protonated imidazolium arm, as in the case of selective nitration.

The *tris*-chlorosulfonyl intermediate $^{Me}_{SO_2Cl}H^{ImH+}_{tBu}$ (**3**) was reacted with various amines to give calix[6]arenes $^{Me}_{SO_2NR_2}H^{Im}_{tBu}$ (**5a**−**d**) presenting three sulfonamide substituents on the anisole units. With NH_3, $NHMe_2$, and TBDMS-protected diethanolamine (DEA),[9] the yields of pure product starting from

(8) According to the ^1H NMR spectra of the crude chlorosulfonyl-calixarenes isolated by precipitation with ether, these reactive intermediates were relatively pure and a unique regio-isomer was identified. Further purification for elemental analyses purpose failed, probably due to partial and uncontrolled hydrolysis or polymerisation when dried under high vacuum. Therefore, they were directly engaged in either hydrolysis or aminolysis.

(9) *O*-Protection of diethanolamine by tertiobutyldimethylsilyl groups (TBDMS) appeared necessary to avoid competitive hydrolysis of the chlorosulfonyl intermediate. Indeed, when unprotected diethanolamine was used, sulfonate derivatives were obtained.

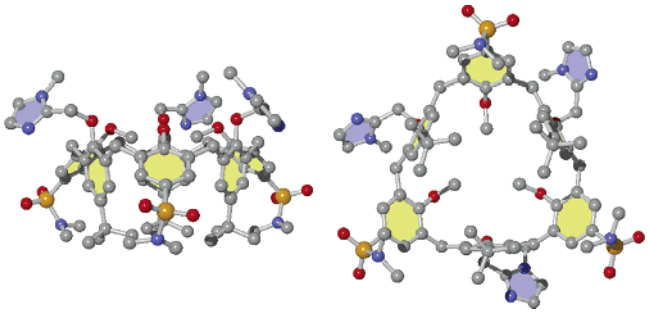


FIGURE 2. X-ray structure of tris-sulfonamide calix[6]ligand $^{Me}_{SO_2NMe_2}H^{Im}_{tBu}$ (**5b**). Left and right: bottom and side views, respectively. Hydrogen atoms and solvents of crystallization are omitted for clarity.

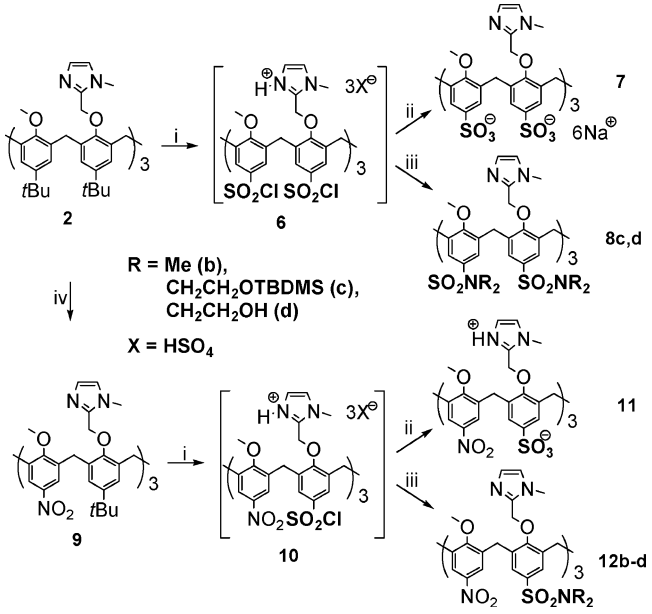
$^{Me}_{tBu}H^{Im}_{tBu}$**2**) were quite good (41%, 56%, and 42%, respectively), considering that the two steps, chlorosulfonylation and aminolysis, involve reactions that are repeated three times on each molecule. Whereas the SO_2NMe_2 and the SO_2DEATBDMS derivatives could be purified by crystallization and chromatography, respectively, $^{Me}_{SO_2NH_2}H^{Im}_{tBu}$ (**5a**) was obtained pure only after the sequential complexation /decomplexation procedure with zinc perchlorate. The TBDMS derivative was deprotected in a final step with TFA to provide $^{Me}_{SO_2DEA}H^{Im}_{tBu}$ (**5d**) (87%).

X-ray quality crystals of tris-sulfonamide $^{Me}_{SO_2NMe_2}H^{Im}_{tBu}$ (**5b**) were grown out of a MeOH solution. The molecular structure is presented in Figure 2. It shows the calix[6]arene derivative in a flattened cone conformation. The three aromatic units linked to the imidazole arms are *para*-substituted by dimethylamino-sulfonamide groups that are in the *in* position relative to the remaining *t*Bu substituents present on the anisole units. All sulfonamide groups point their dipole toward the outside with hydrogen bonding between their oxygen atoms and co-crystallized MeOH solvent molecules. The bulky imidazole arms are projected away from the calixarene C_3 axis while the methoxy substituents are oriented toward the hydrophobic cavity. The overall structure is quite similar to that adopted by the *per*-substituted parent compound with a $C_{tBu}\cdots C_{tBu}$ average distance of 13.45 and 6.57 Å for the *in* and *out* positions, respectively, compared to 12.86 and 6.24 Å for the hexa-*t*Bu pyrazolyle analogue ($^{Me}_{tBu}H^{Pyrazol}_{tBu}$).[10] This shows that the calixarene conformation has been barely affected by the *ipso*-substitution at the lower rim.

***Per*-Chlorosulfonation and Related Calix[6]arene Derivatives.** When the tris-imidazole *t*Bu-substituted ligand $^{Me}_{tBu}H^{Im}_{tBu}$ (**2**) was reacted with HSO_3Cl at higher temperature (reflux of dichloromethane), *per*-chlorosulfonylation occurred and the *hexa*-chlorosulfonyl derivative $^{Me}_{SO_2Cl}H^{Im}_{SO_2Cl}$ (**6**) was obtained. Again, subsequent hydrolysis yielded the corresponding sulfonate compound $^{Me}_{SO_3^-}H^{Im}_{SO_3^-}$ (**7**) (68%) that is identical to the compound obtained through direct sulfonation with concentrated H_2SO_4.[5] $^{Me}_{SO_2Cl}H^{Im}_{SO_2Cl}$ (**6**) was also reacted with an amine (TBDMS-diethanolamine) to give the corresponding *hexa*-sulfonamide (18% yield), which was subsequently deprotected with TFA to provide $^{Me}_{SO_2DEA}H^{Im}_{SO_2DEA}$ (**8d**). Hence, a higher reaction temperature allowed the *ipso*-chlorosulfonylation to proceed on all aromatic rings, including the deactivated *O*-methylimidazolylium units. This stands in contrast to *ipso*-nitration; as in the latter case, more drastic experimental

(10) Sénèque, O.; Rondelez, Y.; Le Clainche, L.; Inisan, C.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *Eur. J. Inorg. Chem.* **2001**, *10*, 2597−2604.

SCHEME 3. Full *Ipso*-Substitution of the *t*Bu-Aromatic Units of Ligand $^{Me}_{tBu}H^{Im}_{tBu}$ (2) through Either *Per*-chlorosulfonylation or Sequential Nitration−Chlorosulfonylation[a]



[a] Reagents and conditions: (i) HSO_3Cl, CH_2Cl_2, 0 °C then reflux; (ii) base, DMSO/H_2O, 80 °C; (iii) HNR_2, base, reflux; (iv) HNO_3/AcOH (1:1) CH_2Cl_2, 0 °C then rt.

conditions only led to the decomposition of the products and *per*-nitration could not be performed.

The versatility of the chlorosulfonylation reaction allowed its combination with *ipso*-nitration. Indeed, when the tris-nitrated derivative $^{Me}_{NO_2}H^{Im}_{tBu}$ (**9**) was reacted with HSO_3Cl at reflux of dichloromethane, *ipso*-chlorosulfonation cleanly[8] proceeded to give $^{Me}_{NO_2}H^{Im}_{SO_2Cl}$ (**10**) (Scheme 3). Subsequent hydrolysis yielded (61%) the *tris*-sulfonate derivative $^{Me}_{NO_2}H^{Im}_{SO_3^-}$ (**11**) that presents anionic substituents in reverse positions relative to the *O*-substituents compared to the above-described $^{Me}_{SO_3^-}H^{Im}_{tBu}$ (**4**) calix[6]arene derivative.

The chlorosulfonylcalix[6]arene intermediate $^{Me}_{NO_2}H^{Im}_{SO_2Cl}$ (**10**) was also reacted with various amines (Scheme 3). The corresponding sulfonamido derivatives $^{Me}_{NO_2}H^{Im}_{SO_2NR_2}$ (**12b**) were isolated with relatively good yields for $NHMe_2$ (R = Me, 44%) and at lower yield (17%) for the bulkier TBDMS-diethanolamine (**12c**) (R = $CH_2CH_2OTBDMS$). Final deprotection of the diethanolsulfonamide substituents led to the corresponding calixarene ($^{Me}_{NO_2}H^{Im}_{SO_2DEA}$ **12d**) in good yield (71%).

^{1}H NMR Analyses. The ^{1}H NMR spectra of the sulfonyl derivatives have been recorded in various solvents, depending on their solubility properties. Table 1 reports the chemical shifts characteristic of each compound at the temperature where sharp resonances could be observed. Under these conditions, all compounds displayed a very simple profile characteristic of a C_{3v} symmetry. Among these, two families can be distinguished.

The first one (top part of Table 1) displays two pairs of doublet for the Ar−CH_2 protons belonging to the calixarene core. One stands for the six axial protons, the other for the six equatorial ones, which denotes a cone−cone inversion that is slow compared to the NMR time scale analyses. These compounds display a high-field shifted OCH_3 resonance (δ ~2.1−2.7 ppm) indicating an *in* position relative to the calixarene cavity. Indeed, the bulkier imidazolyl arms are projected away from the calixarene core that, as a result, adopts a flattened cone conformation. Hence, the remaining *t*Bu groups of compounds $^{Me}_{R_1}H^{Im}_{tBu}$ (**2**−**5** except **9** for which $R^1 = NO_2$) are all stacked together next to the C_{3v} axis (δ ~0.8 ppm), closing the entrance of the cavity, while the anisole substituents are oriented in an *out* position. All calixarenes presenting identical substituents at the lower rim adopt this conformation (depicted

TABLE 1. ^{1}H NMR Chemical Shifts of Calix[6]arenes $^{Me}_{R_1}H^{Im}_{R_2}$ (250 MHz) and Yields of *Ipso*-Substitution

				small rim		calixarene core			large rim			
no.	$^{Me}_{R_1}H^{Im}_{R_2}$	solvent	T (K)	OMe	NMe	Im-CH_2	H_{Ar}	H_{Ar}	*t*Bu	NCH_2	OCH_2	yield (%)
2	$^{Me}_{tBu}H^{Im}_{tBu}$	$CDCl_3$	300	2.13	3.87	4.99	6.60	7.20	0.75/1.35			
9	$^{Me}_{NO_2}H^{Im}_{tBu}$	$CDCl_3$	330	3.18	3.22	4.72	6.94	7.73	1.13			80[a]
3	$^{Me}_{SO_2Cl}H^{ImH+}_{tBu}.3HSO_4^-$	DMSO	350	nd	nd	5.23	6.78	7.51	0.93			70[d]
4	$^{Me}_{SO_3^-}H^{Im}_{tBu}\cdot 3Na^+$	D_2O	300	2.19	3.56	5.04	6.61	7.68	0.77			66[b]
5a	$^{Me}_{SO_2NH_2}H^{Im}_{tBu}$	DMSO	300	2.17	3.73	5.00	6.52	7.77	0.78			41[b]
5b	$^{Me}_{SO_2NMe_2}H^{Im}_{tBu}$	DMSO	350	2.25	3.77	4.99	6.54	7.77	0.78			56[b]
5c	$^{Me}_{SO_2DEATBDMS}H^{Im}_{tBu}$	CD_3CN	340	2.66	3.66	4.94	6.76	7.66	0.90	3.32	3.82	42[b]
5d	$^{Me}_{SO_2DEA}H^{Im}_{tBu}$	CD_3CN	340	2.94	3.43	4.81	6.87	7.63	1.01	3.25	3.68	87
10	$^{Me}_{NO_2}H^{ImH+}_{SO_2Cl}\cdot 3HSO_4^-$	DMSO	350	3.22	3.53	5.15	7.34	7.74				>90[d]
11	$^{Me}_{NO_2}H^{ImH+}_{SO_3^-}$	D_2O[c]	350	2.90	3.55	4.69	7.58	7.65				61[b]
12b	$^{Me}_{NO_2}H^{Im}_{SO_2NMe_2}$	DMSO[c]	350	3.24	3.32	4.89	7.41	7.74				41[c]
12c	$^{Me}_{NO_2}H^{Im}_{SO_2DEATBDMS}$	CD_3CN	300	2.66	3.66	4.94	6.76	7.66		3.32	3.82	17[b]
12d	$^{Me}_{NO_2}H^{Im}_{SO_2DEA}$	CD_3CN	340	3.29	3.37	4.87	7.53	7.86		3.14	3.62	71
6	$^{Me}_{SO_2Cl}H^{ImH+}_{SO_2Cl}\cdot 3HSO_4^-$	DMSO	370	2.97	3.62	5.18	7.31	7.45				>90[d]
7	$^{Me}_{SO_3^-}H^{Im}_{SO_3^-}\cdot 6Na^+$	DMSO	300	2.55	3.73	5.01	7.23	7.54				66[b]
8c	$^{Me}_{SO_2DEATBDMS}H^{Im}_{SO_2DEATBDMS}$	CD_3CN	300	3.72	3.72	4.87	7.31	7.47		3.16/3.30	3.41/3.72	18[b]
8d	$^{Me}_{SO_2DEA}H^{Im}_{SO_2DEA}$	CD_3OD	300	3.26	3.67	5.03	7.30	7.55		3.08/3.15	3.74/3.82	65

[a] See ref 4. [b] Two steps. [c] 1% NaOD/D_2O v/v. [d] Yield estimated from ^{1}H NMR analyses. nd: not determined.

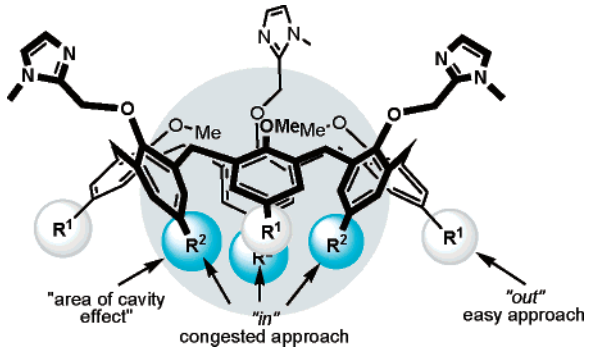


FIGURE 3. Schematized flattened cone conformation adopted by the calixarene ligands.

in Figure 3), which fully corresponds to the one observed in the solid-state structure of $^{Me}_{SO_2NMe_2}H^{Im}_{tBu}$ (**5b**) (Figure 2).

The second family is characterized by a single resonance for the calixarene Ar−C*H*$_2$ protons, indicating a much faster cone-cone inversion. Obviously, this is related to a decrease in steric bulk at the lower rim of the anisol units. Indeed, the replacement of the *t*Bu substituents for nitro groups increases the rate at which the anisol units can flip upside down. As a result, these calixarenes appear much more conformationaly mobile than those belonging to the first family.

The conformation depicted in Figure 3 may well explain the relatively low yields obtained for the aminolysis of the chlorosulfonyl derivatives, $^{Me}_{NO_2}H^{Im}_{SO_2Cl}$ (**10**) and $^{Me}_{SO_2Cl}H^{Im}_{SO_2Cl}$ (**6**), when reacting with the bulky TBDMS-DEA. In both cases, three chlorosulfonyl groups are projected in the *in* position by the imidazolyl arms. This probably decreases their accessibility and therefore their reactivity toward a bulky nucleophile. As a matter of fact, when reacted with the same amine, calixarene $^{Me}_{SO_2Cl}H^{Im}_{tBu}$ (**3**) gives a much higher yield, despite the presence of the *t*Bu groups that are bulkier than SO_2Cl or NO_2, since the chlorosulfonyl groups are in the more accessible *out* position. In the case of aminolysis with small amines (Me_2NH), the congested approach did have a significant effect and their reaction with $^{Me}_{NO_2}H^{Im}_{SO_2Cl}$ (**10**) led to the products with satisfactory yields.

Conclusion

We have herein described a novel reaction leading to the selective *ipso*-functionalization of the large rim of calix[6]arenes. This reaction allows the direct introduction of chlorosulfonyl groups in the *para* position of *O*-alkylated phenolic units with *ipso*-substitution of the corresponding *t*Bu groups. To our knowledge, only one precedent of such a reaction has been reported with a thiacalixarene.[11] Otherwise, only reactions between chlorosulfonic acid and calixarene possessing free *para*-positions have been reported in the literature.[12] Yet, this paper shows the general scope of *ipso*-chlorosulfonylation in the calixarene family. The *ipso*-process revealed itself to be not only highly efficient but also regioselective, provided that the calixarene is functionalized by deactivating, protonable *O*-substituents at the small rim. Hence, the calix[6]arene *tris*-imidazole ligand can either be selectively *tris*-chlorosulfonylated by HSO_3Cl on the anisole units, or *per*-chlorosulfonylated when the reaction temperature is raised. Up to now, the only case of selective chlorosulfonylation concerned the selective substitution of calix[4]arenes presenting unsubstituted phenolic units at their *para*-position.[13]

The versatility of this novel reaction allowed its combination with *ipso*-nitration for the *per*-functionalization of the large rim of the calix[6]arene by hydrophilic substituents. The synthesis of a series of calixarenes bearing sulfonate, sulfonamide and nitro substituents has been achieved. When presenting anionic groups, the compounds are soluble in pure water at 5 mM concentration ($^{Me}_{SO_3^-}H^{Im}_{tBu}$**4**) or higher ($^{Me}_{NO_2}H^{Im}_{SO_3^-}$ **11**, $^{Me}_{SO_3^-}H^{Im}_{SO_3^-}$ **7**). With only neutral substituents, the calixarene ligands are soluble (5 mM) in a 1:1 mixture of an organic solvent (such as MeCN, MeOH, or acetone) and water.

We are currently exploring the coordination of metal ions based on these new calix-ligands in the perspective of comparing the chemical properties of the resulting complexes to those of their organosoluble parent conpounds.

Experimental Section

Safety Note. *Caution!* Although we have not encountered any problem, it is noted that perchlorate salts of metal complexes with organic ligands are potentially explosive and should be handled only in small quantities with appropriate precautions.

Diethanolamine (DEA) was selectively *O*-alkylated under classical conditions to give the corresponding protected amine (TBDMS-DEA) in a quantitative yield.[13]

Selective *ipso*-Sulfonylation ($^{Me}_{SO_2Cl}H^{ImH^+}_{tBu}\cdot 3HSO_4^-$ 3). Chlorosulfonic acid (3.10 mL, 46.69 mmol, 150 equiv) was slowly added (over a 5 min period) to a solution of $^{Me}_{tBu}H^{Im}_{tBu}$ **2** (404 mg, 0.31 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at 0 °C. The solution was stirred for 2 h at room temperature after which dry ether (50 mL) was added. The crude oil was separated from the mother liquor, triturated twice with dry ether (30 mL) to give a tan powder that was finally dried under vacuum (502 mg).

***Per Ipso*-Sulfonylation ($^{Me}_{SO_2Cl}H^{ImH^+}_{SO_2Cl}\cdot 3HSO_4^-$ 6 and $^{Me}_{NO_2}H^{ImH^+}_{SO_2Cl}\cdot 3HSO_4^-$ 10).** Chlorosulfonic acid (50 equiv) was slowly added (over a 5 min period) to a solution of $^{Me}_{tBu}H^{Im}_{tBu}$ (**2**) or $^{Me}_{NO_2}H^{Im}_{tBu}$ (**9**) (1 equiv) in CH_2Cl_2 (11 mL) at 0 °C. The solution mixture was brought to reflux for 2 h under vigorous stirring. After cooling, dry ether (20 mL) was added to the brown nonhomogeneous mixture and the resulting oil separated from the mother liquor. The oil was triturated twice with dry ether (20 mL) to give the desired chlorosulfonyl derivative as a tan powder that was finely dried under vacuum (1.48 g)

In each case, the ^{1}H NMR analysis of the isolated solid compound showed the presence of the desired chlorosulfonyl derivative as the major species. Due to the broadness of the resonances, its purity could only be estimated to be higher than 80%. These products could not be further purified as they readily decompose to give dark polymeric materials. Therefore, they were directly engaged in subsequent hydrolysis or aminolysis.

General Procedure for the Hydrolysis of the Chlorosulfonyl Derivatives. Excess *tris*-ethanolamine (TRIS) was added to a solution of the chlorosulfonyl-calixarene in DMSO. The resulting basic solution was heated to 80 °C for 12 h. Upon addition of CH_2Cl_2, an oil separated that was isolated by centrifugation.

4$\{^{Me}_{SO_3^-}\mathbf{H}^{Im}_{tBu}\cdot 3Na^+\}$**.** The pure sodium salt was obtained from crystallization of the crude product in 1 M $NaOH_{aq}$ (66%): mp > 260 °C dec; MS (ES) (CH_3CN) *m*/*z* 1367.6 (50) (calcd for $[MH_2]^-$

(11) Miyanari, S.; Kumagaya, H.; Hasegawa, S., *Jpn. Kokai Tokkyo Koho*. **1999**, Patent JP 11302275.

(12) Mathieu, A.; Asfari, Z.; Vicens, J. *Tetrahedron Lett*. **2002**, *43*, 1225−1229. Nicod, L.; Pellet-Rostaing, S.; Chitry, F.; Lemaire, M. *Tetrahedron Lett*. **1998**, *39*, 9443−9446. Casnati, A.; Ting, Y.; Berti, D.; Fabbi, M.; Pochini, A.; Ungaro, R.; Sciotto, D.; Lombardo, G. G. *Tetrahedron* **1993**, *49*, 9815−9822.

(13) Morzherin, Y.; Rudkevich, Dmitry. M.; Verbomm, W.; Reinhoudt, David N. *J. Org. Chem.* **1993**, *58*, 7602−7605.

1367.5), 1389.5 (80) (calcd for $[MHNa]^-$ 1389.5); ^{1}H NMR (250 MHz, D_2O, 300 K) δ = 0.77 (s, 27 H, CH_3), 2.19 (s, 9 H, OCH_3), 3.16 (d, 6 H, J = 15 Hz, Ar−CH_2), 3.56 (s, 9 H, NCH_3), 4.21 (d, 6 H, J = 15 Hz, Ar−CH_2), 5.04 (s, 6 H, Im-CH_2), 6.61 (s, 6 H, H_{Ar}), 6.96 (s, 3 H, H_{Im}), 7.11 (s, 3 H, H_{Im}), 7.68 (s, 6 H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO, 300 K) δ 157.1, 151.5, 146.4, 144.5, 144.2, 134.5, 133.2, 129.4, 128.0, 126.6, 123.7, 66.3, 60.4, 34.4, 33.8, 33.4, 31.8, 29.7; IR ν = 1183.3 (SO_3^-) cm^{-1}. The zwitterion could be isolated by precipitation from HCl_{aq} (1 M) and was then dried under vacuum. Anal. Calcd for $^{Me}_{SO_3^-}H^{ImH^+}_{tBu}$(**4**)·4.5$H_2O$: $C_{72}H_{84}N_6O_{15}S_3$·4.5H_2O: C, 59.61; H, 6.46; N, 5.79. Found: C, 59.63; H, 6.17; N, 5.84.

11 $^{Me}_{NO_2}\mathbf{H}^{\mathbf{ImH^+}}_{\mathbf{SO_3^-}}$. This compound was further purified by dissolution of the crude product in 1 M $NaOH_{aq}$, filtration, and precipitation with HCl_{conc} (35%). This method was repeated twice to give a tan solid (61%): mp > 260 dec; ^{1}H NMR (250 MHz, D_2O/NaOD, 350 K; {$^{Me}_{SO_3^-}H^{Im}_{NO_2}$·3$Na^+$}**11**) δ = 2.90 (br s, 9 H, OCH_3), 3.55 (s, 9 H, NCH_3), 3.88 (br s, 12 H, Ar-CH_2), 4.69 (br s, 6 H, Im-CH_2), 6.87 (s, 3 H, H_{Im}), 6.90 (s, 3 H, H_{Im}), 7.58 (s, 6 H, H_{Ar}), 7.65 (s, 6 H, H_{Ar}); IR (KBr): ν = 1611 (NO_2), 1587 (NO_2), 1346, 1522 (SO_3^-), 1216 (SO_3^-), 1042 (SO_3^-) cm^{-1}. Anal. Calcd for $^{Me}_{NO_2}H^{ImH^+}_{SO_3^-}$·5$H_2O$, $C_{60}H_{57}N_9O_{21}S_3$·5H_2O: C, 50.52; H, 4.73; N, 8.84. Found: C, 50.50; H, 4.46; N, 8.74.

7{$^{Me}_{SO_3^-}\mathbf{H}^{Im}_{SO_3^-}$·Na$_6$}. The crude oily product was dissolved in water (1 mL). Addition of HCl_{conc} (35%) led to precipitation of the corresponding tris(imidazolium) salt, which was then redissolved in 4 M $NaOH_{aq}$ (0.5 mL). The *per*-sulfonated sodium salt was isolated from a concentrated aqueous solution by crystallization due to slow diffusion of ether. The pure *hexa*-sulfonate sodium salt was obtained with a 68% yield after trituration with EtOH (2 × 1 mL): MALDI-MS (MeOH) *m*/*z* $[MH]^+$ 1441.0011 (100), $[M - H]^-$ 1439.2155 (100), $C_{60}H_{60}N_6O_{24}S_6$ = $^{Me}_{SO_3^-}H^{Im}_{SO_3^-}$; ^{1}H NMR (250 MHz, DMSO, 300 K) δ = 2.55 (s, 9H, OCH_3), 3.10 (d, 6H, J = 19 Hz, Ar-CH_2), 3.73 (s, 9H, NCH_3), 4.38 (d, 6H, J = 19 Hz, Ar−CH_2), 5.01 (s, 6H, Im-CH_2), 6.90 (s, 3H, H_{Im}), 7.23 (s, 3H, H_{Im}), 7.25 (s, 6H, H_{Ar}), 7.54 (s, 6H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO, 300 K) δ 157.4, 153.9, 144.7, 144.3, 144.1, 134.3, 133.2, 129.6, 128.3, 125.1, 124.0, 67.3, 61.0, 33.6, 28.8; IR ν = 1139 (SO_3^-) cm^{-1}.

Aminolysis with NH_3 and Me_2NH. 5a $^{Me}_{SO_2NH_2}\mathbf{H}^{Im}_{\mathit{t}\mathbf{Bu}}$. Ammoniac was bubbled through a suspension of $^{Me}_{SO_2Cl}H^{ImH^+}_{tBu}$·3$HSO_4^-$ (**3**) (240 mg, 140 μmol) in THF (10 mL) for 45 min. The reaction mixture was then heated to 40 °C for 36 h. Removal of the solvent under vacuum led to a crude solid that was redissolved in THF (15 mL) and stirred with an aqueous saturated Na_2CO_3 solution (15 mL). The aqueous phase was extracted twice with THF (10 mL). The organic phases were dried with Na_2SO_4 and evaporated to give a solid (149 mg) containing 70% of the desired compound according to its ^{1}H NMR analysis (estimated crude yield: 44%). A two-step purification sequence was necessary to obtained the analytically pure product: the crude sulfonamide was converted into its corresponding Zn(II) complex (see below general method).[14] The crude complex (120 mg) was then dissolved in acetonitrile (2.5 mL). Slow diffusion of ether led to precipitation of the impurities. The organic phase was separated and evaporated to dryness to give the pure complex {$^{Me}_{SO_2NH_2}H^{Im}_{tBu}$·Zn($ClO_4^-$)$_2$}. Final decomplexation with sodium hydroxide (vide infra) led to the pure ligand $^{Me}_{SO_2NH_2}H^{Im}_{tBu}$ (**5a**) (41% based on $^{Me}_{tBu}H^{Im}_{tBu}$**2**): MS (ES) (CH_3CN) *m*/*z* 1366.5 (100) (calcd for $[MH]^+$ 1366.6); ^{1}H NMR (250 MHz, DMSO, 300 K) δ 0.78 (s, 27 H, CH_3), 2.17 (s, 9 H, OCH_3), 3.26−3.36 (s (br), 6 H, Ar-CH_2), 3.73 (s, 9 H, NCH_3), 4.33 (d, J = 12.5 Hz, 6 H, Ar−CH_2), 5.00 (s, 6 H, Im-CH_2), 6.52 (s, 6 H, H_{Ar}), 6.89 (s, 3 H, H_{Im}), 7.22 (s, 3 H, H_{Im}), 7.39 (s, 6 H, H_{NH_2}), 7.77 (s, 6 H, H_{Ar}); IR ν = 1336, 1148, 1108 (SO_2NR_2) cm^{-1}.

5b $^{Me}_{SO_2NMe_2}\mathbf{H}^{Im}_{\mathit{t}\mathbf{Bu}}$. Triethylamine (984 μL, 7.01 mmol, 90 equiv) and dimethylammonium chloride (213 mg, 2.65 mmol, 34 equiv) were added to a suspension of $^{Me}_{SO_2Cl}H^{ImH^+}_{tBu}$·3$HSO_4^-$ (**3**) (134 mg, 0.08 mmol) in CH_2Cl_2 (10 mL) at 0 °C, causing dissolution of the starting material. The mixture was heated to 40 °C for 36 h. After removal of the solvents under vacuum, the crude solid was dissolved in THF (10 mL) and washed with aqueous solution (10 mL) saturated with K_2CO_3. The aqueous phase was extracted twice with THF (10 mL). The organic phases were dried with Na_2SO_4 and evaporated to give a crude solid. The pure sulfonamide $^{Me}_{SO_2NMe_2}H^{Im}_{tBu}$ (**5a**) was obtained upon crystallization in methanol (67 mg, 56% based on $^{Me}_{tBu}H^{Im}_{tBu}$**2**): MS (ES) (CH_3CN) *m*/*z* 1450.5 (100) (calcd for $[MH]^+$ 1450.7); ^{1}H NMR (250 MHz, DMSO, 300 K) δ 0.78 (s, 27 H, CH_3), 2.25 (s, 9 H, OCH_3), 2.71 (s, 18 H, $N(CH_3)_2$), 3.56 (d, J = 15 Hz, 6 H, Ar−CH_2), 3.77 (s, 9 H, NCH_3), 4.36 (d, J = 15 Hz, 6 H, Ar-CH_2), 4.99 (s, 6 H, Im-CH_2), 6.54 (s, 6 H, H_{Ar}), 6.90 (s, 3 H, H_{Im}), 7.23 (s, 3 H, H_{Im}), 7.77 (s, 6 H, H_{Ar}); IR ν = 1339, 1145, 1108 (SO_2NR_2) cm^{-1}. Anal. Calcd for $^{Me}_{SO_2NMe_2}H^{Im}_{tBu}$ (**5b**)·3H_2O; $C_{78}H_{99}N_9O_{12}S_3$·3H_2O: C, 63.01; H, 6.98; N, 8.48. Found: C, 63.22; H, 6.65; N, 8.37.

12b $^{Me}_{NO_2}\mathbf{H}^{Im}_{SO_2NMe_2}$. Triethylamine (1.82 mL, 12.99 mmol, 30 equiv) and dimethylammonium chloride (1.05 g, 12.99 mmol, 30 equiv) were added to a suspension of $^{Me}_{NO_2}H^{ImH^+}_{SO_2Cl}$·3$HSO_4^-$ (**10**) (730 mg, 0.43 mmol, 1 equiv) and molecular sieves in CH_2Cl_2 (20 mL) at 0 °C, causing dissolution of the calixarene. The mixture was heated at 40 °C for 48 h. After removal of the solvent under vacuum, the crude solid was dissolved in acetonitrile (50 mL) and washed twice (2 × 20 mL) with an aqueous solution saturated with K_2CO_3 (2 × 20 mL). The organic phases were dried with Na_2SO_4 and evaporated to give a solid (404 mg) containing 80% of the desired compound according to its ^{1}H NMR analysis (estimated crude yield: 63%). A two-step purification sequence was necessary to obtained the analytically pure product: the crude sulfonamide was converted into its corresponding Zn(II) complex (see the general method below).[14] The complex was purified by trituration with 2 × 2 mL of MeOH (322 mg; 44% based on $^{Me}_{NO_2}H^{Im}_{tBu}$ **9**). The pure sulfonamide was obtained after decomplexation (*m* = 300 mg, 41% based on $^{Me}_{NO_2}H^{Im}_{tBu}$**9**): MS (ES) (CH_3CN) *m*/*z* 1317.4 (100) (calcd for $[MH]^+$ 1317.4); ^{1}H NMR (250 MHz, DMSO, 350 K) δ 3.09 (s, 18 H, $N(CH_3)_2$), 3.24 (s, 9 H, OCH_3), 3.32 (s, 9 H, NCH_3), 3.98 (s, 12 H, Ar-CH_2), 4.89 (s, 12 H, Im-CH_2), 6.83 (s, 3 H, H_{Im}), 7.02 (s, 3 H, H_{Im}), 7.41 (s, 6 H, H_{Ar}), 7.74 (s, 6 H, H_{Ar}); ^{13}C NMR (150 MHz, DMSO, 300 K) δ 161.6, 159.1, 144.0, 143.4, 135.3, 135.1, 130.6, 129.1, 127.6, 124.0, 123.3, 66.8, 60.4, 55.6, 37.9, 32.3, 30.4; IR ν = 1523 (NO_2), 1342, 1144, 1100 (SO_2NR_2) cm^{-1}. Anal. Calcd for $^{Me}_{NO_2}H^{Im}_{SO_2NMe_2}$ (**12b**)·1.5NaOH; $C_{66}H_{72}N_{12}O_{18}S_3$·1.5NaOH: C, 53.65; H, 5.01; N, 11.38. Found: C, 53.66; H, 5.01; N, 11.04.

Aminolysis with DEATBDMS. The chlorosulfonylcalixarene (600 mg) was suspended in CH_2Cl_2 (18 mL) with molecular sieves (3 Å) at 0 °C. Triethylamine (30 equiv) and protected diethanolamine (20 equiv) were added, causing dissolution of the starting material. The reaction mixture was refluxed for 48 h. After filtration, the solvent was removed. The resulting oily product was dissolved

(14) The conformational behavior and host properties of the Zn complexes will be described in another paper. For compound **8c**, a sharper spectrum (due to complexation of Zn^{2+}, see ref 1) was obtained upon the addition of $Zn(H_2O)_6(ClO_4)_2$ directly into the NMR tube containing of CD_3CN solution of the ligand: ^{1}H NMR (250 MHz, 340 K) δ 0.03 (s, 36 H, $SiMe_2$), 0.13 (s, 36 H, $SiMe_2$), 0.89 (s, 54 H, Si*t*Bu), 0.96 (s, 54 H, Si*t*Bu), 3.15 (t, 12 H, J = 5.8 Hz, NCH_2), 3.31 (d, 6 H, J = 15.7 Hz, Ar-CH_2), 3.42 (t, 12 H, J = 6.2 Hz, NCH_2), 3.63 (t, 12 H, J = 5.8 Hz, OCH_2), 3.84 and 3.87 (two s, 18 H, OCH_3 and NCH_3), 3.87 (t, 12 H, J = 6.2 Hz, OCH_2), 4.12 (d, J = 15.7 Hz, 6 H, Ar-CH_2), 5.12 (s, 6 H, Im-αCH_2), 6.80 (s, 6 H, H_{Ar}), 7.03 (d, 3 H, J = 1.5 Hz, H_{Im}), 7.54 (d, 3 H, J = 1.5 Hz, H_{Im}), 7.91 (s, 6 H, H_{Ar}).

(15) Bruker-Nonius 1998. Kappa CCD Reference Manual. Nonius B. V., P.O. Box 811, 2600 Av, Delft, The Netherlands.

(16) Otwinowsky, Z.; Minor, W. *Methods Enzymol*. **1997**, *276*, 307−326.

(17) Sheldrick, G. M. 1997. SHELXL97. Program for the refinement of crystal structures. University of Gottingen, Germany.

in CH_3CN (200 mL), washed with pentane (2 × 50 mL) and evaporated to dryness. The product was then dissolved in CH_2Cl_2 (200 mL), washed with 1 M $NaOH_{aq}$ (2 × 50 mL), and dried with Na_2SO_4. Removal of the solvent under reduced pressure lead to the crude sulfonamide.

5c $_{SO_2DEATBDMS}^{Me}H_{tBu}^{Im}$. The crude oil was further purified by column chromatography using CH_2Cl_2/MeOH 97:3 as an eluent. A colorless compound was obtained (42% based on $_{tBu}^{Me}H_{tBu}^{Im}$**2**): ^{1}H NMR (250 MHz, CD_3CN, 340 K) δ 0.08 (s, 36 H, $SiMe_2$), 0.90 (br s, 81 H, CH_3), 2.66 (br s, 9 H, OCH_3), 3.32 (t, 12 H, J = 6.3 Hz, NCH_2), 3.66 (br s, 9 H, NCH_3), 3.82 (t, J = 6.3 Hz, OCH_2), 3.2−4.6 (br s, 12 H, Ar−CH_2), 4.94 (s, 6 H, Im-CH_2), 6.76 (s, 6 H, H_{Ar}), 6.91 (s, 3 H, H_{Im}), 6.99 (s, 3 H, H_{Im}), 7.66 (s, 6 H, H_{Ar}); ^{13}C NMR (150 MHz, CD_3CN, 300 K) δ 161.3, 154.3, 147.5, 144.8, 136.7, 134.7, 134.5, 130.8, 128.5, 124.7, 123.6, 67.5, 63.5, 61.1, 53.2, 34.9, 33.6, 31.9, 30.3, 26.3, 18.9; IR ν = 2928 ($OSiR_3$), 1096 (SO_2NR_2) cm^{-1}. Anal. Calcd for $_{SO_2DEATBDMS}^{Me}H_{tBu}^{Im}$ (**5c**); $C_{120}H_{205}N_9O_{18}S_3Si_6$: C, 2.22; H, 8.48; N, 5.44. Found: C, 62.11; H, 8.57; N, 5.16.

5d $_{SO_2DEA}^{Me}H_{tBu}^{Im}\cdot$ $_{SO_2DEATBDMS}^{Me}H_{tBu}^{Im}$ (**5c**) was suspended in a TFA/water (9:1 v/v) mixture and stirred at room temperature for 12 h. The solvents were then evaporated and toluene was added and evaporated twice, giving an orange oil. Dissolution in acetone and precipitation with TEA lead to the neutral derivative that was finally isolated as a white product (87%) after column chromatography using CH_2Cl_2/MeOH 95:5 as an eluent: MS (ES) (CH_3CN) *m*/*z* 1630.8 (100) (calcd for $[MH]^+$ 1630.7); ^{1}H NMR (250 MHz, CD_3CN, 340 K) δ 1.01 (s, 27 H, CH_3), 2.94 (s_l, 9 H, OCH_3), 3.25 (t, 12 H, J = 6 Hz, NCH_2), 3.43 (br s, 9 H, NCH_3), 3.68 (t, 12 H, J = 6 Hz, OCH_2), 3.88 (br s, 12 H, Ar-CH_2), 4.81 (s, 6 H, Im-CH_2), 6.87 (s, 6 H, H_{Ar}), 6.96 (s, 6 H, H_{Im}), 7.63 (s, 6 H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO, 300 K) δ 163.9, 160.8, 151.6, 150.9, 147.1, 135.9, 134.1, 130.9, 124.0, 61.2, 52.9, 34.6, 31.8, 29.8; IR ν = 2962, 1674, 1334 (SO_2NR_2), 1145 (SO_2NR_2) cm^{-1}. Anal. Calcd for $_{SO_2DEA}^{Me}H_{tBu}^{Im}$ (**5d**)·5H_2O; $C_{84}H_{111}N_9O_{18}S_3$·5$H_2O$: C, 58.62; H, 7.09; N, 7.32. Found: C, 58.48; H, 6.64; N, 7.35.

8c $_{SO_2DEATBDMS}^{Me}H_{SO_2DEATBDMS}^{Im}$. The crude product was purified by column chromatography using CH_2Cl_2/MeOH 95:5 as an eluent. A colorless compound was obtained (18%): MS (ES) (MeOH) *m*/*z* 695.2 (70) (calcd for $[MNa_4H]^{5+}$ 695.3); ^{1}H NMR (250 MHz, CD_3CN, 300 K) δ 0.05 (s, 72 H, CH_3), 0.90 (s, 108 H, CH_3), 2.95 (br s, 6H, Ar−CH_2), 3.16 (br t, 12 H, NCH_2), 3.30 (br t,12 H, NCH_2), 3.41 (br t,12 H, OCH_2), 3.72 (m, 30 H, OCH_3 and NCH_3 and OCH_2), 4.00 (br s, 6 H, Ar-CH_2), 4.87 (s, 6 H, Im-CH_2), 6.83 (s, 3 H, H_{Im}), 6.93 (s, 3 H, H_{Im}), 7.31 (br s, 6 H, H_{Ar}), 7.47 (br s, 6 H, H_{Ar}).[14]

8d $_{SO_2DEA}^{Me}H_{SO_2DEA}^{Im}\cdot$ $_{SO_2DEATBDMS}^{Me}H_{SO_2DEATBDMS}^{Im}$ (**8c**) was suspended in a TFA/water (9:1 v/v) mixture and stirred at room temperature for 1 night. The solvents were evaporated, and toluene was added and evaporated twice, giving a brownish oil. The crude material was dissolved in H_2O/acetone (10:1 v/v) and precipitated by addition of TEA, then purified by trituration in THF (65%): MS (ES) (H_2O/CH_3CN) *m*/*z* 982.39 (100) (calcd for $[MH_2]^{2+}$ 982.31), 1964.72 (22) (calcd for $[MH]^+$ 1964.62); ^{1}H NMR (250 MHz, CD_3OD, 300 K) δ = 2.90 (br, 6 H; Ar−CH_2), 3.08 (t, 12 H, J = 5.4 Hz, NCH_2), 3.15 (t, 12 H, J = 5.1 Hz, NCH_2), 3.26 (s, 9 H, OCH_3), 3.67 (s, 9 H, NCH_3), 3.74 (t, 12 H, J = 5.4 Hz, OCH_2), 3.82 (t, 12 H, J = 5.1 Hz, OCH_2), 4.10 (br, 6 H; Ar-CH_2), 5.03 (s, 6 H; Im-CH_2), 6.93 (s, 3 H; H_{Im}), 7.14 (s, 3 H; H_{Im}), 7.30 (br s, 6 H; H_{Ar}), 7.55 (br s, 6 H; H_{Ar}); IR ν = 2952, 1738, 1335 (SO_2N), 1146 (SO_2N), 990 cm^{-1}.

12c $_{NO_2}^{Me}H_{SO_2DEATBDMS}^{Im}\cdot$ The crude product was purified by column chromatography using CH_2Cl_2/MeOH 97:3 as an eluent, yielding a colorless compound (17%): MS (ES) (MeOH) *m*/*z* 1159.1 (100) (calcd for $[MNaH]^{2+}$ 1158.6); ^{1}H NMR (250 MHz, CD_3CN, 300 K) δ 0.09 (s, 36 H, CH_3), 0.90 (s, 54 H, CH_3), 2.66 (s_l, 9 H, OCH_3), 3.32 (t, 12 H, J = 6.3 Hz, NCH_2), 3.66 (s_l, 9 H, NCH_3), 3.82 (t, 12 H, J = 6.3 Hz, OCH_2), 3.2−4.6 (br, 12 H, Ar-CH_2), 4.94 (s, 6 H, Im-CH_2), 6.76 (s, 6 H, H_{Ar}), 6.91 (s, 3 H, H_{Im}), 6.99 (s, 3 H, H_{Im}), 7.66 (s, 6 H, H_{Ar}).

12d $_{NO_2}^{Me}H_{SO_2DEA}^{Im}\cdot$ $_{NO_2}^{Me}H_{SO_2DEATBDMS}^{Im}$ (**12c**) was then suspended in a TFA/water (9:1 v/v) mixture and stirred at room temperature for 12 h. The solvents were then evaporate,d and toluene was added and evaporated twice, giving a brownish oil. The solid was dissolved in an acetone/TEA (8:2 v/v) mixture and precipitation with ether led to a colorless compound (71%): MS (ES) (CH_3CN) *m*/*z* 1598.4 (100) (calcd for $[MH]^+$ 1598.7), 1619.1 (100) (calcd for $[MNa]^+$ 1619.5); ^{1}H NMR (250 MHz, CD_3CN/CD_3OD (3/1), 340 K) δ 3.14 (t, 12 H, J = 5.5 Hz, NCH_2), 3.29 (s, 9 H, OCH_3), 3.37 (s, 9 H, NCH_3), 3.62 (t, 12 H, J = 5.5 Hz, OCH_2), 3.92 (s_l, 12 H, Ar-CH_2), 4.87 (s, 6 H, Im-CH_2), 6.89 (s, 3 H, H_{Im}), 6.99 (s, 3 H, H_{Im}), 7.53 (s, 6 H, H_{Ar}), 7.86 (s, 6 H, H_{Ar}); ^{13}C NMR (75 MHz, CD_3CN/CD_3OD 3:1, 300 K) δ 161.6, 159.0, 144.0, 142.3, 135.4, 129.0, 127.0, 124.2, 123.7, 66.6, 60.9, 60.5, 52.0, 46.8, 32.5, 30.7. Anal. Calcd for $_{NO_2}^{Me}H_{SO_2DEA}^{Im}$ (**12d**)·2H_2O·CH_2Cl_2; $C_{72}H_{84}N_{12}O_{24}S_3$·2$H_2O$.$CH_2Cl_2$: C, 51.02; H, 5.28; N, 9.78. Found: C, 51.02; H, 5.11; N, 9.58.

General Procedure for Zn(II) Complexation and Decomplexation.[14] Zinc perchlorate hexahydrate (1 equiv) was added to a solution or suspension of the calixarene-ligand in dry THF. The mixture was stirred for 1 h under argon, after which the desired Zn(II) calixarene complex precipitated. The corresponding salt was isolated by centrifugation, triturated twice with ether and finally dried under vacuum.

The free ligand was obtained by treatment of the corresponding zinc complex (ca. 100 mg), which was suspended in acetonitrile (0.5 mL) and dissolved by slow addition of $NaOH_{aq}$ (1M, 1 mL). The solution was stirred 1 h. After partial removal of acetonitrile under vacuum a solid product was obtained, which was filtered, washed twice with cold water, and finally dried 2 days under vacuum.

{$_{SO_2NH_2}^{Me}H_{tBu}^{Im}$·**Zn(ClO$_4$)$_2$**}: *m* = 120 mg, 43% based on $_{tBu}^{Me}H_{tBu}^{Im}$ (**2**); ^{1}H NMR (250 MHz, CD_3CN, 300 K) δ 1.44 (s, 27 H, CH_3), 3.44 (s, 9 H, OCH_3), 3.44−3.6 (d, 6 H, Ar-CH_2), 3.64 (s, 9 H, NCH_3), 4.11 (d, J = 15 Hz, 6 H, Ar-CH_2), 5.08 (s, 6 H, Im-CH_2), 5.50 (s, 6 H, SO_2NH_2), 6.78 (s, 6 H, H_{Ar}), 6.96 (s, 3 H, H_{Im}), 7.47 (s, 3 H, H_{Im}), 7.48 (s, 6 H, H_{Ar}); IR ν = 1721, 1151 (SO_2NR_2), 1328, 623 (ClO_4) cm^{-1}. Anal. Calcd for $C_{72}H_{87}Cl_2N_9O_{20}S_3Zn$·2$H_2O$: C, 51.87; H, 5.50; N, 7.56. Found: C, 51.73; H, 5.52; N, 7.75.

{$_{NO_2}^{Me}H_{SO_2NMe_2}^{Im}$·**Zn(ClO$_4$)$_2$**}: *m* = 322 mg, 44% based on $_{NO_2}^{Me}H_{tBu}^{Im}$ (**9**); ^{1}H NMR (250 MHz, CD_3CN, 300 K) δ 2.83 (s, 18 H, $N(CH_3)_2$), 3.70 (s, 9 H, OCH_3), 3.80 (s, 9 H, NCH_3), 3.88 (d, J = 16 Hz, 6 H, Ar-CH_2), 4.08 (d, J = 16 Hz, 6 H, Ar-CH_2), 5.23 (s, 6 H, Im-CH_2), 7.05 (s, 3 H, H_{Im}), 7.18 (s, 6 H, H_{Ar}), 7.53 (s, 3 H, H_{Im}), 7.96 (s, 6 H, H_{Ar}); IR ν = 1523 (NO_2), 1343, 1147, 1103 (SO_2NR_2), 623 (ClO4) cm^{-1}. Anal. Calcd for $C_{66}H_{72}Cl_2N_{12}O_{26}S_3Zn$·$H_2O$: C, 46.63; H, 4.39; N, 9.89. Found: C, 46.58; H, 4.42; N, 10.12.

Crystallographic data for the structural analysis of $_{SO_2NMe_2}^{Me}H_{tBu}^{Im}$ (**5b**) have been deposited within the Cambridge Crystallographic Data Centre (CCDC) as no. 291094. Copies of this information may be obtained from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk) or http//www.ccdc.cam.ac.uk.

Supporting Information Available: General methods; crystal structure data of **5b**; ^{1}H NMR spectra of compounds **7**, **8c**, and **12c**; ^{13}C NMR spectra of compounds **4**, **7**, **5c**, **12b**,**d**; HMBC and HMQC spectra of compound **4**; X-ray structure and crystallographic data of $_{SO_2NMe_2}^{Me}H_{tBu}^{Im}$ (**5b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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