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Synthesis and structural features of sulfur-substituted calix[4]pyrrole for a bottom-up control of the substrate-directed self-assembly of supramolecular structures

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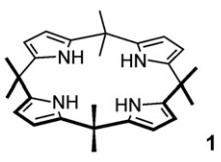
ABSTRACT

The synthesis of six new calix[4]pyrroles, containing sulfur-substituted phenylene units is reported. Halogen-anions and organic aromatic mono- and bis-anions have been selected to explore the formation of host–guest complexes and the possible self-assembly of multi-component structures with the six calixpyrroles. The type of aryl substitution modulates the strength of binding and the selectivity towards different anions and, in some cases, the combination of receptors and bis-anionic precursors, offers a way to build systems in which capsular assemblies are observed.

1. Introduction

Molecular recognition phenomena have been extensively investigated and exploited for the self assembly of supramolecular structures.[1–3] The possibility of controlling molecular motion within supramolecular systems lies some steps beyond simple molecular recognition, and has the attractive goal of constructing molecular machines.[4] Numerous examples have been described in which molecular motion is controlled by means of changing a given property of one (or more) of the components of a supramolecular structure, e.g., the oxidation state of dipyridinium dications in catenanes and rotaxanes[5] or changes in the pH of the medium.[6] The supramolecular chemistry of anions has been comparatively less investigated in this area as a means to build molecular switches and machines.[7–9] Over the last decade calixpyrroles, calix[4]pyrrole **1** being the simplest example, have emerged as very interesting molecular receptors that can bind anions.[10,11] They also have the potential to act as ditopic receptors in which, while the anion is bound by hydrogen bonding interactions with the NH units, the calix adopts a cone conformation that is capable of hosting cations (e.g., Cs^+).[12] Recently we described the first examples of pH-driven molecular switches based on complexes of calixpyrrole **2** with aromatic bis-anions. In these supramolecular systems different anionic centres could be generated as a function of the pH of the medium.[13] Calixpyrrole **2** was also found to form capsular 2:1 complexes with several bis-anions. Recently the capsular self-assembly of calixpyrrole derivatives containing ureido units and encapsulating pyridine *N*-oxide derivatives has also been reported.[14–17]



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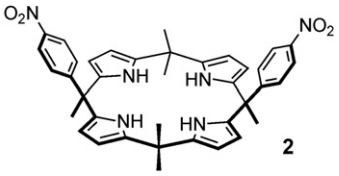

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As a development of our previous work using receptor **2**,[13,18] and taking into account the above, we decided to explore whether molecular switches and capsules could be assembled using analogues of **2** having different phenylene units as *meso*-substituents. In particular, we decided to design and realize the synthesis of sulfur-substituted calix[4]pyrroles; indeed, sulfur is one of the most versatile elements in organic synthesis since it can easily be introduced in different substrates as a nucleophile or electrophile substituent and due to its ability to change oxidation state.[19] We considered it significant that the new receptors contain sulfur-substituted phenylene units in which the electron density could be easily 'adjusted' without major changes in the proximity of the NH array, which is responsible for hydrogen-bonding to the anions. In fact, aromatic substituents at the *meso* positions may modulate the complexation strength of calixpyrroles towards anions by

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providing either additional CH-anion[20] or anion–π-interactions.[21,22]

We also considered it important that the *meso* substituents contain functional groups that could be exploited to use the calixpyrroles in the synthesis of linear polymers[23] and/or for their anchoring onto surfaces (e.g., gold),[24] the ultimate target being the potential use of these molecules for the construction of materials that would produce a mechanical response in the presence of specific guests.[25] Here we report our initial findings on the host–guest chemistry with halogen anions and several aromatic mono and bis-anions for a number of sulfur-substituted calixpyrrole derivatives that fulfil the characteristics outlined above.

2. Results and discussion

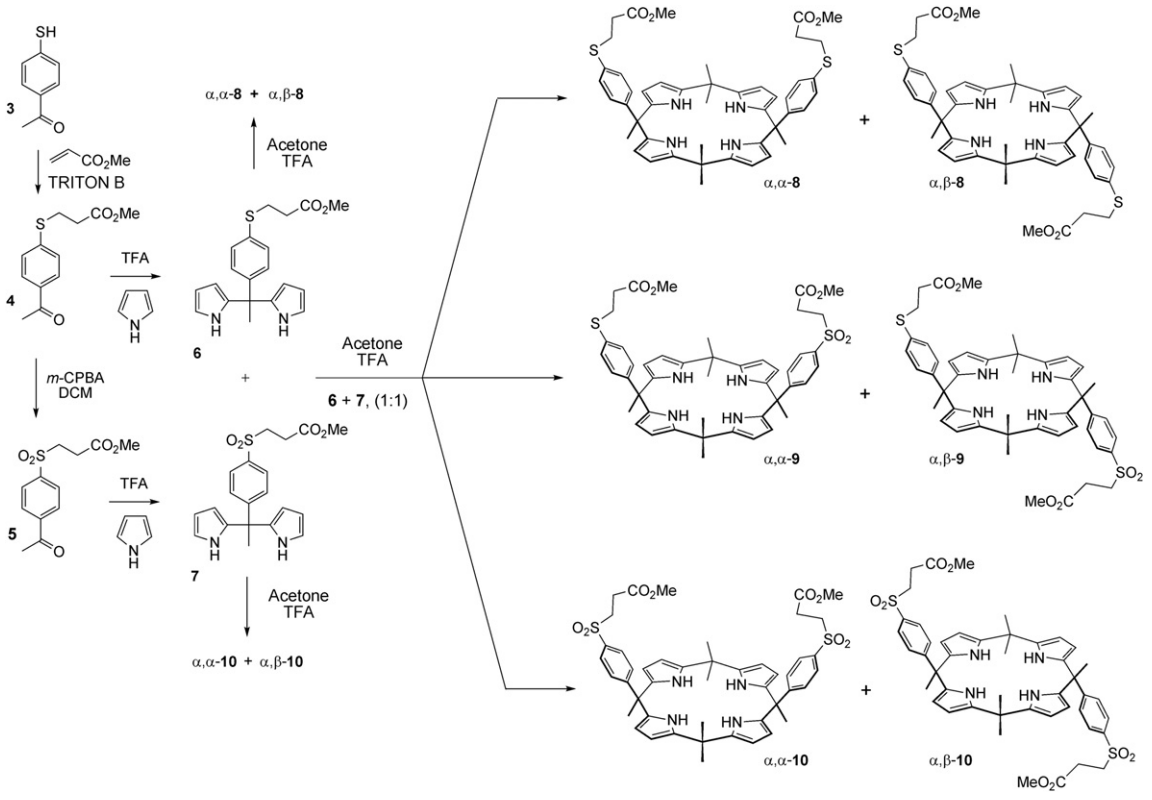
2.1. Synthesis of the receptors

The calixpyrroles α,α- and α,β-(**8**–**10**) were synthesized as shown in Scheme 1. We selected the thiophenol **3** as the starting material.[26] It was reacted with methyl acrylate in the presence of a catalytic amount of trimethylbenzylammonium hydroxide (TRITON B) to obtain sulfide **4** in 80% yield.[27] The ester function was considered useful for potential chemical modifications, while the sulfide moiety could be oxidized, thus modulating the electron-density of the phenylene unit. Sulfone **5** was easily prepared by the oxidation of **4** with *m*-chloroperbenzoic acid (*m*-CPBA) at room temperature. We did not stop the oxidation at the sulfoxide stage in order to avoid stereochemical complications in subsequent steps. Although the sulfoxide units provide a means to obtain interesting chiral calixpyrroles, we did not explore this issue in the current work. The reaction of **4** or **5** with excess pyrrole gave dipyrromethanes **6** and **7**, respectively, in good yields.

We were aware that the 1:1 condensation with acetone of **6** and **7** would allow the one-pot formation of the six calixpyrrole derivatives α,α- and α,β-(**8**–**10**) shown in Scheme 1, including the α,α- and α,β-**9** derivatives in which the two phenylene rings have different electron-densities. The α,α- and α,β-isomers were obtained in equal amounts, and single isomers were isolated by a combination of flash chromatography and crystallization (overall yield ca. 39%). Condensation with acetone of either compounds **6** or **7**, severally led to the formation of calixes (α,α-+α,β-) **8** and **10** in 25 and 40% yields, respectively. The alternative route to **9** by oxidation of the sulfide units in calixpyrroles **8** gave complex mixtures of decomposition products.

The stereochemistries of calixes **8** and **10** were attributed on the basis of their ^{1}H NMR spectra and by comparison with previously synthesized calixpyrrole derivatives that show structural analogies.[13] Assignment of the stereochemistry of α,α- and α,β-**9** was complicated by the different groups (SR and SO_2R) that these two calixpyrroles exhibit at the two aryl *meso*-substituents. However, even in this case, discrimination between α,α-**9** and α,β-**9** was possible on the basis of ^{1}H NMR. Thus, the methyl protons of α,α-**9**, which are directly linked to the aryl-substituted carbon atom of the macroring, resonate as two singlets at 1.80 and 1.89 ppm, while the other four methyls appear as two singlets at 1.60 and 1.50 ppm (1:1:2:2 ratio for the four signals). Two signals at 1.88 and 1.83 ppm are also observed for the methyl groups on the *meso*-aryl-substituted carbon atoms of α,β-**9**, while the other four *meso*-methyl groups resonate as a singlet at 1.60 ppm (overall intensity ratio 1:1:4, respectively). The isochrony of the *meso*-methyl groups at 1.60 ppm in α,β-**9** is consistent with the two faces of the macrocycle being more similar than in α,α-**9**, hence, we assigned to this compound the α,β stereochemistry shown in Scheme 1. These assignments were found to be consistent with the ^{1}H NMR data recorded for the interactions of each isomer with the various anionic and bis-anionic guests (vide infra).

The six receptors shown in Scheme 1 constitute a toolbox suited to explore several issues concerning the molecular recognition of



Scheme 1.

anions. These include the facial selectivity of binding both as a function of the configuration of the substituents (α,α- vs α,β-) and as a function of their relative electronic densities (possible anion-π interactions).[12] Therefore, we selected halogen–anions and organic aromatic mono- and bis-anions to explore the formation of host–guest complexes and the possible self-assembly of multicomponent structures similar to those previously observed with calixpyrrole derivative **2**.[13]

2.2. Host–guest chemistry

The host–guest chemistry of **8**–**10** with anions was investigated by means of ^{1}H NMR titrations using the complexation induced shifts (CISs). Typically, the interaction between the calixpyroles and the anions produces a downfield shift (higher δ values) of the NH resonances. Upon binding, the protons of the organic anions are shifted to lower δ values, this effect being larger when the guest is sandwiched between the *meso*-aryl substituents in the α,α-receptors.

2.2.1. Mono-anions. Table 1 shows the mono-anions that were chosen to study the binding ability of receptors **8**–**10**. Halide anions (entries 1 and 2) were used as their *n*-Bu_4N^+ salts and spectra were recorded in CD_2Cl_2 in order to obtain data that would be comparable with previous studies conducted on calix[4]pyrrole **2**.[13] All of the other mono-anions were used as their Cs^+ salts, generated in situ with Cs_2CO_3 in CD_3CN (entries 3–5).

Table 1
Mono-anions and receptors used in the complexation tests

	α,α-**8**	α,β-**8**	α,α-**9**	α,β-**9**	α,α-**10**	α,β-**10**
1[a]	F^-	NT	F^-	NT	F^-	NT
2[a]	Cl^-	NT	Cl^-	NT	Cl^-	NT
3[b]	PhO^-	PhO^-	PhO^-	PhO^-	PhO^-	PhO^-
4[b]	*p*-$MeOC_6H_4O^-$	*p*-$MeOC_6H_4O^-$	NT	*p*-$MeOC_6H_4O^-$	NT	*p*-$MeOC_6H_4O^-$
5[b]	*p*-$NO_2C_6H_4O^-$	*p*-$NO_2C_6H_4O^-$	*p*-$NO_2C_6H_4O^-$	*p*-$NO_2C_6H_4O^-$	*p*-$NO_2C_6H_4O^-$	*p*-$NO_2C_6H_4O^-$

NT: not tested.
[a] As *n*-butylammonium salts in CD_2Cl_2.
[b] As caesium salt in CD_3CN.

The binding of fluoride with α,α-(**8**–**10**) was too strong for NMR titration. The presence of a coupling constant between fluoride and the pyrrole NH signal at low field, which appeared as doublets (Fig. S1–S3), indicated very strong and kinetically slow complexations on the NMR time scale. The corresponding complexes with chloride were kinetically fast (Fig. S4–S6) and ^{1}H NMR titration data could be fitted for the 1:1 models[28] to give K_a values of 74±7 M^{-1}, 316±14 M^{-1}, 2200±320 M^{-1}, for α,α-**8**, α,α-**9** and α,α-**10**, respectively. These values are consistent with an increasingly electron deficient character of the *meso*-phenylene unit in these receptors. A competition experiment for the binding of F^- was conducted between α,α-**9** and α,α-**10** in which an equimolar solution of these two receptors was titrated with F^-. In the mixture, the NH resonances of the two complexes were detectable as separate doublets. The complexation of α,α-**9** was observed only after almost quantitative complexation of α,α-**10**.

The organic mono-anions, shown in Table 1 (entries 3–5), were chosen because they have a varied charge density at the phenolic oxygen as well as different charge distributions and electron densities over their aromatic rings. Equimolar solutions of the receptors and the phenols led to the quantitative formation of 1:1 complexes only upon addition of the base, whilst no interaction (CISs) was detected with the protonated phenols.

The up-field shifts of phenolates in all of the complexes with α,α-(**8**–**10**) indicated that binding was occurring on the face containing the aromatic *meso*-substituents.[13] Moreover, the observation of just one NH resonance in the complexes of α,α-**8** and α,α-**10**, and two sets of NH units in α,α-**9** is consistent with total facial selectivity (Fig. 1 and Fig. S7–S9). A competition experiment for the binding of *p*-$MeOC_6H_4O^-$ was conducted between α,α-**8** and α,α-**10**. In the presence of 1 equiv of salt the corresponding complexes with α,α-**8** and α,α-**10** were present in 3:7 ratio, indicating that $K_{a\ \alpha,\alpha\text{-}\mathbf{10}} = -5.4\ K_{a\ \alpha,\alpha\text{-}\mathbf{8}}$ for this anion (Fig. 1). In the complexation tests of α,β-**8** and α,β-**10** with $C_6H_5O^-$ and *p*-$MeOC_6H_4O^-$, the broad signal for the two NH units in each of the two free receptors became two rather sharp low-field signals in each of the two complexes (Figs. S10b,c and S11b,c). This is consistent with a slow binding on the NMR time-scale. In fact, at room temperature there is only one NH resonance in the free receptors since the NH units flip within the calixpyrrole cavity and give a time-averaged signal; α,β-**8** and α,β-**10** have 2 equiv faces when they are not complexed. Upon complexation with the anions, a cone conformation of the calix is stabilized by the NH···O^- bonds, with the anion sitting on one face of the macrocycle. This situation creates two different sets of NH units, and in fact two NH signals are observed at low fields for the complexes of α,β-**8** and α,β-**10**. However, when α,β-**8** or α,β-**10** are treated with *p*-$NO_2C_6H_4O^-$ only one NH signal is observed in the complexes (δ 11.2 and 11.1, Fig. S10c and S11c, respectively). This is consistent with a fast exchange of this anion between the two faces of either of the macrocycles. In these complexes the resonances of the anionic guests were all shifted up-field.

Receptor α,β-**9** has two configurationally different faces with respect to the calixpyrrole moiety mean plane. One face contains a phenylene unit, that is, more electron-rich (the sulfide side) than the other (the sulfone side), therefore, an anionic guest might exhibit facial selectivity. The spectrum of the free α,β-**9** showed two different NH resonances (two pyrrole rings adjacent to the *meso*-phenylenesulfone and two pyrrole rings adjacent to the *meso*-phenylenesulfide unit, respectively). In the spectra of the complexes of α,β-**9** and PhO^- or *p*-$OMePhO^-$ we observed four NH resonances at low fields that were of equal intensities. Therefore these anions bind to either faces (sulfide or the sulfone side) of α,β-**9** without face selectivity, forming 1:1 complexes that are kinetically slow on the NMR time-scale (Fig. 2b and c). In the complex of α,β-**9** with *p*-$NO_2C_6H_4O^-$ two low-field NH resonances with a 1:1 intensity were observed (Fig. 2d). This originates from a fast exchange between the two faces of the receptor, resembling the situation already observed for α,β-**8** and α,β-**10**. Therefore, none of these complexation experiments provided conclusive evidence for the preferential binding of the tested anions onto either face of α,β-**9**.

2.2.2. Bis-anions. The formation of pH-controlled switchable assemblies and molecular capsules was investigated using only the α,α-receptors with the bis-anions listed in Table 2. This choice was based on a similar study conducted using receptor **2**.[13] The different regiochemistries of the hydroxybenzoic acids appeared useful for studying the steric requirements of capsular assembly. In particular, receptor α,α-**9** with two different groups at the aryl *meso*-

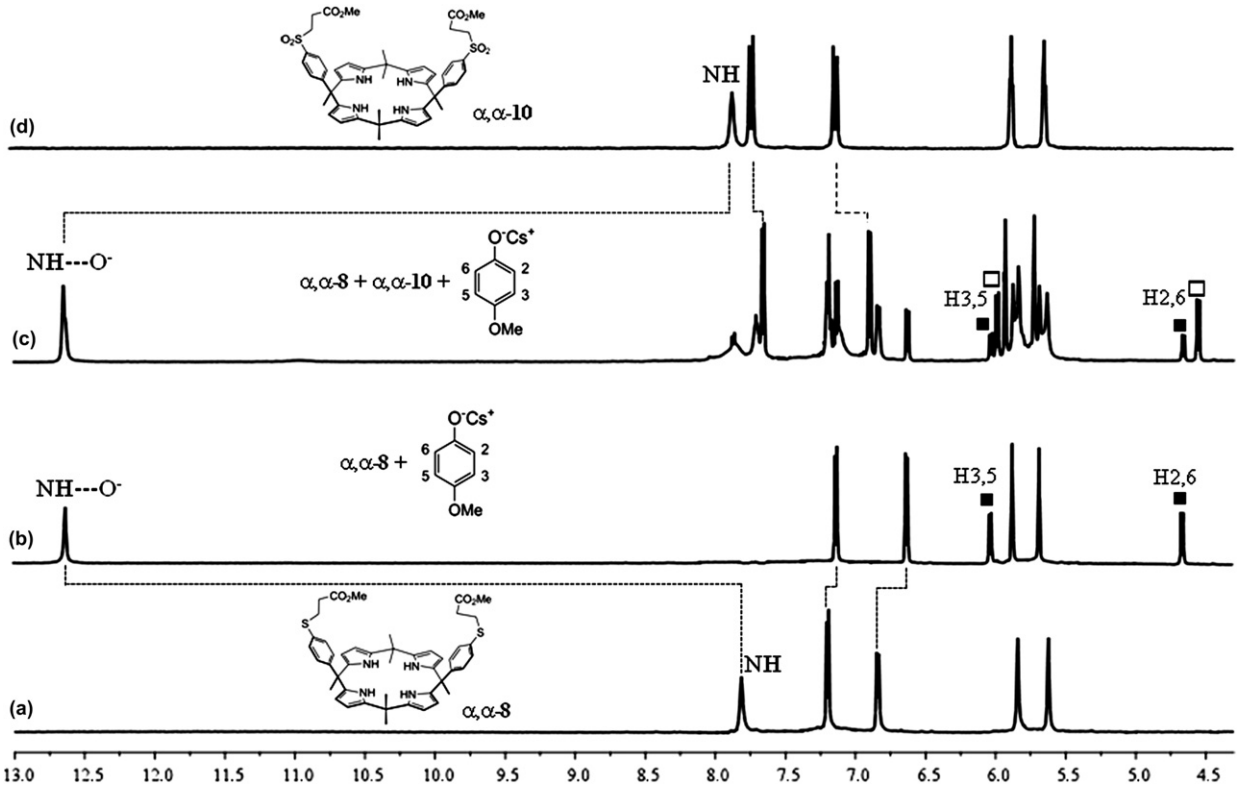


Fig. 1. Partial ^{1}H NMR spectra (500 MHz, CD_3CN) for the competitive binding of *p*-$MeOC_6H_4O^-Cs^+$ by receptors α,α-**8** and α,α-**10**. Black and white squares mark resonances for the anion included in either receptor α,α-**8** or receptor α,α-**10**, respectively; (a) α,α-**8**; (b) α,α-**8**+*p*-$MeOC_6H_4O^-Cs^+$ (1:0.85); (c) α,α-**8**+α,α-**10**+*p*-$MeOC_6H_4O^-Cs^+$ (1:1:1); (d) α,α-**10**. At 20 °C the intensities of the 'black and white' H2,6 resonances have a 3:7 ratio.

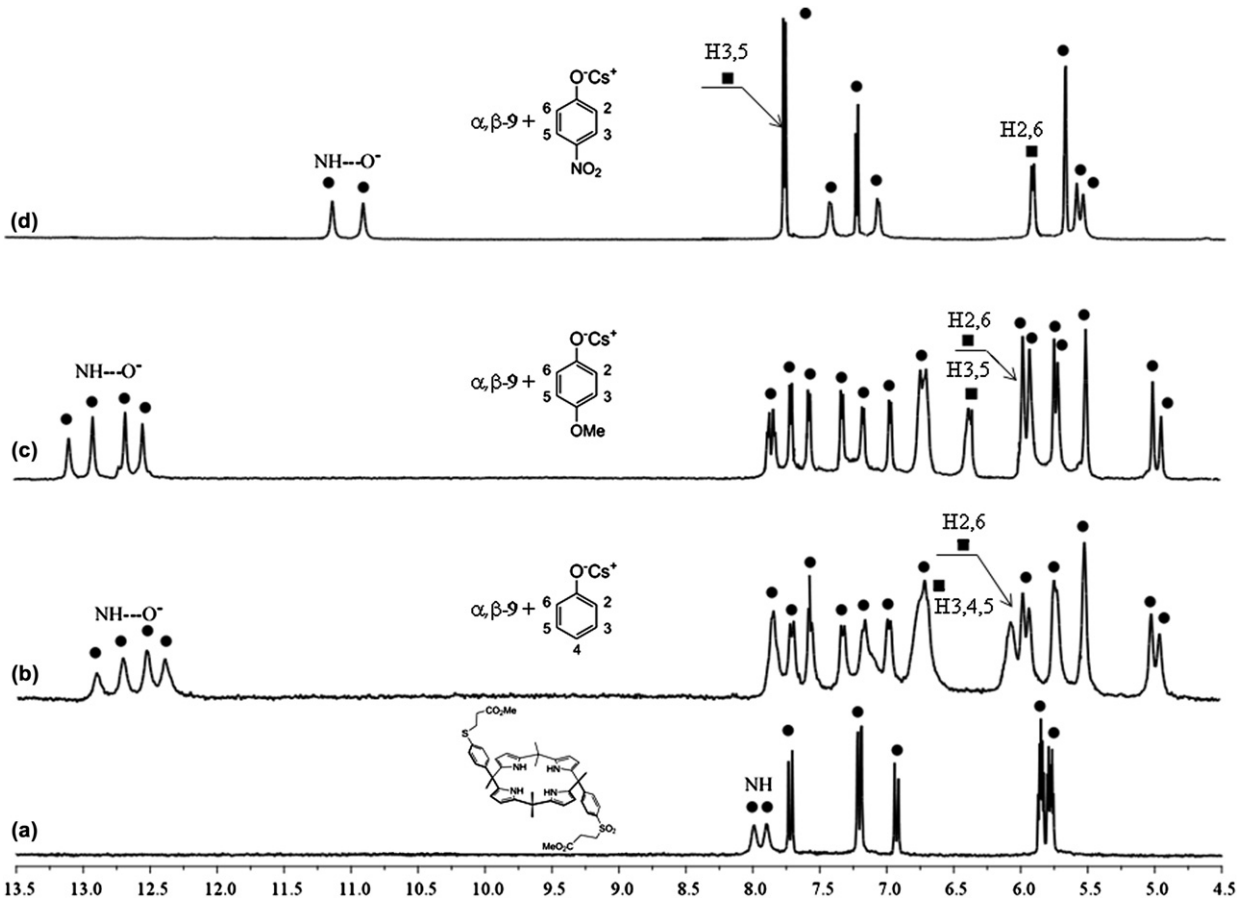


Fig. 2. Partial ^{1}H NMR spectra (300 MHz, CD_3CN, 20 °C) for the binding of PhO^-Cs^+, *p*-$MeOC_6H_4O^-Cs^+$ and *p*-$NO_2C_6H_4O^-Cs^+$ by receptor α,β-**9**. Black circles and squares mark the resonances for the receptor and the anion in each trace, respectively; (a) α,β-**9**; (b) α,β-**9**+PhO^-Cs^+ (1:1); (c) α,β-**9**+*p*-$MeOC_6H_4O^-Cs^+$ (1:1); (d) α,α-**9**+*p*-$NO_2C_6H_4O^-Cs^+$ (1:1). In traces b and c the intensities of the four NH resonances are equivalent within experimental error, hence no preference of the anions for either of the two different faces α,β-**9** can be detected.

Table 2
Bis-anions (as cesium salts) and receptors used in the complexation tests conducted in CD_3CN

	α,α-**8**	α,α-**9**	α,α-**10**
1	*m*-$^-$O–C_6H_4–COO^-	*m*-$^-$O–C_6H_4–COO^-	*m*-$^-$O–C_6H_4–COO^-
2	*p*-$^-$O–C_6H_4–COO^-	*p*-$^-$O–C_6H_4–COO^-	*p*-$^-$O–C_6H_4–COO^-

substituents of the receptor could lead to interesting stereochemical outcomes (chiral species) as consequence of capsule formation by a process analogous to that described by Rebek.[29]

When Cs_2CO_3 was added to a 2:1 solution of α,α-**10** and *m*-OH–C_6H_4–COOH in CD_3CN, the formation of a kinetically slow carboxylate-bound complex was observed. Immediately after sonication of the sample, two new signals for the pyrrolic NH resonance were detected with a 1:1: ratio, respectively (Fig. 3). The spectrum is consistent with the formation of a capsular assembly involving two units of calix and one of the bis-anion. The two chemical shifts observed for the NH units of the two receptors are consistent with one being involved in binding the carboxylate unit and the other binding the phenolate anionic sites, respectively. Similar results were observed using DBU as the base (13 equiv for total deprotonation of the acidic sites, Fig. S12). In a solution (2.5×10^{-3} M) that contained the bis-anion and the calix in a 1:1 stoichiometry there was no evidence for the presence in of any of the two (carboxylate or phenolate-bound) 1:1 complexes that can be formed. This observation is consistent with a remarkable synergic effect of the initial 1:1 calix/bis-anion binding event(s) that favours the formation of the capsular assembly.

The addition to Cs_2CO_3 in a 1:1 solution of α,α-**10** and *p*-OH–C_6H_4–COOH acid in CD_3CN induced the formation of a precipitate, thus preventing solution studies. The same experiment using DBU generated the carboxylate-bound complex that cleanly evolved to the phenolate-bound complex with the addition of a second equivalent of DBU (Fig. S13). We could not detect the formation of any capsular 2:1 complex. Addition of one more equivalent of α,α-**10** still did not produce the capsule.

The 1:1 solution of α,α-**9** and *m*-OH–C_6H_4–COOH, in CD_3CN, in the presence of Cs_2CO_3 showed the initial formation of the carboxylate-bound complex (deprotonation of the carboxyl unit is fast) that cleanly evolved to the phenolate-bound complex (after sonication). However, even after the addition of one more equivalent of α,α-**9** the phenolate-bound complex was the only species present in solution (Fig. S14). Hence, no capsular assembly could be detected for α,α-**9** with the bis-anion of the *m*-OH–C_6H_4–COOH.

When Cs_2CO_3 was added to a 1:1 solution of α,α-**9** and *p*-OH–C_6H_4–COOH in CD_3CN, of the carboxylate-bound complex was initially observed, but the species in solution evolved to give a complicated mixture of carboxylate-bound and phenolate-bound complexes and as well as capsular complex. The addition of 1 equiv of α,α-**9** led to the unique presence of capsules in solution (Fig. 4).

The proton resonances of the guest clearly indicate that it fits inside two receptors (two molecules of α,α-**9**), that assemble each others as two interlocking horseshoes having two different ends (sulfide and sulfone groups). The interlocked calix units produce a chiral structure.[29] However, the different possible orientations of the anionic guest (e.g., the direction of the phenolate–carboxylate vector within the capsule and the different 'Y' modes of binding of the carboxylate with the NH units of one of the calyxes[30,31]) can

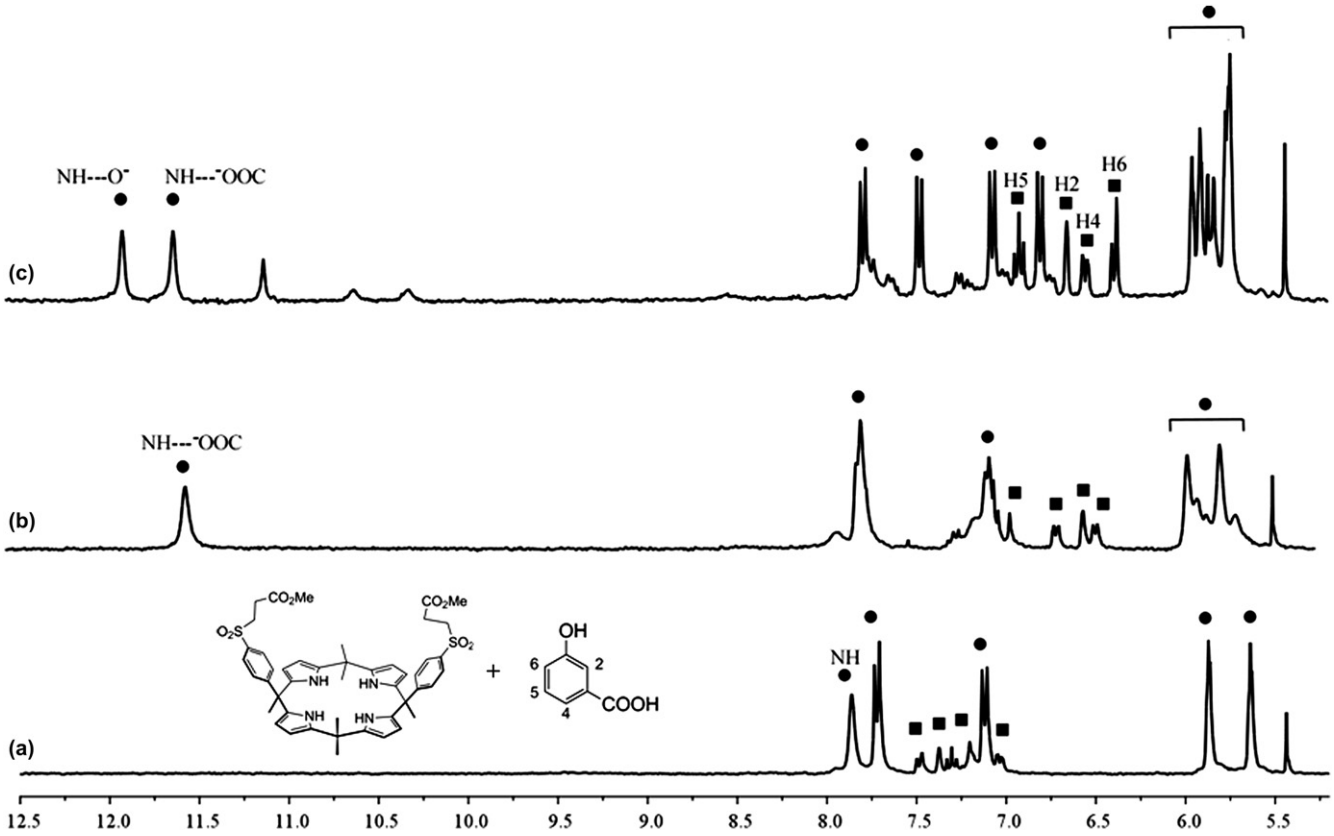


Fig. 3. Partial ^{1}H NMR (300 MHz, CD_3CN, 20 °C) spectra of: (a) α,α-**10**+*m*-HO-C_6H_4–COOH (2:1); (b) α,α-**10**+*m*-HO–C_6H_4–COOH (2:1)+Cs_2CO_3 (in excess as a solid) shortly after the addition of the base; (c) same as (b), but after several minutes of sonication. Since each macrocycle in the capsule interacts with either a phenolate or a carboxylate unit, the two receptors appear as distinguishable units. The NH units which in each macrocycle are hydrogen-bonded to either of the two anionic centres of the guest are assigned. Black circles mark the resonances for the receptor(s), black squares mark the resonances of *m*-HO–C_6H_4–COOH (a) or of the complexed anion (b and c).

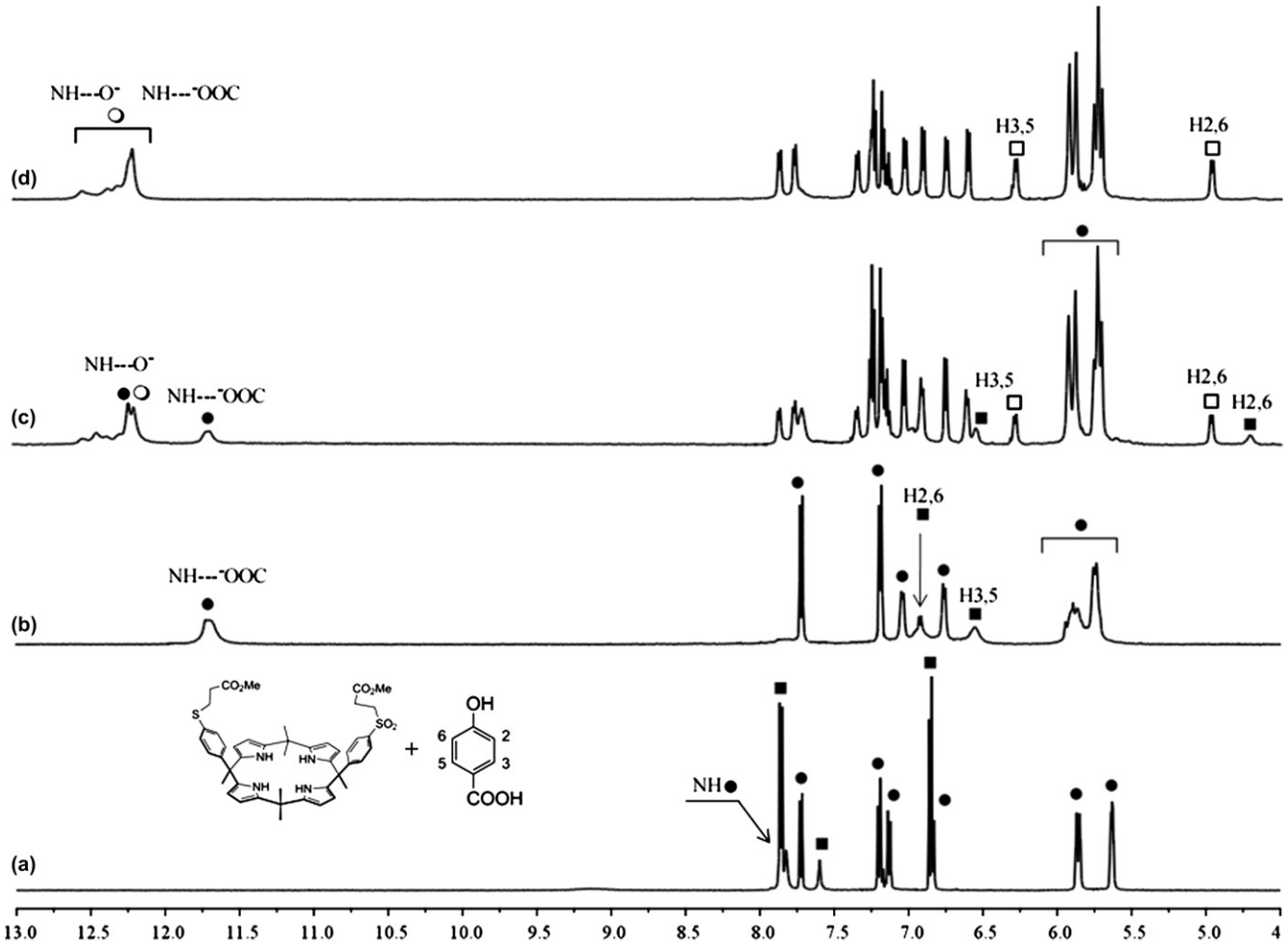


Fig. 4. Partial ^{1}H NMR (500 MHz, CD_3CN, 20 °C) spectra of: (a) α,α-**9**+*p*-OH−C_6H_4−COOH (1:1); (b) α,α-**9**+*p*-OH−C_6H_4−COOH (1:1)+Cs_2CO_3 (in excess as a solid) shortly after the addition of the base; (c) same as (b), but after several minutes of sonication; (d) α,α-**9**+*p*-OH−C_6H_4−COOH (2:1)+Cs_2CO_3 (in excess as a solid) after sonication. Since each macrocycle in the capsule interacts with either a phenolate or a carboxylate unit, the two receptors appear as distinguishable units. Black circles mark the resonances for the free receptor in (a) or of the receptor in its 1:1 complex in traces (b) and (c). The white circles mark resonances of the NH units in the capsules (c) and (d). Black squares mark the resonances of *p*-OH−C_6H_4−COOH (a), or of the anion in its 1:1 complex (b) and (c). The white squares mark the resonance for the encapsulated bis-anion (c and d).

produce different sets of diastereomeric three-component-assemblies. The diastereomeric sets of capsules are not distinguishable in the ^{1}H NMR spectrum at 500 MHz, and the NH resonances are rather broad and partially overlapping. However, conclusive evidence for the formation of capsules is provided by the signals of the aromatic benzo-protons of the calyxes which all appear at different chemical shifts (diastereotopic) in the racemic mixtures of 'supramolecules'. The spectrum is consistent with an NMR time-averaged structure in which the bis-anion is spinning around its O−CO_2 axis (Fig. 5).

When the *m*-$^-$O−C_6H_4−COO^- was used as guest for receptor α,α-**8**, we always observed two types of NH resonances, typical for phenolate-bound and carboxylate-bound 1:1 complexes. Thus, it appears that the combination of steric requirements and relative strengths of interaction of the anionic centres with the NH units results in a lack of significant selectivity between the two negatively charged sites. No capsular assemblies were detected.

Macrocycle α,α-**8** was observed to produce both the 1:1 and the 2:1 complexes in the presence of the *p*-$^-$O−C_6H_4−COO^- (S15). When the relative stoichiometry was 1.5:1 (α,α-**8**/bis-anion), the phenolate-bound complex and the capsular assembly were observed in a 6:4 ratio, respectively. This proportion was shifted towards the nearly quantitative formation of the capsule in the presence of 2 equiv of receptor. This dominant formation of the three-component 'supramolecule' indicates that there is a positive synergism between the two binding events.

All of the solutions used in the NMR study on the capsules were also examined by ESI-MS (negative mode). However, none of the recorded spectra show signals that can be assigned to the presence of capsules. Indeed, the solutions used in these experiments were considerably (100 times) more diluted than those used in the NMR study, and we speculate that the dissociation induced by the high dilution accounts for this result.

3. Conclusions

This work demonstrates that the previously studied self assembly of capsular structures from calixpyrrole **2** and selected aromatic bis-anions can be extended to novel derivatives in which the aryl substituents have different functional groups. The type of aryl substitution modulates the strength of binding and the selectivity towards different anions. Moreover, appropriate combinations of receptors and bis-anionic precursors provides a means to construct systems in which, under increasing basic conditions, there is a switch in the mode of binding of the anionic guest or alternatively capsular assemblies are formed.

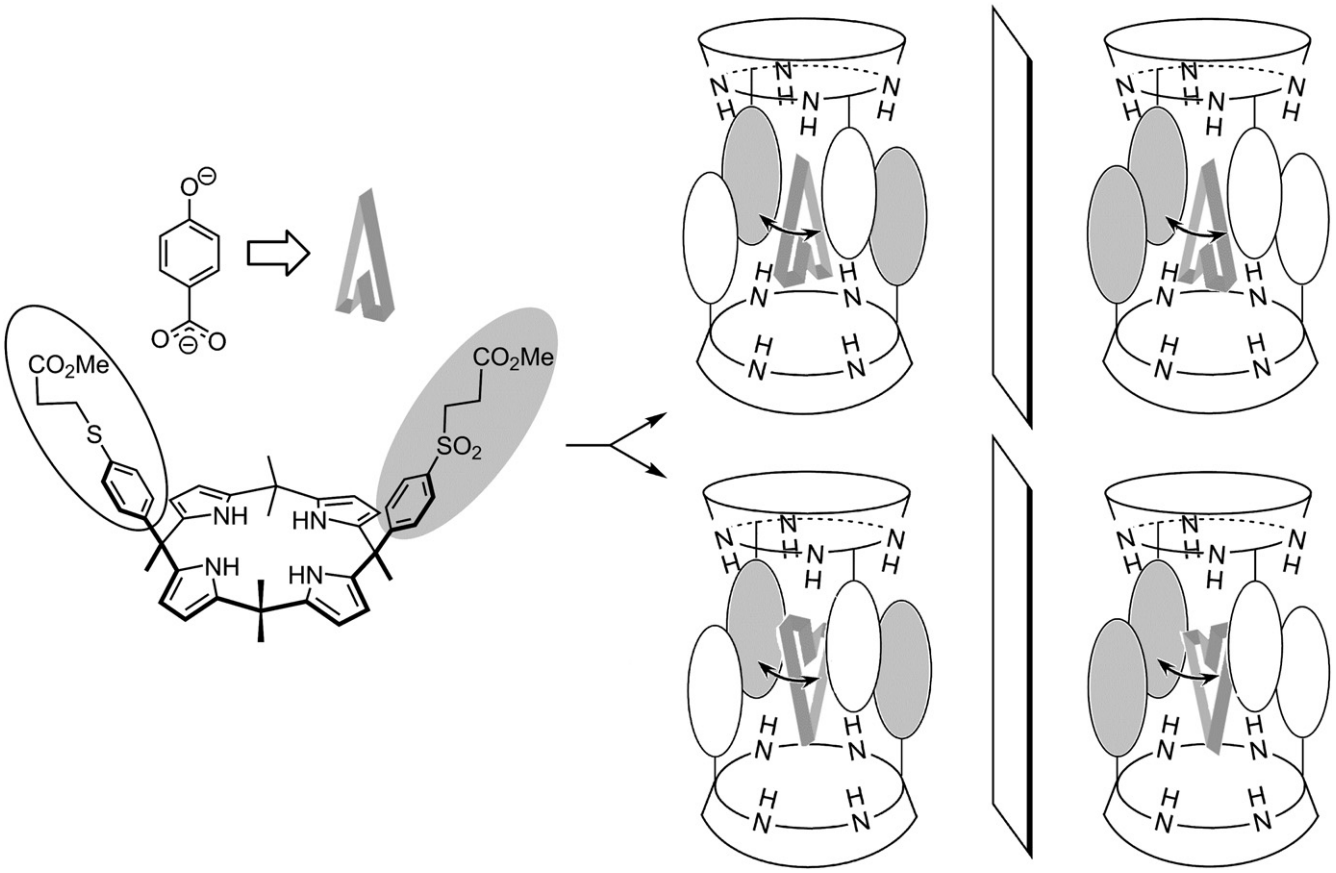


Fig. 5. The possible stereoisomers that can be formed by the three-component capsular assemblies made up by two molecules of α,α-**9** and one unit of the bis-anion *p*-$^{-}$OH-C_6H_4–COO^{-} assuming that this is spinning along its O–CO_2 axis within the capsules as indicated by circular arrows. This spinning is consistent with ^{1}H NMR spectrum of the mixture at room temperature. The shaded shape within the capsule represents the bis-anion. The rectangular elements represent mirror planes by which the capsules on the same row are related trough reflection.

4. Experimental section

4.1. General methods and instrumentation

Acetone was distilled from dry $CaCO_3$. Pyrrole was distilled before use. All other chemicals were of standard reagent grade and were used without further purification. All air-sensitive and/or moisture-sensitive reactions were conducted under a dry argon atmosphere. Thin layer chromatography (TLC) was conducted on Merck SiO_2 60 F_{254} plastic plates. Compounds were visualized with vanillin or by examination under UV light. Column chromatography was conducted on Aldrich Silica gel 230–400 mesh, 60 Å. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-300 at 300 and 75 MHz, respectively, and a Varian 500 spectrometer at 500 and 125 MHz, respectively, using the residual proton resonances of the solvents ($CDCl_3$, CD_2Cl_2 and CD_3CN) as δ reference. Melting points were determined on a Kofler hot stage apparatus, and are not corrected.

4.1.1. ^{1}H NMR titrations. The *n*-tetrabutylammonium salts were dried in a vacuum oven for at least 24 h. For measurements in CD_2Cl_2 this was stored on dry alumina and care was taken to minimize exposure to the atmosphere during sample preparation and titration. The anions were added as measured volumes of solutions (ca. 0.031 M) in CD_2Cl_2 to the solution of the macrocycle under investigation (0.0025 M) in the same solvent (0.7 mL). The sample volume was kept constant by evaporating the excess solvent with a flow of dry nitrogen. After each addition the stoichiometric ratios between the salt and macrocycle were also re-determined from the intensities of the resonance of the pyrrole protons of the host versus those of the *n*-tetrabutylammonium cation. Quantitative ^{1}H NMR integrations were obtained by the use of appropriate pulse delays in all cases. Processing the data with the WinEQNMR program[28] produced the reported K_a values for the 1:1 complexation model. For the complexation experiments, receptor was dissolved in CD_3CN to a concentration of 2.5×10^{-3} M and 1 M equivalent of the neutral putative guest was added. No cis could be detected that would suggest interactions between neutral compounds and receptors. The mixtures were treated with a base, namely, Cs_2CO_3 or DBU. Because Cs_2CO_3 is only sparingly soluble in CD_3CN, it had to be added as a solid and was always used in excess. DBU could be added in known amounts from stock solutions of suitable concentrations, which provided a practical means of adjusting the concentration of the base in the mixtures to achieve the stepwise deprotonation of the carboxylic and phenolic units in the guests.

*4.1.2. 3-[(4-Acetylphenyl)thio]-propanoic acid, methyl ester (**4**)*[27]. Triton B (40% w/w solution in MeOH, 377 mg, 0.1 mmol) was added to a solution of thiol **3** (1 g, 6.6 mmol) in dry THF (12 mL) at −78 °C and after 5′ methyl acrylate (0.570 g, 6.6 mmol) was added. The mixture was stirred under argon atmosphere at room temperature until complete disappearance of the starting material, then it was quenched with water and extracted with Et_2O. The organic phase was extracted with aqueous NaCl (saturated solution), dried ($MgSO_4$) and concentrated to give 3-[(4-*acetylphenyl*) *thio*]-*propanoic acid, methyl ester* (**4**) (95%) as a white solid, mp

88 °C; δ_H (300 MHz, $CDCl_3$); 7.87 and 7.35 (AA′BB′ system, 2×2H, Ar–H), 3.71 (s, 3H, OCH_3), 3.27 (t, J=7.4 Hz, 2H, CH_2–S), 2.70 (t, J=7.4 Hz, 2H, CH_2–COOMe), 2.58 (s, 3H, CH_3); δ_C (75 MHz, $CDCl_3$) 197.0 (*C*OOCH$_3$), 171.8 (CO), 142.9, 134.3 (Cq), 128.8, 127.0 (CH), 51.9 (COO*C*H$_3$), 33.6 (CH_2–S), 27.1 (*C*H$_2$–COOMe), 26.4 (*C*H$_3$).

*4.1.3. 3-[(4-Acetylphenyl)sulfonyl]-propanoic acid, methyl ester (**5**).* *m*-CPBA in CH_2Cl_2 (80%, 10 mL/*m*-CPBA mmol, 3 equiv) was added to a solution of 3-[(4-acetylphenyl)thio]-propanoic acid, methyl ester **4** (1 equiv) in CH_2Cl_2 (10 mL) at −78 °C. After 1 h the reaction was quenched by addition of an $Na_2S_2O_3$ solution (10%, 10 mL). The organic phase was extracted with aqueous $NaHCO_3$ (saturated solution), dried ($MgSO_4$) and concentrated to give 3-[(4-*acetylphenyl)sulfonyl*]-*propanoic acid, methyl ester* (**5**) (96%) as white solid, mp 105 °C; δ_H (300 MHz, $CDCl_3$); 8.15 and 8.05 (AA′BB′ system, 2×2H, Ar–H), 3.66 (s, 3H, OCH_3), 3.47 (t, J=7.4 Hz, 2H, CH_2–SO_2), 2.78 (t, J=7.4 Hz, 2H, CH_2–COOMe), 2.68 (s, 3H, CH_3); δ_C (75 MHz, $CDCl_3$) 196.5 (*C*OOCH$_3$), 170.2 (CO), 142.2, 141.0 (Cq), 129.0, 128.6 (CH), 52.3 (COO*C*H$_3$), 51.4 (CH_2–SO_2), 27.4 (*C*H$_2$–COOMe), 26.9 (*C*H$_3$).

4.2. Dipyrromethane derivatives (6) and (7). General procedure

TFA (1.5 equiv) was added to a solution of the propanoic acid methyl ester **4** or **5** (1 equiv) in pyrrole (15 equiv), at 0 °C. The mixture was stirred under argon atmosphere at room temperature for 1.5 h, then neutralized (NaOH 1 M) and extracted (CH_2Cl_2). The organic phase was dried ($MgSO_4$) and concentrated to fractionally remove CH_2Cl_2 and excess pyrrole under reduced pressure. The crude brown oil was subjected to column chromatography (SiO_2, CH_2Cl_2/EtOAc in polarity gradient) to give the dipyrromethane derivative.

*4.2.1. 5-Methyl-5-[4-(2-methoxycarbonylethyl-1-thio)phenyl]dipyrromethane (**6**).* After column chromatography (R_f 0.4), 5-methyl-5-[4-(2-methoxycarbonylethyl-1-thio)phenyl]dipyrromethane (**6**) (50%) was obtained as a white solid, mp 102 °C; δ_H (300 MHz, $CDCl_3$) 7.80 (br s, 2H, NH), 7.25 and 7.04 (AA′BB′ system, 2×2H, Ar–H), 6.68 (m, 2H, pyrrole α-CH), 6.17 and 5.96 (2×m, 2×2H, pyrrole β-CH), 3.67 (s, 3H, OCH_3), 3.14 (t, J=7.4 Hz, 2H, CH_2–S), 2.63 (t, J=7.4 Hz, 2H, CH_2–COOMe), 2.03 (s, 3H, CH_3); δ_C (75 MHz, $CDCl_3$) 172.1 (*C*OOCH$_3$), 145.9, 137.0, 133.3 (Cq), 129.7, 128.1, 117.0, 108.3, 106.3 (CH), 51.8 (COO*C*H$_3$), 44.4 (Cq), 34.2, 28.9 (CH_2), 28.7 (CH_3).

*4.2.2. 5-Methyl-5-[4-(2-methoxycarbonylethyl-1-sulfonyl)phenyl]dipyrromethane (**7**).* After column chromatography (R_f 0.5), 5-methyl-5-[4-(2-methoxycarbonylethyl-1-sulfonyl)phenyl]dipyrromethane (**7**) (65%) as white solid, mp 135 °C; δ_H (300 MHz, $CDCl_3$) 7.87 (br s, 2H, NH), 7.80 and 7.32 (AA′BB′ system, 2×2H, Ar–H), 6.73 (m, 2H, pyrrole α-CH), 6.19 and 5.96 (2×m, 2×2H, pyrrole β-CH), 3.64 (s, 3H, OCH_3) 3.42 (t, J=7.4 Hz, 2H, CH_2–SO_2), 2.77 (t, J=7.4 Hz, 2H, CH_2–COOMe), 2.08 (s, 3H, CH_3); δ_C (75 MHz, $CDCl_3$) 170.4 (*C*OOCH$_3$), 154.3, 136.6, 135.8 (Cq), 128.5, 127.9, 117.7, 108.5, 106.8 (CH), 52.3 (COO*C*H$_3$), 51.4 (*C*H$_2$–SO_2), 45.0 (Cq), 28.5 (CH_3), 27.6 (*C*H$_2$–CO).

4.3. Macrocycles α,α-(8–10) and α,β-(8–10). General procedure

TFA (5 equiv) was added to a solution of dipyrromethane **6** (1 equiv) and dipyrromethane **7** (1 equiv) in dry acetone (0.14 M), at 0 °C. The mixture was stirred under argon atmosphere at room temperature for 1 h, then it was neutralized (NaOH 1 M) and extracted (CH_2Cl_2). The organic phase was dried ($MgSO_4$), concentrated and the brown oil was subjected to column chromatography (SiO_2, CH_2Cl_2/EtOAc, 95:5) to give the mixture of the α-α and the α-β isomers of each macrocycle. This mixture was then subjected to fractional crystallization from toluene to separate α,α-macrocycles from α,β-macrocycles.

*4.3.1. 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α,20α-bis-[4-(2-methoxycarbonylethyl-1-thio)phenyl]-calix[4]pyrrole (α,α-**8**).* 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α,20α-bis-[4-(2-methoxycarbonylethyl-1-thio)phenyl]-calix[4]pyrrole (α,α-**8**) was obtained from toluene as a white solid (R_f: 0.5, 7%), mp 197 °C; δ_H (300 MHz, $CDCl_3$) 7.28 and 7.05 (AA′BB′ system, 2×4H, Ar–H), 7.15 (br s, 4H, NH), 5.92 and 5.76 (2×m, 2×4H, pyrrole β-CH), 3.69 (s, 6H, OCH_3), 3.15 (t, J=7.1 Hz, 4H, CH_2–S), 2.63 (t, J=7.1 Hz, 4H, CH_2–COOMe), 1.88, 1.62 and 1.56 (3×s, 3×6H, CH_3); δ_H (300 MHz, CD_2Cl_2) 7.30 (br s, 4H, NH), 7.21 and 6.89 (AA′BB′ system, 2×4H, Ar–H), 5.92 and 5.64 (2×m, 2×4H, pyrrole β-CH), 3.64 (s, 6H, OCH_3), 3.12 (t, J=7.3 Hz, 4H, CH_2–S), 2.60 (t, J=7.3 Hz, 4H, CH_2–COOMe), 1.86, 1.62 and 1.52 (3×s, 3×6H, CH_3); δ_H (300 MHz, CD_3CN) 7.82 (br s, 4H, NH), 7.18 and 6.84 (AA′BB′ system, 2×4H, Ar–H), 5.84 and 5.63 (2×m, 2×4H, pyrrole β-CH), 3.60 (s, 6H, OCH_3), 3.12 (t, J=7.1 Hz, 4H, CH_2–S), 2.58 (t, J=7.1 Hz, 4H, CH_2–COOMe), 1.83, 1.63 and 1.48 (3×s, 3×6H, CH_3); δ_C (75 MHz, $CDCl_3$) 172.1 (*C*OOCH$_3$), 146.8, 138.8, 136.5, 133.1 (Cq), 129.6, 128.3, 106.1, 103.4 (CH), 52.0 (COO*C*H$_3$), 44.6, 35.3 (Cq), 34.5 (*C*H$_2$–S), 30.3 (CH_3), 29.2 (*C*H$_2$–COOCH$_3$), 28.1, 27.9 (CH_3); *m*/*z* (ESI-MS) calcd for $C_{46}H_{52}N_4O_4S_2$ M=788.3, found $[M+H]^+$ 789.4.

*4.3.2. 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α,20β-bis-[4-(2-methoxycarbonylethyl-1-thio)phenyl]-calix[4]pyrrole (α,β-**8**).* 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α,20β-bis-[4-(2-methoxycarbonylethyl-1-thio)phenyl]-calix[4]pyrrole (α,β-**8**) was obtained from toluene as a white solid (R_f: 0.48, 6%), mp 187 °C; δ_H (300 MHz, $CDCl_3$) 7.23 and 7.04 (AA′BB′ system, 2×4H, Ar–H), 7.12 (br s, 4H, NH), 5.92 and 5.74 (2×m, 2×4H, pyrrole β-CH), 3.68 (s, 6H, OCH_3), 3.14 (t, J=7.1 Hz, 4H, CH_2–S), 2.62 (t, J=7.1 Hz, 4H, CH_2–COOMe), 1.87 (s, 6H, CH_3), 1.52 (s, 12H, CH_3); δ_H (300 MHz, CD_3CN) 8.00 (br s, 4H, NH), 7.19 and 6.95 (AA′BB′ system, 2×4H, Ar–H), 5.83 and 5.75 (2×m, 2×4H, pyrrole β-CH), 3.60 (s, 6H, OCH_3), 3.12 (t, J=7.1 Hz, 4H, CH_2–S), 2.58 (t, J=7.1 Hz, 4H, CH_2–COOMe), 1.83 (s, 6H, CH_3), 1.51 (s, 12H, CH_3); δ_C (75 MHz, $CDCl_3$) 172.1 (*C*OOCH$_3$), 145.5, 138.6, 136.0, 133.0 (Cq), 129.5, 128.0, 105.7, 103.2 (CH), 51.8 (COO*C*H$_3$), 44.3, 35.2 (Cq), 34.2 (*C*H$_2$–S), 29.0 (*C*H$_2$–COOCH$_3$), 29.2, 28.9 (*C*H$_3$); *m*/*z* (ESI-MS) calcd for $C_{46}H_{52}N_4O_4S_2$ M=788.3, found $[M+H]^+$ 789.4.

*4.3.3. 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α-[4-(2-methoxycarbonylethyl-1-sulfonyl)phenyl]-20α-[4-(2-methoxycarbonylethyl-1-thio)phenyl]-calix[4]pyrrole (α,α-**9**).* 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α-[4-(2-methoxycarbonylethyl-1-sulfonyl)phenyl]-20α-[4-(2-methoxycarbonylethyl-1-thio)phenyl]-calix[4]pyrrole (α,α-**9**) was obtained as a white solid (R_f: 0.60, 6%) from toluene, mp 124 °C; δ_H (300 MHz, $CDCl_3$) 7.76 and 7.19 (AA′BB′ system, 2×2H, Ar–H), 7.39 and 7.35 (2×br s, 2×H, NH), 7.22 and 6.89 (AA′BB′ system, 2×2H, Ar–H), 5.93, 5.62 and 5.59 (4×m, 4×2H, pyrrole β-CH), 3.67 and 3.65 (2×s, 2×3H, OCH_3), 3.41 (t, J=7.1 Hz, 2H, CH_2–SO_2), 3.13 (t, J=7.1 Hz, 2H, CH_2–S), 2.76 and 2.62 (2×t, J=7.1 Hz, 2×2H, CH_2–COOMe), 1.90 and 1.87 (2×s, 2×3H, CH_3), 1.62 and 1.56 (2×s, 2×6H, CH_3); δ_H (300 MHz, CD_2Cl_2) 7.72 and 7.19 (AA′BB′ system, 2×2H, Ar–H), 7.32 and 7.29 (2×br s, 2×H, NH), 7.21 and 6.90 (AA′BB′ system, 2×2H, Ar–H), 5.94 and 5.63 (4×m, 4×2H, pyrrole β-CH), 3.65 and 3.62 (2×s, 2×3H, OCH_3), 3.40 (t, J=7.2 Hz, 2H, CH_2–SO_2), 3.12 (t, J=7.2 Hz, 2H, CH_2–S), 2.71 and 2.61 (2×t, J=7.2 Hz, 2×2H, CH_2–COOMe), 1.91 and 1.86 (2×s, 2×3H, CH_3), 1.63 and 1.53 (2×s, 2×6H, CH_3); δ_H (300 MHz, CD_3CN) 7.90 and 7.88 (2×br s, 2×H, NH), 7.71 and 7.14 (AA′BB′ system, 2×2H, Ar–H), 7.19 and 6.85 (AA′BB′ system, 2×2H, Ar–H), 5.87 and 5.64 (4×m, 4×2H, pyrrole β-CH), 3.59 and 3.54 (2×s, 2×3H, OCH_3), 3.41 (t, J=7.1 Hz, 2H,

CH_2–SO_2), 3.12 (t, J=7.1 Hz, 2H, CH_2–S), 2.63 and 2.58 (2×t, J=7.1 Hz, 2×2H, CH_2–COOMe), 1.89 and 1.83 (2×s, 2×3H, CH_3), 1.64 and 1.51 (2×s, 2×6H, CH_3), δ_C (75 MHz, $CDCl_3$) 172.1, 170.9 (*C*OOCH$_3$), 154.1, 145.5, 139.5, 138.7, 136.7, 136.4, 135.2, 133.4 (Cq), 129.6, 128.7, 128.4, 128.0, 106.5, 105.9, 103.7, 103.5 (CH), 52.7, 52.6 (COO*C*H$_3$), 51.7 (CH_2–SO_2), 45.2, 44.6, 44.6, 35.5 (Cq), 34.3 (CH_2–S), 29.6, 29.4, 29.2 (CH_3), 29.1, 28.0 (*C*H$_2$–COOCH$_3$), 28.0 (CH_3); m/z (ESI-MS) calcd for $C_{46}H_{52}N_4O_6S_2$ M=821.06, found $[M+H]^+$ 821.5.

*4.3.4. 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α-[4-(2-methoxycarbonylethyl-1-sulfonyl)phenyl]-20β-[4-(2-methoxycarbonylethyl-1-thio)phenyl]-calix[4]pyrrole (α,β-**9**).* 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α-[4-(2-methoxycarbonylethyl-1-sulfonyl)phenyl]-20β-[4-(2-methoxycarbonylethyl-1-thio)phenyl]-calix[4]pyrrole (α,β-**9**) was obtained as a white solid (R_f: 0.60, 5%) from toluene, mp 190 °C; δ_H (300 MHz, $CDCl_3$) 7.77 and 7.24 (AA′BB′ system, 2×2H, Ar–H), 7.27 and 7.26 (2×br s, 2×H, NH), 7.28 and 7.04 (AA′BB′ system, 2×2H, Ar–H), 5.93, 5.78 and 5.73 (4×m, 4×2H, pyrrole β-CH), 3.68 and 3.64 (2×s, 2×3H, OCH_3), 3.42 (t, J=7.1 Hz, 2H, CH_2–SO_2), 3.15 (t, J=7.1 Hz, 2H, CH_2–S), 2.76 and 2.63 (2×t, J=7.1 Hz, 2×2H, CH_2–COOMe), 1.91 and 1.87 (2×s, 2×3H, CH_3), 1.54 (s, 12H, CH_3); δ_H (300 MHz, CD_3CN) 7.99 and 7.90 (2×br s, 2×H, NH), 7.71 and 7.19 (AA′BB′ system, 2×2H, Ar–H), 7.19 and 6.94 (AA′BB′ system, 2×2H, Ar–H), 5.86 and 5.79 (4×m, 4×2H, pyrrole β-CH), 3.60 and 3.53 (2×s, 2×3H, OCH_3), 3.41 (t, J=7.1 Hz, 2H, CH_2–SO_2), 3.12 (t, J=7.1 Hz, 2H, CH_2–S), 2.62 and 2.58 (2×t, J=7.1 Hz, 2×2H, CH_2–COOMe), 1.88 and 1.83 (2×s, 2×3H, CH_3), 1.52 (s, 12H, CH_3); δ_C (75 MHz, $CDCl_3$) 172.3, 171.4 (*C*OOCH$_3$), 154.1, 145.6, 139.5, 138.7, 136.7, 136.5, 135.2, 133.4 (Cq), 129.8, 128.7, 128.3, 128.0, 106.5, 105.9, 103.7, 103.5 (CH), 52.6, 52.5 (COO*C*H$_3$), 51.7 (CH_2–SO_2), 45.2, 44.6, 35.5, 34.5 (Cq), 29.6, 29.4, 29.3 (CH_3), 29.3, 27.9 (*C*H$_2$–COOCH$_3$); m/z (ESI-MS) calcd for $C_{46}H_{52}N_4O_6S_2$ M=821.06, found $[M+H]^+$ 821.5.

*4.3.5. 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α,20α-bis[4-(2-methoxycarbonylethyl-1-sulfonyl)phenyl]-calix[4]pyrrole (α,α-**10**).* 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α,20α-bis[4-(2-methoxycarbonylethyl-1-sulfonyl)phenyl]-calix[4]pyrrole (α,α-**10**) was obtained as a white solid (R_f: 0.40, 8%) from toluene, mp 160 °C. δ_H (300 MHz, $CDCl_3$) 7.76 and 7.18 (AA′BB′ system, 2×4H, Ar–H), 7.27 (br s, 4H, NH), 5.96 and 5.61 (2×m, 2×4H, pyrrole β-CH), 3.66 (s, 6H, OCH_3), 3.42 (t, J=7.1 Hz, 4H, CH_2–SO_2), 2.77 (t, J=7.1 Hz, 4H, CH_2–COOMe), 1.91, 1.64 and 1.56 (3×s, 3×6H, CH_3); δ_H (300 MHz, CD_2Cl_2) 7.73 and 7.18 (AA′BB′ system, 2×4H, Ar–H), 7.35 (br s, 4H, NH), 5.95 and 5.63 (2×m, 2×4H, pyrrole β-CH), 3.62 (s, 6H, OCH_3), 3.39 (t, J=7.1 Hz, 4H, CH_2–SO_2), 2.71 (t, J=7.1 Hz, 4H, CH_2–COOMe), 1.91, 1.64 and 1.54 (3×s, 3×6H, CH_3); δ_H (300 MHz, CD_3CN) 7.86 (br s, 4H, NH), 7.71 and 7.14 (AA′BB′ system, 2×4H, Ar–H), 5.88 and 5.64 (2×m, 2×4H, pyrrole β-CH), 3.54 (s, 6H, OCH_3), 3.41 (t, J=7.3 Hz, 4H, CH_2–SO_2), 2.63 (t, J=7.3 Hz, 4H, CH_2–COOMe), 1.89, 1.65 and 1.49 (3×s, 3×6H, CH_3); δ_C (75 MHz, $CDCl_3$) 170.4 (*C*OOCH$_3$), 154.7, 138.9, 136.4, 135.2 (Cq), 128.5, 127.5, 106.3, 103.4 (CH), 52.3 (COO*C*H$_3$), 51.3 (*C*H$_2$–SO_2), 44.9, 35.1 (Cq), 30.0 (CH_3), 27.6 (*C*H$_2$–COOCH$_3$), 27.4, 27.4 (CH_3); m/z (ESI-MS) calcd for $C_{46}H_{52}N_4O_8S_2$ M=852.3, found $[M+H]^+$ 853.2.

*4.3.6. 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α,20β-bis[4-(2-methoxycarbonylethyl-1-sulfonyl)phenyl]-calix[4]pyrrole (α,β-**10**).* 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α,20β-bis[4-(2-methoxycarbonylethyl-1-sulfonyl)phenyl]-calix[4]pyrrole (α,β-**10**) was obtained as a white solid (R_f: 0.40, 7%) from toluene, mp 220 °C. δ_H (300 MHz, $CDCl_3$) 7.80 and 7.33 (AA′BB′ system, 2×4H, Ar–H), 7.26 (br s, 4H, NH), 5.96 and 5.76 (2×m, 2×4H, pyrrole β-CH), 3.65 (s, 6H, OCH_3), 3.43 (t, J=7.1 Hz, 4H, CH_2–SO_2), 2.77 (t, J=7.1 Hz, 4H, CH_2–COOMe), 1.92 (s, 6H, CH_3), 1.56 (s, 12H, CH_3); δ_H (300 MHz, CD_3CN) 8.00 (br s, 4H, NH), 7.72 and 7.20 (AA′BB′ system, 2×4H, Ar–H), 5.87 and 5.82 (2×m, 2×4H, pyrrole β-CH), 3.53 (s, 6H, OCH_3), 3.41 (t, J=7.1 Hz, 4H, CH_2–SO_2), 2.62 (t, J=7.1 Hz, 4H, CH_2–COOMe), 1.88 (s, 6H, CH_3), 1.53 (s, 12H, CH_3); δ_C (75 MHz, $CDCl_3$) 170.4 (*C*OOCH$_3$), 153.6, 139.1, 136.5, 135.0 (Cq), 128.4, 127.8, 106.2, 103.5 (*C*H), 52.3 (COO*C*H$_3$), 51.4 (*C*H$_2$–SO_2), 45.0, 35.3 (Cq), 30.2 (*C*H$_2$–COOCH$_3$), 29.2, 27.6 (*C*H$_3$); m/z (ESI-MS) calcd for $C_{46}H_{52}N_4O_8S_2$ M=852.3, found $[M+H]^+$ 853.2.

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Supplementary data

Supplementary material contains the figures for the partial ^{1}H NMR spectra cited in the main text as S1–S15. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.082.

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