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Graphical Abstract

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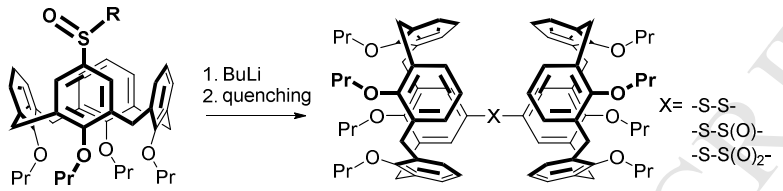

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Unexpected formation of disulfide-based biscalix[4]arenes

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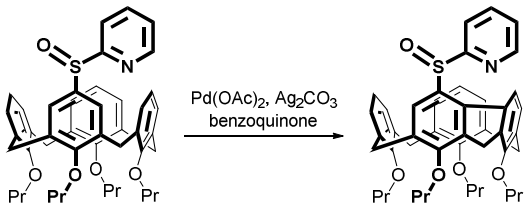
ABSTRACT

Attempts at Pd-catalyzed bridging in sulfoxide-bearing calixarenes containing various substituents (phenyl, ethyl, pyrimidin-2-yl) gave the expected compound only in the case of the ethyl derivative. However, the reaction of sulfoxides with BuLi revealed the ability of the pyrimidin-2-yl group to function unexpectedly as a leaving group. This enabled, depending on the reaction conditions, preparation of unique bis-calixarenes connected together via two sulfur atoms spacers: -S-S-, -S(O)-S- or $-S(O)_2$-S-. As documented by ^{1}H NMR titrations these compounds, otherwise not easily accessible by common synthetic methods, showed recognition ability towards selected cations of the N-methylpyridinium type.

1. Introduction

Calix[n]arenes[1] are well-known macrocyclic compounds that have become very popular in supramolecular chemistry. Typical features of these compounds include: (i) variability in the size of the cavity, (ii) well established chemistry allowing for almost limitless derivatization of the basic skeleton, (iii) multigram scale of the synthesis, and (iv) excellent complexation properties depending on the substitution. Moreover, the smallest member of this family, calix[4]arene, possesses a unique three-dimensional shape of the cavity that can be tuned by simple alkylation of the lower rim (phenolic functions) to form four basic conformations (atropisomers) - *cone*, *partial cone*, *1,3-alternate*, and *1,2-alternate*.[1] This makes calix[4]arene an especially attractive molecular scaffold for the design of novel receptors[2] and/or a valuable building block for the construction of more sophisticated supramolecular systems.

Although the chemistry of calix[4]arenes is well developed and many synthetic methods allowing for the regioselective introduction of substituents at the *para* position of aromatic subunits are known in the art,[3] direct substitution at the *meta* position is still very rare. In this context, *meta*-substitution can be *inter alia* achieved using *ortho*-directing groups introduced into the *para* position of the calixarene moiety. Thus, it was shown that using groups with strong *ortho*/*para* directing effects like hydroxy and/or alkoxy groups[4] or amidic functionality[5] aromatic electrophilic substitution (bromination, nitration, formylation) can easily be used to introduce an electrophile into the *meta* position of the calixarene skeleton. Similarly, an oxazoline moiety as an *ortho*-lithiation directing group was introduced into calix[4]arene to allow functionalization of the upper rim at the *meta*-position.[6]



Scheme 1. Preparation of meta bridged calix[4]arene.

Recently, we published an alternative procedure based on the introduction of the 2-pyridyl sulfoxide moiety into the upper rim of calix[4]arene. The presence of the 2-pyridyl moiety subsequently enabled Pd-catalyzed double C-H activation offering an access to unprecedented derivatives with intramolecular bridge between the *meta* positions of the two neighboring aromatic subunits (Scheme 1).[7] In this paper we report on our attempts to expand the above bridging reaction to install other sulfoxide-tethered substituents including ethyl, phenyl, and pyrimidin-2-yl moieties.

2. Results and discussion

We commenced the synthesis with monobromo derivative **1** which is accessible in 95% yield by bromination[7] of

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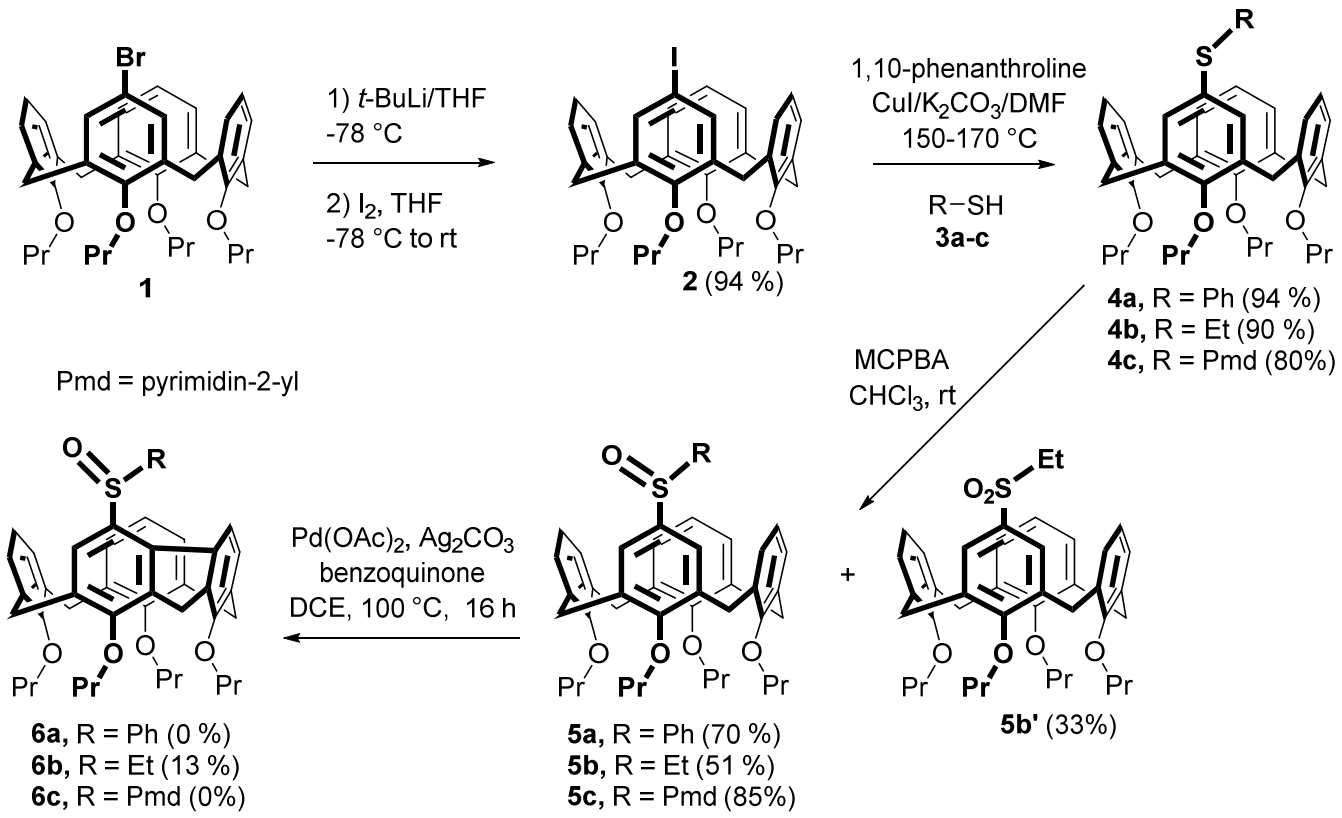
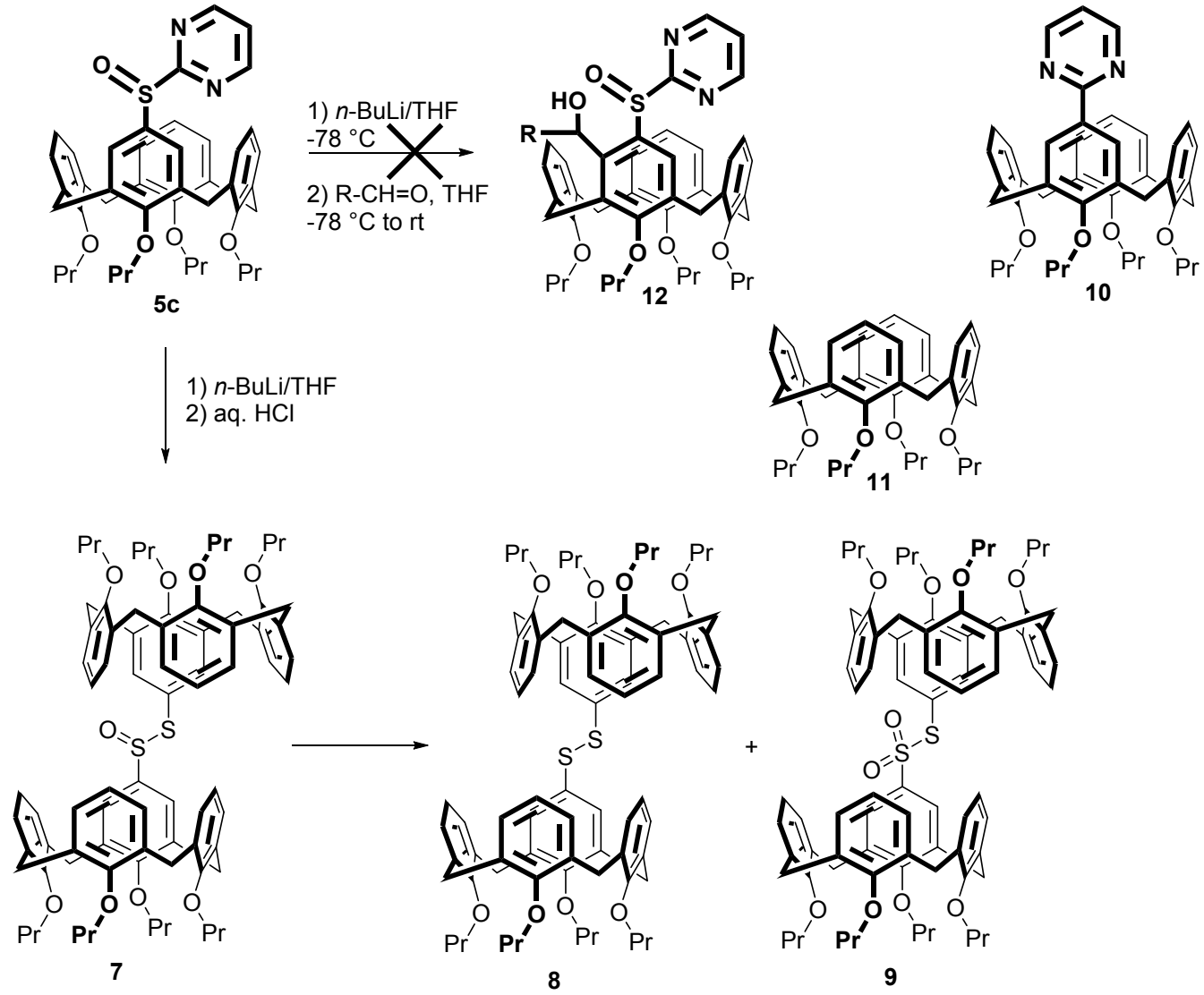


Scheme 1. Attempted bridging reaction in calixarene series.

tetrapropoxycalix[4]arene with NBS in butan-2-one at room temperature. To avoid potential problems stemming from the reduced reactivity of the bromine atom, compound **1** was transformed into the corresponding iodide **2** in 94% yield by metalation with *tert*-BuLi and subsequent reaction with I_2. This compound was then reacted with thiols **3a-3c** in DMF in the presence of CuI/1,10-phenanthroline/K_2CO_3 as the catalytic system. Prolonged stirring (5 days) at high temperature (150-170 °C) provided the respective sulfides **4a-4c** in very high yields after column chromatography on silica gel (**4a**, 94%; **4b**, 90%, and **4c**, 80% yields). Efficient oxidation to sulfoxides **5** was achieved using *meta*-chloroperoxybenzoic acid (MCPBA) in chloroform. While the reaction with 1 equiv of MCPBA led selectively to high yields of phenyl and pyrimidin-2-yl sulfoxide derivatives **5a** (70%) and **5c** (85%), the corresponding ethylsulfoxide **5b** was accompanied by substantial amount of sulfone **5b'**. The crude reaction mixture was separated by chromatography on Chromatotron[tm] (SiO_2/EtOAc) to provide **5b** and **5b'** in 51% and 33% yield, respectively.

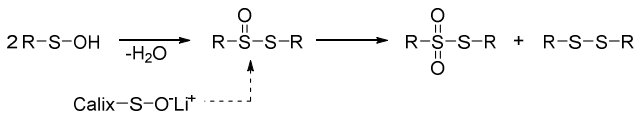
Sulfoxides **5a-5c** were bridged using literature conditions[7]: $Pd(OAc)_2$ (20 mol%), Ag_2CO_3 + benzoquinone (oxidants) in DCE at 100 °C overnight. Unfortunately, unlike the pyrydin-2-yl substituent (see Scheme 1), no bridging occurred in the case of the phenyl or pyrimidin-2-yl derivatives. Thus, compound **5a** was entirely unreactive, while **5c** led to the formation of a complex reaction mixture where among others tetrapropoxycalix[4]arene **11**, disulfide **8** and thiosulfonic derivative **9** were confirmed by MS analysis. Reaction with ethyl derivative **5b** provided the expected bridged compound **6b** in only 2% yield, accompanied by a small amount of compounds **8** and **9**. Slight modification of the reaction conditions (addition of 0.2 equiv of *p*-nitroiodobenzene, 1 equiv of $Pd(OAc)_2$) increased the yield of **6b** to 13%. The structure of bridged product **6b** was assigned by MS ESI^+ analysis which showed signals at *m/z* = 667.3448, 689.3269 and 705.3002, perfectly corresponding to the calculated values 667.3452 $[M+H]^+$, 689.3271 $[M+Na]^+$, and 705.3011 $[M+K]^+$. Despite this partial success, the overall results indicated, that none of the selected substituents in the sulfoxide part of the molecule (phenyl, ethyl, pyrimidin-2-yl) are synthetically useful for bridging reactions. In other words, the role of 2-pyridyl substituent seems to be irreplaceable in this reaction.

As the sulfoxide is a strong *ortho*-directing functional group, it is used frequently for directed *ortho*-lithiation[8] of aromatic moieties. To verify the synthetic applicability of pyrimidin-2-yl sulfoxide **5c**, we attempted *ortho*-lithiation of this compound. Thus, compound **5c** was reacted with butyllithium in THF at -78 °C and finally quenched by acetaldehyde or butyraldehyde at the same temperature (Scheme 3). Unfortunately, the formation of expected *meta*-substituted calixarene **12** was not observed at all. The complex reaction mixtures consisted of many products, among which compounds **7-11** were isolated or identified. The presence of compound **10** with a direct bond between the pyrimidine and calixarene moiety was deduced from HRMS spectra showing a peak at *m/z* = 729.4628 which is in good accordance with the theoretical value for $C_{48}H_{61}O_4N_2+H^+$ (*m/z* = 729.4626 $[M+H]^+$. This behaviour of aromatic sulfoxides (extrusion of SO group) is well documented in the literature[7,9] and is based on a rapid ligand-exchange reaction upon treatment with organolithium reagents.



Scheme 3. Attempted *ortho*-lithiation and the formation of biscalix[4]arenes **7**-**9**.

As we found the yields of compounds **7**-**9** and their mutual ratio in the reaction mixtures widely varied with different reaction and/or quenching conditions. We carried out a series of reactions to find the optimized conditions leading to the highest yields of the corresponding products. Interestingly, the addition of BuLi (3 equiv) to a THF solution of **5c** at -78 °C, then stirring the mixture for 30 minutes at the same temperature, and finally quenching with aq. HCl gave thiosulfinate **7** in 62% yield after radial chromatography. No isolatable amounts of **8** or **9** were obtained under these reaction conditions.



Scheme 4. A tentative mechanism showing the formation of thiosulfinate, thiosulfonate and disulfide from sulfenic acid (based on Ref. 10-12).

On the other hand, the same reaction mixture (a THF solution of **5c**, 3 equiv of BuLi at -78 °C) stirred for two hours with gradual warming from -78 °C to room temperature (25 °C) gave completely different products, as only disulfide **8** and thiosulfonate **9** were isolated in 33% and 28% yields, respectively. Derivative **7** was not isolated at all in this case.

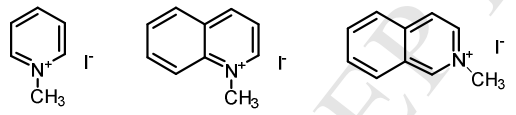
As the formation of the above compounds **7**-**9** was entirely unexpected it brought us to the careful inspection of literature sources. As we found the concomitant formation of these types of compounds (disulfide, thiosulfinate and thiosulfonate) were described for flash vacuum pyrolysis of the corresponding sulfoxides at high temperatures[10] or by the thermolysis of sulfoxides at 110 °C in toluene.[11] Low yields of all three products were also isolated using steady-state irradiation or nanosecond laser flash photolysis of the solutions containing aryl *tert*-butyl sulfoxides in MeCN.[12] The authors of these papers proposed the initial formation of sulfenic acid (R-SOH) which is extremely reactive and usually can be neither detected nor isolated. This sulfenic acid rapidly dimerizes to form the thiosulfinate ester (R-S(O)S-R), which is unstable,[13] and undergoes a disproportionation reaction to yield an equimolar mixture of disulfide (R-SS-R) and thiosulfonate ester (R-S(O)$_2$S-R) (see Scheme 4).

The reaction sequence shown in Scheme 4 was in accordance with our own experiments: thiosulfinate **7** was isolated as the kinetic product (short reaction time/low temperature = 30 min at -78 °C) while the mixture of disulfide **8** and thiosulfonate **9**

represents the thermodynamic products (2 h, -78 °C to rt). As the formation of free sulfenic acid under our basic reaction conditions could be excluded, it seemed that the same reaction sequence can be carried out with a salt of sulfenic acid. The pyrimidine moiety does not induce *ortho*-lithiation, but rather serves as a good leaving group to form the lithium sulfenate of calixarene which undergoes the same reaction as the free acid itself. To the best of our knowledge, no systematic study on reactivity of sulfenic acid salts has been reported so far. Nevertheless, we found a recent paper[14] showing the reaction of *p*-tolyl aryl sulfoxide with LDA in THF. The reaction conditions (-78 °C, 30 min then rt, 90 min) led to isolation *inter alia* of bis(*p*-tolyl)disulfide which indicated that dimerization is possible even under strongly basic conditions.[15] The crucial role of the pyrimidine moiety in the formation of biscalixarenes **7**-**9** can be also demonstrated by the same reaction with phenyl derivative **5a**. Using otherwise identical reaction conditions tetrapropoxycalixarene **11** was isolated in 60% yield while the presence of bis-calixarenes **7**-**9** was only detectable by TLC analysis.

Derivatives **7**-**9** represent unique structures otherwise inaccessible by other synthetic methods. The cavities of both calixarene subunits might cooperate to create a bigger cavity which could be useful for the complexation of suitable guest molecules. To confirm this assumption we carried out a complexation study of **8** and **9** towards selected organic cations which could be bound via cation-π interactions[16] within the bis-calixarene cavity. The addition of 1-methylpyridinium iodide (NP) or 1-methylquinolinium iodide (1-MQ) to a solution of **8** or **9** in $CDCl_3$: CD_3CN = 4:1 led to reproducible downfield shifts of the aromatic signals (complexation under fast exchange conditions). As shown in Figure 1, a typical titration curve corresponded to the formation of 1:1 complexes and the appropriate complexation constants were collected in Table 1. While MP and 1-MQ are bound by calixarenes, isoquinolinium derivative 2-MQ showed no measurable interactions indicating possible shape-recognition properties of the novel calixarenes.

Table 1. Binding constants of calixarenes **8** and **9** towards selected organic cations[a)]



Guest [b)]	compound 8 K [M^{-1}]	compound 9 K [M^{-1}]
MP	21.6 ± 0.5	17.6 ± 0.8
1-MQ	6.1 ± 0.7	6.7 ± 0.7
2-MQ	nc[c)]	nc

[a)] ^{1}H NMR titration, 400 MHz, $CDCl_3$: CD_3CN = 4:1 v/v, 298 K; [b)]MP = 1-methylpyridinium iodide, 1-MQ = 1-methylquinolinium iodide, 2-MQ = 2-methylisoquinolinium iodide, [c)] no complexation observed.

3. Conclusions

Contrary to 2-pyridyl substituted calixarene sulfoxide, the other substituents (phenyl, ethyl, pyrimidin-2-yl) gave the expected intramolecularly bridged compound only in the case of the ethyl derivative. Interestingly, the reaction of sulfoxides with BuLi revealed the unique ability of pyrimidin-2-yl function to play the role of the leaving group. This enabled, depending on the reaction conditions, preparation of otherwise not easily accessible bis-calixarenes connected together via a two-sulfur-atom spacer: -S-S-, -S(O)-S- or $-S(O)_2$-S-. The ^{1}H NMR titrations of these compounds showed their recognition ability towards selected cations of the N-methylpyridinium type by cation-π interactions.

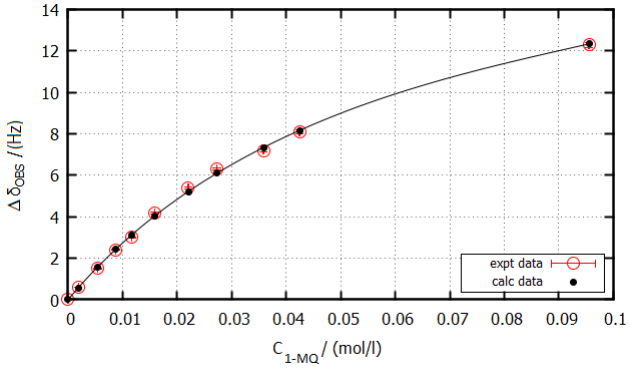


Figure 1. ^{1}H NMR titration curve of **9** with 1-methylquinolinium iodide ($CDCl_3$: CD_3CN = 4:1 v/v, 300 MHz, 298 K).

4. Experimental

4.1. General

All chemicals were purchased from commercial sources and used without further purification. 1,2-Dichloroethane, dichloromethane and *N*,*N*'-dimethylformamide used for the reactions were dried with CaH_2 or $MgSO_4$ and stored over molecular sieves. THF was dried using sodium/benzophenone method. Melting points were measured on Heiztisch Mikroskop-Polytherm A (Wagner & Munz, Germany) and were not corrected. The IR spectra were measured on FT-IR spectrometer Nicolet 740 in KBr transmission mode. NMR spectra were recorded on spectrometers Varian Gemini 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) and Agilent 400-MR DDR2 (^{1}H: 400 MHz, ^{13}C: 100 MHz). Chemical shifts (δ) are expressed in parts per million and are referenced to the residual peak of solvent or TMS as an internal standard, coupling constants (J) are in hertz. The mass analyses were performed using ESI technique on a FT-MS (LTQ Orbitrap Velos) spectrometer. Purity of the substances and courses of the reactions were monitored by TLC using TLC aluminium sheets with Silica gel 60 F_{254} (Merck) and analyzed at 254 or 365 nm. Preparative TLC chromatography was carried out on a Chromatotron (Harrison Research) with plates covered by Silica gel 60 GF_{254} (Merck). Starting compound **1** (5-bromo-25,26,27,28-tetrapropoxycalix[4]arene) was prepared according to a known procedure.[7]

4.2. NMR titration experiments

NMR titration experiments were carried out on a Varian Mercury 300 MHz spectrometer equipped with a 5 mm PFG autoswitchable VT probe. To solubilize both the calix[4]arenes and the pyridinium/quinolinium salts a mixture of deuterated solvents ($CDCl_3$:CD_3CN = 4:1 v/v) was used. The measurements were performed at 25 °C. In all the cases measured, the complexation took place under fast exchange conditions. Thus, the complexation constants were obtained from the dependency of the calixarene aromatic proton chemical shifts on the concentration of pyridinium/quinolinium salts added. During the titration, the concentration of calixarene was kept constant to avoid possible shift of signals due to dilution of the sample. For the estimation of the stability constants and the corresponding

errors a self-made calculating program using orthogonal distance regression[17] was employed.

4.3. Synthesis of 5-iodo-25,26,27,28-tetrapropoxy-calix[4]arene (2)

A 250 mL flask charged with 5-bromotetrapropoxy-calix[4]arene **1** (9.5 g, 14.1 mmol) and freshly distilled THF (60 mL) was cooled to -78 °C under a blanket of argon. *t*-BuLi (3 eq, 25 mL, 42.3 mmol) was added and the reaction was stirred for 30 minutes. Iodine (2 eq, 7.2 g, 28.2 mmol) was then added and the reaction was stirred overnight during which the mixture was slowly warmed to room temperature. The solvent was evaporated, the residue was dissolved in CH_2Cl_2 (100 mL) and rinsed with a saturated aqueous solution of Na_2SO_3 (200 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phases were rinsed with water (50 mL), dried over $MgSO_4$ and solvent evaporated *in vacuo*. The crude residue was purified using column chromatography (SiO_2, EtOAc:cyclohexane = 1:15 v/v, R_f = 0.40) to give 9.5 g (94%) of a white solid, mp: 129-130 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ(ppm): 6.80 – 6.69 (m, 9H, Ar-**H**); 6.48 (m, 2H, Ar-**H**); 4.46 (d, *J* = 13.8 Hz, 2H, Ar-C**H$_2$**-Ar); 4.38 (d, *J* = 13.5 Hz, 2H, Ar-C**H$_2$**-Ar); 3.92 – 3.74 (m, 8H, OC**H$_2$**); 3.18 (d, *J* = 13.8 Hz, 2H, Ar-C**H$_2$**-Ar); 3.09 (d, *J* = 13.5 Hz, 2H, Ar-C**H$_2$**-Ar); 1.97 – 1.84 (m, 8H, C**H$_2$**); 1.06 – 0.93 (m, 12H, C**H$_3$**) All characterizations including ^{13}C NMR, IR and MS spectra are in agreement with previously published data.[7]

4.4. Synthesis of 5-phenylsulfanyl-25,26,27,28-tetrapropoxy-calix[4]arene (4a)

A 100 mL Schlenk flask was charged with compound **2** (500 mg, 0.696 mmol), CuI (1 eq, 133 mg, 0.696 mmol), 1,10-phenanthroline (1 eq, 125 mg, 0.696 mmol), K_2CO_3 (4 eq, 385 mg, 2.78 mmol), thiophenol **3a** (6 eq, 0.43 mL, 4.18 mmol), and anhydrous DMF (42 mL). The flask was flushed with nitrogen and stirred at 150 °C for 5 days. After that, DMF was evaporated *in vacuo* and the crude mixture dissolved in CH_2Cl_2 (20 mL) and purified using column chromatography (SiO_2, EtOAc:cyclohexane = 1:20 v/v, R_f = 0.75) to give 460 mg (94%) of white powder, mp: 103-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K) δ (ppm): 7.20 (t, *J* = 7.4 Hz, 2H, Ar-**H**); 7.12 (t, *J* = 7.4 Hz, 1H, Ar-**H**); 6.97 (m, 2H, Ar-**H**); 6.69 – 6.73 (m, 4H, Ar-**H**); 6.60 – 6.65 (m, 7H, Ar-**H**); 4.46 (t, *J* = 13.5 Hz, 4H, Ar-C**H$_2$**-Ar); 3.83 – 3.91 (m, 8H, O-C**H$_2$**); 3.19 (d, *J* = 13.5 Hz, 2H, Ar-C**H$_2$**-Ar); 3.12 (d, *J* = 13.5 Hz, 2H, Ar-C**H$_2$**-Ar); 1.90 – 1.98 (m, 8H, C**H$_2$**); 0.98 – 1.06 (m, 12H, C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K) δ (ppm) 156.71; 156.51; 156.34; 136.19; 135.44; 134.83; 134.72; 132.78; 128.73; 128.43; 128.18; 128.08; 127.95; 125.36; 122.10; 122.04; 76.90; 76.76; 30.98; 30.85; 23.30; 23.28; 23.19; 10.40; 10.38; 10.24. IR (KBr) ν (cm^{-1}): 2961.0, 2930.7, 2873.9, 1582.7, 1455.3, 1383.7, 1247.2, 1210.1. HRMS-ESI ($C_{46}H_{52}O_4S$) m/z calcd: 723.34785 $[M+Na]^+$, 739.32179 $[M+K]^+$, found: 723.34860 $[M+Na]^+$, 739.32123 $[M+K]^+$.

4.5. Synthesis of 5-ethylsulfanyl-25,26,27,28-tetrapropoxy-calix[4]arene (4b)

A 100 mL Schlenk flask was charged with 5-iodo derivative **2** (500 mg, 0.696 mmol), CuI (1 eq, 133 mg, 0.696 mmol), 1,10-phenanthroline (1 eq, 125 mg, 0.696 mmol), K_2CO_3 (4 eq, 385 mg, 2.78 mmol), ethanethiol **3b** (4 eq, 0.20 mL, 2.78 mmol), and anhydrous DMF (45 mL) and flushed with nitrogen. The mixture was stirred at 170 °C for 5 days. The DMF was then removed *in vacuo*, the crude residue dissolved in CH_2Cl_2 (30 mL) and purified using column chromatography (silica gel, EtOAc: cyclohexane = 1:9 v/v, R_f = 0.80) to give 410 mg (90%) of a white solid, mp: 43-44 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K) δ (ppm): 6.57-6.70 (m, 11H, Ar-**H**); 4.45 (t, *J* = 13.5 Hz, 4H, Ar-C**H$_2$**-Ar); 3.80 – 3.90 (m, 8H, O-C**H$_2$**); 3.17 (d, *J* = 13.3 Hz, 2H, Ar-C**H$_2$**-Ar); 3.12 (d, *J* = 13.3 Hz, 2H, Ar-C**H$_2$**-Ar); 2.63 (q, *J* = 7.3 Hz, 2H, Ar-C**H$_2$**); 1.88 – 1.99 (m, 8H, C**H$_2$**); 1.12 (t, *J* = 7.3 Hz, 3H, C**H$_3$**); 0.97 – 1.04 (m, 12H, C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K) δ (ppm): 156.65; 156.33; 155.48; 135.46; 135.40; 135.12; 134.91; 134.77; 128.36; 128.16; 128.08; 128.01; 122.01; 121.95; 76.81; 76.74; 76.65; 30.96; 30.91; 28.91; 23.28; 23.25; 23.19; 14.61; 10.39; 10.32; 10.24. IR (KBr) ν (cm^{-1}): 2961.2, 2927.5, 2873.7, 1455.3, 1209.9. HRMS-ESI ($C_{42}H_{52}O_4S$) *m/z* calcd: 653.36591 $[M+H]^+$, 670.39246 $[M+NH_4]^+$, 675.34785 $[M+Na]^+$, 691.32179 $[M+K]^+$, found: 653.36603 $[M+H]^+$, 670.39303 $[M+NH_4]^+$, 675.34819 $[M+Na]^+$, 691.32143 $[M+K]^+$.

4.6. Synthesis of 5-(pyrimidin-2-ylsulfanyl)-25,26,27,28-tetrapropoxycalix[4]arene (4c)

A 250 mL double-necked flask was charged with compound **2** (1.0 g, 1.39 mmol), CuI (0.5 eq, 132 mg, 0.696 mmol), 1,10-phenanthroline (1 eq, 250 mg, 1.39 mmol), K_2CO_3 (4 eq, 768 mg, 5.56 mmol), 2-sulfanylpyrimidine **3c** (4 eq, 624 mg, 5.56 mmol), and anhydrous DMF (90 mL). The flask was flushed with nitrogen and the reaction mixture was stirred at 170 °C for 5 days. After that, the DMF was evaporated *in vacuo*, the crude mixture dissolved in CH_2Cl_2 (30 mL) and purified using column chromatography (silica gel, EtOAc:cyclohexane = 1:4 v/v, R_f = 0.45) to give 780 mg (80%) of a white solid, mp: 73-74 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K) δ (ppm): 8.44 (d, *J* = 4.7 Hz, 2H, pyr-**H**); 6.90 (t, *J* = 4.7 Hz, 1H, pyr-**H**); 6.70 – 6.73 (m, 6H, Ar-**H**); 6.61 – 6.65 (m, 3H, Ar-**H**); 6.52 (d, *J* = 7.3 Hz, 2H, Ar-**H**); 4.46 (d, *J* = 13.3 Hz, 2H, Ar-C**H$_2$**-Ar); 4.45 (d, *J* = 13.3 Hz, 2H, Ar-C**H$_2$**-Ar); 3.79 – 3.93 (m, 8H, Ar-O-C**H$_2$**-); 3.18 (d, *J* = 13.3 Hz, 2H, Ar-C**H$_2$**-Ar); 3.17 (d, *J* = 13.3 Hz, 2H, Ar-C**H$_2$**-Ar); 1.87 – 1.98 (m, 8H, C**H$_2$**); 0.95 – 1.06 (m, 12H, C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K) δ (ppm): 157.37; 156.80; 156.28; 136.09; 135.87; 135.60; 135.08; 134.94; 134.72; 128.50; 128.33; 127.99; 122.02; 121.99; 121.20; 116.43; 77.19; 76.91; 76.62; 30.99; 30.92; 23.38; 23.28; 23.16; 10.42; 10.40; 10.21. IR (KBr) ν (cm^{-1}): 2960.7, 2930.1, 2873.7, 1560.9, 1546.2, 1454.7, 1379.1, 1190.4. HRMS-ESI ($C_{44}H_{50}N_2O_4S$) *m/z* calcd: 703.35641 $[M+H]^+$, 720.38295 $[M+NH_4]^+$, 725.33835 $[M+Na]^+$, 741.31229 $[M+K]^+$, found: 703.35710 $[M+H]^+$, 720.38318 $[M+NH_4]^+$, 725.33853 $[M+Na]^+$, 741.31210 $[M+K]^+$.

4.7. Synthesis of 5-phenylsulfinyl-25,26,27,28-tetrapropoxy-calix[4]arene (5a)

A 100 mL flask charged with 5-phenylsulfanyl derivative **3a** (490 mg, 0.699 mmol) and anhydrous CH_2Cl_2 (60 ml) was flushed with nitrogen. The mixture was cooled to 0 °C and *m*-chloroperbenzoic acid (1 eq, 157 mg, 0.699 mmol) was added. The reaction mixture was stirred for 1 hour during which time the temperature rose to room temperature. Then, a saturated solution of Na_2SO_3 (150 mL) was added and the organic phase was washed with $NaHCO_3$ (30 mL), water (40 mL), dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The mixture was then subjected to Chromatotron^{tm} (silica gel, EtOAc:cyclohexane = 1:15 v/v, R_f = 0.15) to give 354 mg (70%) of a white crystalline solid, mp: 145-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K) δ (ppm): 7.41 – 7.48 (m, 5H, Ar-**H**); 7.08 (d, *J* = 2.2 Hz, 1H, Ar-**H**); 6.66 – 6.71 (m, 4H, Ar-**H**); 6.52 – 6.60 (m, 4H, Ar-**H**); 6.47 (t, *J* = 7.4 Hz, 1H, Ar-**H**); 6.36 (m, 1H, Ar-**H**); 4.40 – 4.47 (m, 4H, Ar-C**H$_2$**-Ar); 3.74 – 3.87 (m, 8H, O-C**H$_2$**); 3.08 – 3.20 (m, 4H, Ar-C**H$_2$**-Ar); 1.86 – 1.94 (m, 8H, C**H$_2$**); 0.95 – 1.00 (m, 12H, C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K) δ (ppm): 159.53; 156.60; 156.23; 137.52; 137.01; 136.68; 135.28; 135.10; 135.03; 133.84; 133.77; 130.41; 128.92; 128.48; 128.39;

128.08; 127.77; 125.60; 124.91; 122.30; 122.17; 121.97; 77.20; 76.92; 76.76; 30.99; 30.92; 23.22; 23.21; 10.32; 10.27; 10.19. IR (KBr) ν (cm^{-1}): 2956.7, 2914.3, 2871.4, 2360.1, 2339.9, 1455.0, 1248.7, 1210.1. HRMS-ESI ($C_{46}H_{52}O_5S$) *m/z* calcd: 739.34277 $[M+Na]^+$, 755.31670 $[M+K]^+$, found: 739.34381 $[M+Na]^+$, 755.31610 $[M+K]^+$.

4.8. Synthesis of 5-ethylsulfinyl-25,26,27,28-tetrapropoxy-calix[4]arene (5b)

A 100 mL flask charged with compound **3b** (114 mg, 0.175 mmol) and anhydrous CH_2Cl_2 (15 mL) was flushed with nitrogen. The mixture was cooled to 0 °C and *m*-chloroperbenzoic acid (1 eq, 40 mg, 0.175 mmol) was added. The reaction was stirred for 1 h during which time the temperature rose to room temperature. Then, a saturated solution of Na_2SO_3 (50 mL) was added and the organic phase was washed with aq. $NaHCO_3$ (20 mL), water (30 mL), dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The mixture was then subjected to Chromatotron^{tm} (silica gel, EtOAc:cyclohexane = 1:6 v/v, R_f = 0.20) to give 60 mg (51%) of a white crystalline solid, m.p.: 57-59 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K) δ (ppm): 6.84 (d, *J* = 1.8 Hz, 1H, Ar-**H**); 6.73 – 6.79 (m, 5H, Ar-**H**); 6.66 – 6.71 (m, 2H, Ar-**H**); 6.54(d, *J* = 7.5 Hz, 2H, Ar-**H**); 6.47 (t, *J* = 7.5 Hz, 1H, Ar-**H**); 4.50 (d, *J* = 13.5 Hz, 2H, Ar-C**H$_2$**-Ar); 4.44 – 4.48 (m, 2H, Ar-C**H$_2$**-Ar); 3.88 – 3.98 (m, 4H, O-C**H$_2$**); 3.85 (t, *J* = 7.3 Hz, 2H, O-C**H$_2$**); 3.80 (t, *J* = 7.3 Hz, 2H, O-C**H$_2$**); 3.15 – 3.24 (m, 4H, Ar-C**H$_2$**-Ar); 2.35 – 2.46 (m, 2H, Ar-C**H$_2$**); 1.88 – 2.02 (m, 8H, C**H$_2$**); 0.95 – 1.07 (m, 15H, C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K) δ (ppm): 158.53; 156.63; 156.14; 136.32; 135.86; 135.63; 134.66; 134.62; 134.50; 128.72; 128.29; 128.24; 127.95; 127.91; 124.18; 123.63; 122.37; 122.32; 121.92; 77.15; 76.96; 76.67; 50.38; 31.04; 31.01; 30.92; 23.31; 23.30; 23.13; 10.44; 10.40; 10.15; 6.42. IR (KBr) ν (cm^{-1}): 2962.4, 2932.1, 2874.4, 1455.1, 1210.0. HRMS-ESI ($C_{42}H_{52}O_5S$) m/z calcd: 691.34277 $[M+Na]^+$, 707.31670 $[M+K]^+$, found: 691.34263 $[M+Na]^+$, 707.31623 $[M+K]^+$.

4.9. Synthesis of 5-ethylsulfonyl-25,26,27,28-tetrapropoxy-calix[4]arene (5b').

Compound was obtained as a by-product in the above described synthesis of derivative **4b**. The title compound (R_f = 0.55) was isolated (147 mg, 33% yield) as a white crystalline solid, m.p.: 68-69 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K) δ (ppm): 7.07 (s, 2H, Ar-**H**); 6.83 (t, *J* = 7.6 Hz, 4H, Ar-**H**); 6.73 (t, *J* = 7.6 Hz, 2H, Ar-**H**); 6.52 (d, *J* = 7.5 Hz, 2H, Ar-**H**); 6.41 (t, *J* = 7.4 Hz, 1H, Ar-**H**); 4.51 (d, *J* = 13.3 Hz, 2H, Ar-C**H$_2$**-Ar); 4.46 (d, *J* = 13.3 Hz, 2H, Ar-C**H$_2$**-Ar); 3.89 – 4.03 (m, 4H, O-C**H$_2$**); 3.86 (t, *J* = 7.3 Hz, 2H, O-C**H$_2$**); 3.79 (t, *J* = 7.3 Hz, 2H, O-C**H$_2$**); 3.24 (d, *J* = 13.3 Hz, 2H, Ar-C**H$_2$**-Ar); 3.19 (d, *J* = 13.3 Hz, 2H, Ar-C**H$_2$**-Ar); 2.66 (q, *J* = 7.3 Hz, 2H, Ar-C**H$_2$**); 1.90 – 2.03 (m, 8H, C**H$_2$**); 1.06 (t, *J* = 6.9 Hz, 3H, C**H$_3$**); 1.05 (t, *J* = 6.9 Hz, 3H, C**H$_3$**); 0.99 (t, *J* = 6.9 Hz, 6H, C**H$_3$**); 0.94 (t, *J* = 7.4 Hz, 3H, C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K) δ (ppm): 160.51; 156.64; 156.00; 135.98; 135.82; 134.49; 134.27; 131.40; 128.99; 128.34; 128.08; 127.87; 122.56; 121.93; 77.10; 76.70; 50.74; 30.93; 30.90; 23.35; 23.10; 10.50; 10.43; 10.10; 7.63. IR (KBr) ν (cm^{-1}): 2962.5, 2933.1, 2874.8, 1455.0, 1309.5, 1260.6, 1210.8, 1130.7. HRMS-ESI ($C_{42}H_{52}O_6S$) *m/z* calcd: 707.33768 $[M+Na]^+$, 723.31162 $[M+K]^+$, found: 707.33769 $[M+Na]^+$, 723.31128 $[M+K]^+$.

4.10. Synthesis of 5-(pyrimidin-2-ylsulfinyl)-25,26,27,28-tetrapropoxycalix[4]arene (5c)

A 250 mL flask was charged with compound **3c** (676 mg, 0.962 mmol), anhydrous CH_2Cl_2 (70 mL) and flushed with nitrogen. Mixture was cooled to 0 °C and *m*-chloroperbenzoic acid (1 eq, 216 mg, 0.962 mmol) was added. Reaction was stirred for 1 hour during which temperature was raised to room temperature. A saturated solution of Na_2SO_3 (150 mL) was added and the organic phase was extracted with $NaHCO_3$ (40 mL), water (60 mL), dried over $MgSO_4$ and the solvent was evaporated. Mixture was then subjected to Chromatotron^{tm} (SiO_2, EtOAc:CH_2Cl_2:cyclohexane = 1:1:7 v/v/v, R_f = 0.10) to give 582 mg (85%) of white crystalline substance, m.p.: 218-220 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K) δ (ppm): 8.82 (d, *J* = 4.7 Hz, 2H, pyr-**H**); 7.30 – 7.33 (m, 2H, Ar-**H**); 7.14 (d, *J* = 2.4 Hz, 1H, Ar-**H**); 6.69 (m, 3H, Ar-**H**); 6.43 – 6.51 (m, 4H, Ar-**H**); 6.33 – 6.37 (m, 2H, Ar-**H**); 4.41 – 4.45 (m, 4H, Ar-C**H$_2$**-Ar); 3.79-3.91 (m, 8H, Ar-O-C**H$_2$**-); 3.13 – 3.20 (m, 4H, Ar-C**H$_2$**-Ar); 1.84 – 1.96 (m, 8H, C**H$_2$**); 0.93 – 1.02 (m, 12H, C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K) δ (ppm): 174.38; 159.99; 158.39; 156.75; 156.11; 156.03; 137.38; 136.86; 135.49; 135.34; 134.93; 134.85; 134.71; 133.50; 133.44; 128.43; 128.35; 128.31; 128.23; 128.08; 127.75; 125.84; 124.68; 122.21; 122.09; 122.00; 121.30; 76.80; 76.76; 76.74; 76.57; 31.01; 30.95; 30.92; 23.25; 23.21; 23.15; 10.39; 10.19; 10.11. IR (KBr) ν (cm^{-1}): 2961.4, 2929.2, 2874.5, 1557.2, 1454.8, 1380.5, 1209.5. HRMS-ESI ($C_{44}H_{50}N_2O_5S$) *m/z* calcd: 741.33326 $[M+Na]^+$, found: 741.33374 $[M+Na]^+$.

4.11. Synthesis of bridged compound 6b

A 50 mL Schlenk flask charged with 5-ethylsulfinyl derivative **5b** (120 mg, 0.179 mmol), benzoquinone (0.5 eq, 10 mg, 0.09 mmol), $Pd(OAc)_2$ (1 eq, 40 mg, 0.179 mmol), Ag_2CO_3 (2 eq, 99 mg, 0.358 mmol), p-nitroiodobenzene (0.2 eq, 9 mg, 0.036 mmol), anhydrous 1,2-dichloroethane (10 mL), was flushed with argon and stirred at 90 °C overnight. The reaction mixture was then poured onto a short silica gel column (EtOAc:cyclohexane = 1:3 v/v) to remove the inorganic materials. The eluate was evaporated and subjected to Chromatotron^{tm} (SiO_2, EtOAc: CH_2Cl_2:cyclohexane = 1:1:10 v/v/v, R_f = 0.20) to give 14 mg (13%) of a white crystalline solid, m.p.: 60-61 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K) δ (ppm): 7.11 – 7.14 (m, 2H, Ar-**H**); 7.00 (m, 1H, Ar-**H**); 6.94 (m, 1H, Ar-**H**); 6.86 (m, 1H, Ar-**H**); 6.78 (t, *J* = 7.6 Hz, 1H, Ar-**H**); 6.71 (s, 2H, Ar-**H**); 6.66 (t, *J* = 7.6 Hz, 1H, Ar-**H**); 4.39 (d, *J* = 12.5 Hz, 2H, Ar-C**H$_2$**-Ar); 3.85-4.22 (m, 9H, Ar-C**H$_2$**-Ar, O-C**H$_2$**); 3.32-3.50 (m, 4H, Ar-C**H$_2$**-Ar, O-C**H$_2$**); 2.92 (d, *J* = 13.3 Hz, 1H, Ar-C**H$_2$**-Ar); 1.72-1.99 (m, 8H, C**H$_2$**); 1.52 – 1.57 (m, 2H, C**H$_2$**); 1.12 – 1.17 (m, 6H, C**H$_3$**); 0.93 – 0.98 (m, 6H, C**H$_3$**); 0.16 (t, *J* = 7.4 Hz, 3H, C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K) δ (ppm): 156.69; 156.27; 155.66; 142.40; 138.58; 138.52; 138.03; 137.19; 134.56; 131.72; 131.21; 130.25; 129.70; 128.80; 128.61; 127.77; 127.51; 123.01; 122.58; 121.20; 77.20; 76.83; 75.90; 75.77; 50.26; 34.28; 33.71; 33.46; 25.54; 25.36; 23.64; 23.16; 10.77; 10.74; 10.08; 9.92; 7.33. IR (KBr) ν (cm^{-1}): 2963.2, 2932.4, 2875.1, 2360.0, 2339.5, 1453.5, 1382.5, 1267.9, 1215.2. HRMS-ESI ($C_{42}H_{50}O_5S$) m/z calcd: 667.34517 $[M+H]^+$, 689.32712 $[M+Na]^+$, 705.30105 $[M+K]^+$, found: 667.34475 $[M+H]^+$, 689.32687 $[M+Na]^+$, 705.30024 $[M+K]^+$.

4.12. Synthesis of thiosulfinate 7

A 50 mL Schlenk flask charged with 5-(pyrimidin-2-ylsulfinyl)-tetrapropoxycalix[4]arene **5c** (50 mg, 0.070 mmol) and freshly distilled THF (15 mL) under an argon atmosphere was cooled to -78 °C. *n*-BuLi (3 eq, 0.10 mL, 0.209 mmol) was added and the mixture was stirred for 30 minutes at the same temperature. Aqueous HCl (1M, 10 mL) was added to quench the reaction and the reaction mixture was stirred at room temperature

for 1 hour. CH_2Cl_2 (20 mL) was added and the resulting mixture was washed with water (40 mL) and dried over $MgSO_4$. After evaporation of solvent *in vacuo* the mixture was subjected to Chromatotron^{tm} (SiO_2, EtOAc: cyclohexane = 1:20 v/v, R_f = 0.35) to give 27 mg (62%) of a white crystalline solid, m.p.: 103-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K) δ (ppm): 6.98 (d, *J* = 2.1 Hz, 1H, Ar-**H**); 6.45 – 6.81 (m, 21H, Ar-**H**); 4.40 – 4.53 (m, 8H, Ar-C**H$_2$**-Ar); 3.79 – 3.94 (m, 16H, O-C**H$_2$**); 3.13 – 3.26 (m, 8H, Ar-C**H$_2$**-Ar$_2$); 1.87 – 1.96 (m, 16H, C**H$_2$**); 0.96 – 1.06 (m, 24H, C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K) δ (ppm): 159.40; 158.66; 156.80; 156.74; 156.61; 156.52; 156.34; 156.30; 136.56; 136.35; 136.19; 136.16; 136.08; 135.60; 135.57; 135.50; 135.46; 135.32; 135.20; 134.88; 134.84; 134.79; 134.77; 134.72; 134.29; 128.68; 128.56; 128.38; 128.29; 128.21; 128.11; 127.96; 127.93; 127.87; 124.17; 123.78; 122.37; 122.35; 122.33; 122.17; 122.14; 122.07; 121.86; 77.19; 76.91; 76.82; 76.79; 76.76; 76.61; 31.07; 31.06; 30.99; 30.95; 30.89; 23.30; 23.26; 23.24; 23.21; 23.19; 23.16; 23.14; 10.41; 10.36; 10.33; 10.30; 10.24; 10.21; 10.20; 10.18. IR (KBr) ν (cm^{-1}): 2961.6, 2931.8, 2874.5, 1454.6, 1383.9, 1291.6, 1248.1, 1209.8, 1088.3, 1037.5, 1005.6. HRMS-ESI ($C_{80}H_{94}O_9S_2$) m/z calcd: 1285.62315 $[M+Na]^+$, 1301.59708 $[M+K]^+$, found: 1285.62391 $[M+Na]^+$, 1301.60099 $[M+K]^+$.

4.13. Synthesis of disulfide 8 and thiosulfonate 9

A 50 mL Schlenk flask charged with 5-(pyrimidin-2-ylsulfinyl)-tetrapropoxycalix[4]arene **5c** (150 mg, 0.209 mmol) and freshly distilled THF (25 mL) under argon atmosphere was cooled to -78 °C. *n*-BuLi (1.5 eq, 0.157 mL, 0.314 mmol) was added and the reaction mixture was stirred for 2 h during which time the reaction was gradually warmed to room temperature. The reaction was quenched by the addition 1M HCl (aq) (15 mL), diluted by CH_2Cl_2 (50 mL) and washed with water (40 mL). The mixture was then subjected to Chromatotron^{tm} (SiO_2, EtOAc:cyclohexane = 1:20 v/v) to give 44 mg (33%) of disulfide **8** (R_f = 0.30) and 37 mg (28%) of thiosulfonate **9** (R_f = 0.45), both in the form of a white crystalline solid.

Analytical data for compound **8**: M.p.: 107-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K) δ (ppm): 6.75 (s, 4H, Ar-**H**); 6.54 – 6.63 (m, 18H, Ar-**H**); 4.41 – 4.47 (m, 8H, Ar-C**H$_2$**-Ar); 3.77 – 3.89 (m, 16H, O-C**H$_2$**); 3.14 (t, *J* = 13.5 Hz, 8H, Ar-C**H$_2$**-Ar$_2$); 1.85 – 1.97 (m, 16H, C**H$_2$**); 0.97 – 1.02 (m, 24H, C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K) δ (ppm): 156.85; 156.63; 156.43; 136.13; 135.21; 135.09; 134.40; 129.67; 129.59; 128.27; 128.17; 127.95; 121.99; 121.97; 77.21; 76.79; 76.58; 30.98; 29.70; 23.25; 23.22; 10.36; 10.30; 10.27. IR (KBr) ν (cm^{-1}): 2961.0, 2926.9, 2874.3, 1455.3, 1210.3. HRMS-ESI ($C_{80}H_{94}O_8S_2$) m/z calcd: 1269.62823 $[M+Na]^+$, 1285.60217 $[M+K]^+$, found: 1269.62875 $[M+Na]^+$, 1285.60179 $[M+K]^+$.

Analytical data for compound **9**: M.p.: 131-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K) δ (ppm): 7.01 (s, 2H, Ar-**H**); 6.74 (s, 2H, Ar-**H**); 6.47-6.68 (m, 16H, Ar-**H**); 6.31 – 6.34 (m, 2H, Ar-**H**); 4.45 (t, *J* = 13.9 Hz, 8H, Ar-C**H$_2$**-Ar); 4.07 (t, *J* = 7.6 Hz, 2H, O-C**H$_2$**); 3.71-3.95 (m, 14H, O-C**H$_2$**); 3.10 – 3.18 (m, 8H, Ar-C**H$_2$**-Ar$_2$); 1.85 – 2.02 (m, 16H, C**H$_2$**); 0.95 – 1.06 (m, 24H, C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K) δ (ppm): 161.59; 159.51; 156.84; 156.62; 156.41; 155.92; 136.63; 136.43; 136.37; 136.04; 135.55; 135.52; 134.86; 134.77; 134.43; 132.90; 128.66; 128.55; 128.47; 128.04; 128.02; 127.78; 127.62; 122.38; 122.15; 121.79; 120.14; 77.23; 76.91; 76.83; 76.82; 76.67; 76.61; 30.99; 30.93; 23.32; 23.28; 23.19; 10.48; 10.40; 10.37; 10.24; 10.18; 10.15. IR (KBr) ν (cm^{-1}): 2962.3, 2932.0, 2874.9, 1455.1, 1384.1, 1326.3, 1248.8, 1209.8, 1131.4. HRMS-ESI ($C_{80}H_{94}O_{10}S_2$) m/z calcd: 1301.61806 $[M+Na]^+$, 1317.59200 $[M+K]^+$, found: 1301.61877 $[M+Na]^+$, 1317.59155 $[M+K]^+$.

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References and notes

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