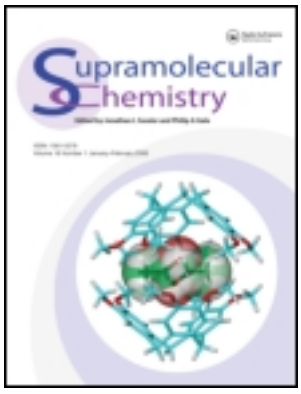

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Paraquat guest-induced conformational templation of dicarboxylatocalixarenes†

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Proximal dicarboxylatocalix[4]arene **4** and distal dicarboxylatocalix[6]arene **5** have been synthesised in good yields and their complexation abilities towards dicationic paraquat guest **3** have been studied by NMR spectroscopy. Both hosts are able to complex **3** through an induced-fit mechanism, which originates from the conformational flexibility of calixarene macrocycle. A pH-dependent switching system was realised in which guest inclusion can be controlled through an acid/base external stimulus.

Keywords: calixarenes; carboxylatocalixarenes; paraquat recognition; induced-fit; switching system; association constant

1. Introduction

Calix[*n*]arene macrocycles (*1*) have gained a pivotal role in several fields of supramolecular chemistry such as self-assembly (*2*), molecular recognition and sensing (*3*), catalysis (*4*), nanoscience (*5*) and biomimetism (*6*). In this regard, an aspect of particular relevance is their conformational mobility, which has allowed the synthesis of specific calixarene hosts able to recognise appropriate guests by means of adaptive structural changes (*6a*, *7–9*). An early example concerns an alkali metal cation conformational templation observed for a tetramethoxy-calix[4]arene derivative, for which four different conformers are present in solution (*cone*, *partial-cone*, *1,2-alternate* and *1,3-alternate*), yet it adopts only a *cone* conformation after addition of Li^+ or Na^+, due to their interaction with the oxygen atoms at the lower rim (*8a*). In a similar way, our group has shown that alkali metal cations are able to template the conformation of larger calix[7-8]arene macrocycles (*9*). In another example concerning conformationally flexible larger calixarenes, mutually induced conformational changes were observed during the binding of cationic cholinergic guests by the water-soluble host *p*-sulphonatocalix[8]arene (*7a*). In several reports, it has been shown that the high conformational flexibility of the calix[6]arene macrocycle allows beautiful examples of induced-fit processes (*6*, *7b*).

Recently, we have outlined that the supramolecular properties of calixarenes bearing anionic carboxylato groups have been only scarcely studied. In particular, the solid-state self-assembly of nanotubes based on a *p*-carboxylatocalix[4]arene was reported by Dalgarno et al. (*10*), while we have very recently shown that *p*-carboxylatocalix[4]arene derivatives **1** and **2** are able to 'grab' a dicationic guest such as paraquat dichloride **3** (Chart 1) through an induced-fit mechanism (*11*). In particular, tetramethoxy-*p*-carboxylatocalix[4]arene **1**, which mainly exists in solution as a mixture of *partial-cone* (with two distal carboxy-groups in *anti* orientation) and *cone* conformations, adopts a single new *cone* conformation after addition of paraquat dichloride **3** (*11*).

These results prompted us to extend the study to the behaviour of other carboxylatocalixarene hosts in the presence of dicationic paraquat guest **3**. In particular, we wish to report here the synthesis and the conformational templation of proximal dicarboxylatocalix[4]arene **4** and distal dicarboxylatocalix[6]arene **5** upon complexation with **3**.

2. Results and discussion

2.1 Proximal dicarboxylatocalix[4]arene 4

The sodium salt of 5,11-dicarboxylato-25,26,27,28-tetramethoxycalix[4]arene (**4**) was synthesised exploiting the reaction sequence shown in Scheme 1. In particular, bromination of the known proximal dimethoxy-*p*-H-calix[4]arene **6** (*12*) with Br_2 in $CHCl_3$ gave the corresponding proximal *p*-dibromo-diol derivative **7** in 64% yield, which was alkylated with MeI in the presence of Cs_2CO_3 as the base, to give 5,11-dibromo-25,26,27,28-

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†In memory of our dear friend Prof Dmitry Rudkevich.

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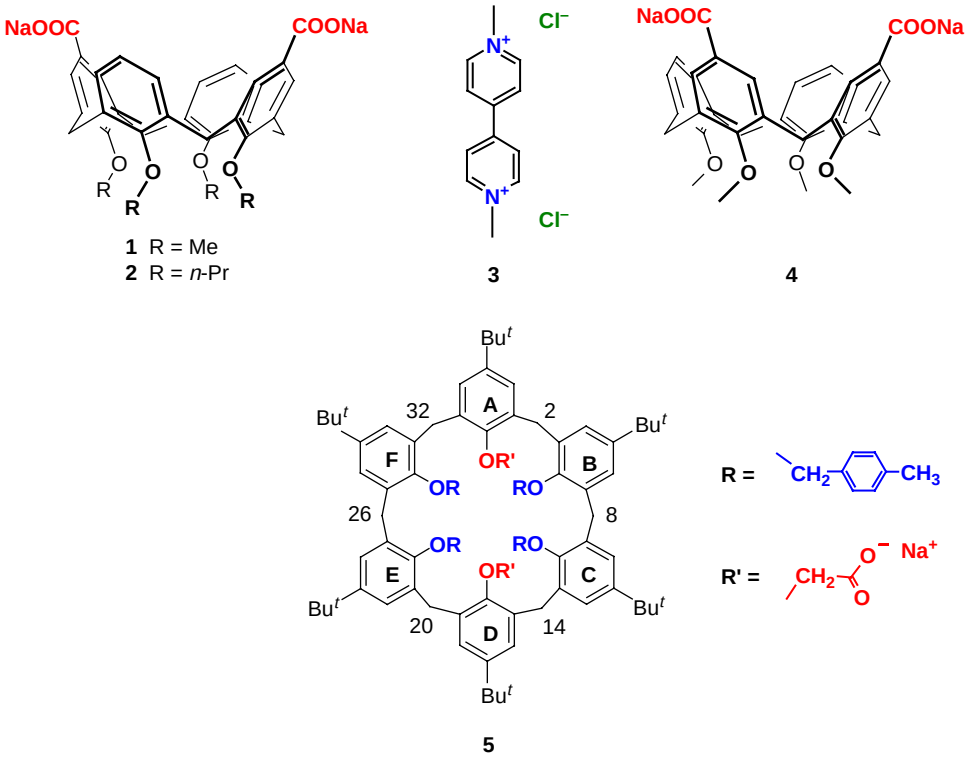
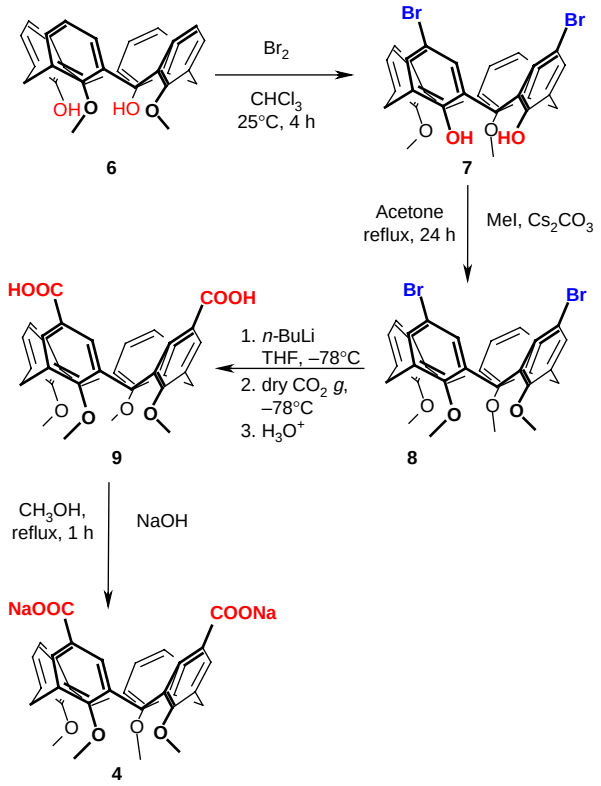


Chart 1. Structure of compounds **1**–**5**.



Scheme 1. Synthesis of proximal dicarboxylatocalix[4]arene **4**.

tetramethoxycalix[4]arene derivative (**8**) in 90% yield. Tetramethoxy derivative **8** was 5,11-dilithiated by reaction with *n*-BuLi in THF at −30°C (*13*) and quenched, after 30 min, with dry CO_2 to give, after acidic work-up, the 5,11-dicarboxylic acid **9** in 51% yield. Then, the corresponding 5,11-dicarboxylato sodium salt **4** was easily obtained by treatment of **9** with an aqueous solution of NaOH in MeOH heated at reflux for 1 h.

The ^{1}H NMR spectrum (400 MHz, $CDCl_3/CD_3OD$, 1/8, v/v) of **4** at 298 K (Figure 1, bottom) shows broad signals indicating a slow conformational interconversion. This is due to the small dimension of the methoxy groups at the lower rim, which allows their through-the-annulus passage (*14*). Therefore, at room temperature, compound **4** is conformationally mobile and exists as an equilibrium mixture of all possible conformational isomers. At lower temperatures, the ^{1}H NMR spectrum (400 MHz, $CDCl_3/CD_3OD$, 1/8, v/v, 263 K) of **4** indicated the prevalence of an asymmetrical conformer. In fact, it shows the presence of two $ArCH_2Ar$ AX systems at 4.04/2.92 and 3.77/2.86 ppm (Figure 1, top), which correlates in the 2D heteronuclear single quantum coherence (HSQC) spectrum (Figure 2) (400 MHz, $CDCl_3/CD_3OD$, 1/8, v/v, 263 K) with two signals at 31.55 and 31.49 ppm, respectively, both attributable to $ArCH_2Ar$ carbons between *syn*-oriented aromatic rings.

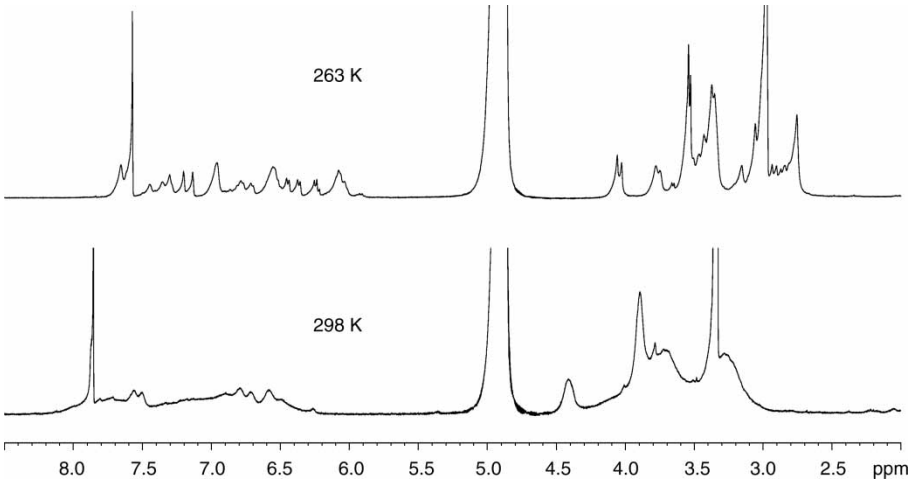


Figure 1. ^{1}H NMR spectrum [400 MHz, $CDCl_3/CD_3OD$, (1/8, v/v)] of **4** at relevant temperatures.

In addition, the 2D HSQC spectrum (Figure 2) shows intense cross-peaks between broad ^{1}H signals in the region of 3.3–3.6 ppm and two pertinent carbon resonances at 37.1 and 37.2 ppm, which can be assigned to $ArCH_2Ar$ groups between *anti*-oriented aromatic rings.

These data are compatible with a *partial-cone* conformation for **4**, which lacks symmetry elements due to its proximal disubstitution. In particular, two *partial-cone* conformations are possible (Figure 3): one with the two proximal carboxylato-groups in an *anti* orientation (*anti-partial-cone* **4a**) and another with those groups in a *syn* orientation (*syn-partial-cone* **4b**).

Molecular mechanics calculations (*15*) (optimised potentials for liquid simulations (OPLS), $CHCl_3$ solvent) indicated the *anti-partial-cone* conformation **4a** to be the most stable. In fact, the *anti*-orientation between the carboxylato-groups permits the minimisation of repulsive electrostatic interactions between the negative charges.

A careful analysis of the methoxyl region of the 2D HSQC spectrum at 263 K clearly evidenced that in addition to **4a**, other equilibrium conformers exist at lower concentration. Their relative stability can be estimated, in accordance with the molecular mechanics calculations, as follows: *anti-partial-cone* > *syn-partial-cone* > *cone* > *1,3-alternate* > *anti-1,2-alternate* > *syn-1,2-alternate* (Figure 4).

When paraquat dichloride **3** was added to a solution of conformationally, mobile proximal calix[4]arene dicar-

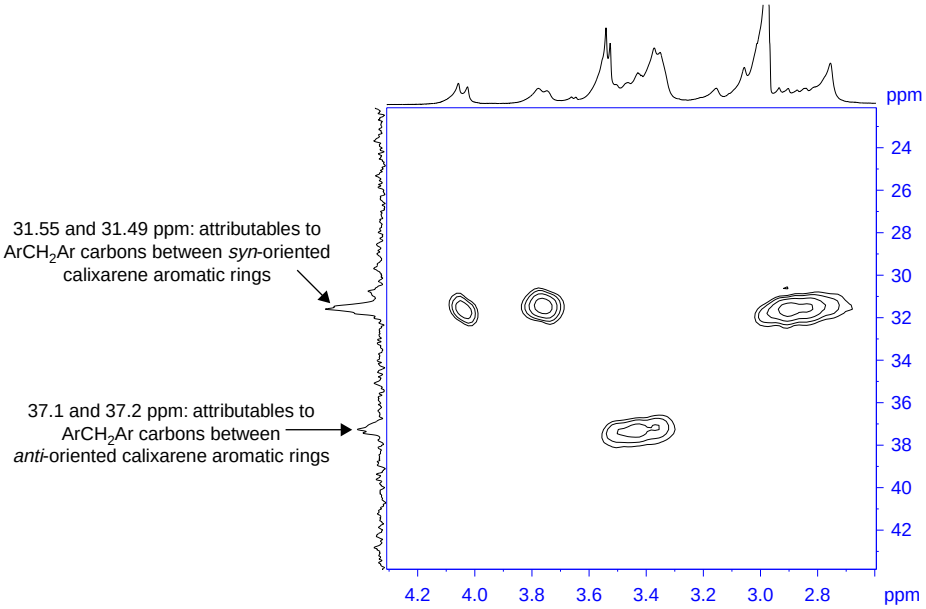


Figure 2. 2D HSQC spectrum of **4** [400 MHz, $CDCl_3/CD_3OD$, (1/8, v/v), 263 K].

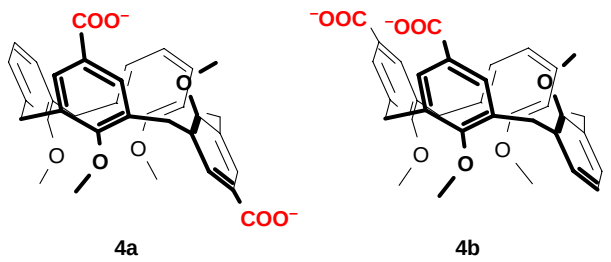


Figure 3. The two possible *partial-cone* conformations for derivative **4**.

boxylate **4** in $CDCl_3/CD_3OD$ (1/8, v/v), new ^1H NMR signals appeared that were assignable to the **3·4** complex (Figure 5). In particular, three $ArCH_2Ar$ AX systems at 4.50/3.38 (4H), 4.53/3.39 (2H) and 4.48/3.39 ppm (2H) emerged, which were indicative of a C_s-symmetrical *cone* conformation. The presence of a symmetry plane bisecting the opposite methylene bridges was also confirmed by inspection of the aromatic region of the ^1H NMR spectrum of **3·4** complex. In fact, two *meta*-coupled doublets at 7.55 (2H, $J = 1.5$ Hz) and 7.43 (2H, $J = 1.0$ Hz) ppm, due to the protons *ortho* to the carboxylato groups, were present. In addition, two *ortho*-coupled doublets and one *ortho*-coupled *pseudo*-triplet relative to the protons of the unsubstituted aromatic rings, were present at 7.00 (2H, $J = 7.7$ Hz), 6.87 (2H, $J = 7.0$ Hz) and 6.44 ppm (2H, $J = 7.5$ Hz), respectively.

The chemical shift of guest protons shifted to higher fields in the presence of the host. These shifts are very likely determined by the shielding effects of the calixarene aromatic nuclei consequent to the penetration of the guest into the cavity of the host. This binding mode was confirmed by the lowest OPLS-energy structure of **3·4** complex, obtained with the program MacroModel-9.0 and is shown in Figure 6, where it is possible to observe the close disposition of the anionic carboxylato groups and the cationic nitrogen atom(s) to give electrostatic interactions.

Therefore, the presence of **3** induces the oxygen-through-the-annulus rotation of the inverted $ArCOO^-$ ring (spanned angle $\sim 160°$ (*11*)) of the prevalent *anti-partial-cone* conformer **4a** to 'wrap' the guest (Scheme 2). Concomitantly, the less-concentrated conformers undergo adaptative conformational changes in order to host the guest (Scheme 2). The entire guest-induced conformational templation can be visualised with the corresponding lowest OPLS-energy structures as shown in Scheme 2.

The association constant of **3·4** complex was determined by standard ^1H NMR titrations [298 K, 400 MHz, $CDCl_3/CD_3OD$ (1/8, v/v)] (*16*), in which the guest concentration was kept constant while the host concentration was varied (Figure 7). The addition of increasing amounts of a 46.0 mM solution of **4** in $CDCl_3/CD_3OD$ (1/8, v/v) to a 2.98 mM solution of paraquat in the same solvent caused upfield shifts of its signals indicating a fast complexation equilibrium (*16*). The titration data were analysed by nonlinear regression analysis using the WinEQNMR program (*16c*) to give a K_{ass} of $11000 \pm 2000\ M^{-1}$, while a 1:1 stoichiometry for **3·4** complex was estimated by means of a molar ratio plot (*17*).

The inclusion of paraquat **3** into the calixarene cavity of **4** is mainly driven by electrostatic interactions between the anionic carboxylato groups and the cationic paraquat nitrogens. Therefore, considering that *p*-carboxylatocalixarene hosts are pH sensitive, their recognition abilities versus organic quaternary ammonium ions should depend on the pH of the solution. Thus, we decided to study the ^1H NMR spectrum of **3·4** complex at different pH values. When 2 equiv. of DCl (35% w/w solution in D_2O) were added to a solution of **3·4** complex in $CDCl_3/CD_3OD$ (1/8, v/v) (Figure 8(b)), drastic changes in the ^1H NMR spectrum were observed (Figure 8(c)). In particular, the aromatic signals of **3** were shifted downfield indicating the presence of free paraquat in solution (Figure 8(c)). In addition, the lack of conformational templation on the calix[4]arene skeleton was evidenced by the extensive line broadening (Figure 8(c)), typical of several slowly exchanging conformations on the NMR time scale.

The original ^1H NMR spectrum of **3·4** complex shown in Figure 8(b) was regenerated in every detail upon addition of 2.5 equiv of NaOD (2.0 μl of a 6.5 M solution in CD_3OD) (see Figure 8(d)) to the NMR sample previously treated with DCl. Thus, the paraquat guest goes back completely into the calixarene cavity, being driven by electrostatic interactions with the anionic carboxylato groups regenerated by reaction with NaOD. The DCl/NaOD addition cycle

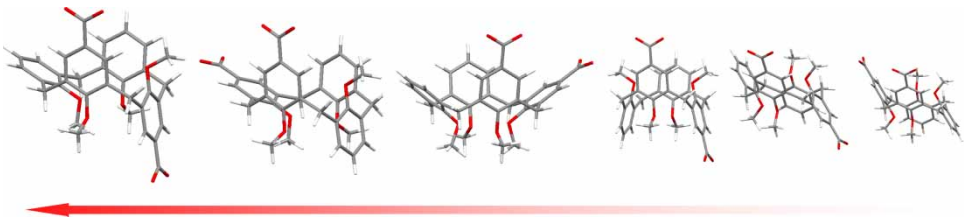


Figure 4. Energy-minimised structures of all possible conformations of derivative **4**. The size of each conformer is approximately proportional to its relative stability.

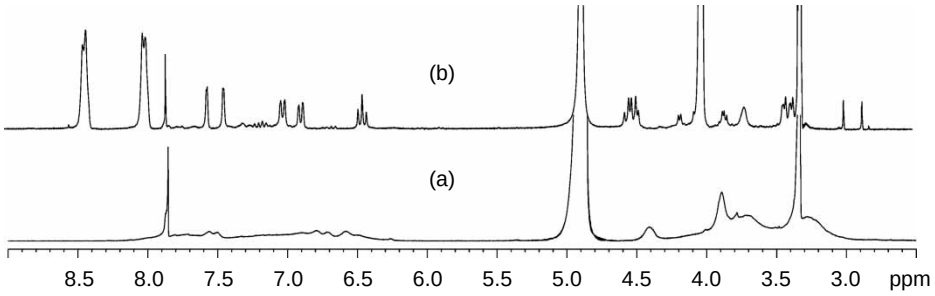


Figure 5. ^{1}H NMR spectra [$CDCl_3/CD_3OD$ (1/8, v/v), 400 MHz, 298 K] of (a) **4**; (b) equimolar solution of **4** and paraquat dichloride **3**.

was repeated once again, demonstrating that the process is reversible. Thus, to the best of our knowledge, this is the first example of a carboxylato-based calixarene host which shows recognition abilities heavily dependent on the pH of the medium (*18*). Interestingly, *p*-carboxylatocalixarene host **4** offers the possibility to switch the inclusion of the dicationic paraquat guest in or out of the calixarene cavity through an acid/base external stimulus as a type of 'molecular switch' (*19*).

2.2 Distal dicarboxylatocalix[6]arene 5

Prompted by these results we decided to study the recognition properties of larger calixarene carboxylate derivatives versus dicationic paraquat guest. Thus, we synthesised distally substituted calix[6]arene derivative **5** by using the reaction sequence shown in Scheme 3. Alkylation of the known 1,2,4,5-tetrakis-(*p*-methylbenzyloxy)-calix[6]arene **10** (*20*) with ethyl bromoacetate in refluxing acetone for 5 days, using K_2CO_3 as the base, gave diester derivative **11** in 15% yield. Then, **5** was easily obtained by hydrolysis of **11** with an aqueous solution of NaOH in refluxing EtOH for 12 h.

Characterisation of dicarboxylatocalix[6]arene **5** was performed by spectral analysis, in particular the presence of a *pseudo*-molecular ion peak (MH^+) at *m/z* 1506 in the ESI(+) mass spectrum confirmed the molecular formula. The ^{1}H NMR spectrum (400 MHz, 298 K, CD_3OD) of **5** at 298 K indicates the presence of a mixture of different conformations, which are frozen on the NMR timescale due to the presence of bulky substituents at the lower rim. The most abundant species present in CD_3OD shows a singlet at 0.99 ppm integrating for four *t*-Bu groups, and an unusually shielded signal at -0.28 ppm relative to the two *t*-Bu groups of the equivalent calixarene rings bearing an acetate group. A sharp singlet was present at 2.33 ppm (12H) relative to the methyl protons of the equivalent *p*-methylbenzyl substituents at the lower rim. Regarding the $ArCH_2Ar$ protons, a singlet (4H) due to H8 (and H26) (Chart 1, Scheme 3) was present at 3.96 ppm, which correlated in the 2D HSQC spectrum (298 K, 400 MHz, CD_3OD) with a ^{13}C signal at 38.8 ppm. In accordance with Gutsche's '^{1}H NMR $\Delta\delta$ rule' (*20*, *21*) and de Mendoza's '^{13}C NMR single rule' (*22*), these data clearly indicated (*23*) the *anti* orientation of benzylated rings B and C (E and F) (Chart 1, Scheme 3). In addition, an AB system was present at 3.88/3.95 ppm ($J = 13.9$ Hz, 8H), which is related to $ArCH_2Ar$ groups linking differently alkylated rings (H2, H14, H20 and H32) (Chart 1, Scheme 3). This AB system correlates in the 2D HSQC spectrum (298 K, 400 MHz, CD_3OD) with a ^{13}C signal at 31.4 ppm. These data are compatible with a *syn* disposition of the pertinent aromatic rings coupled to an *inward* orientation of carboxylato-bearing ring A (and D), which explains the shielding of its *t*-Bu group resonating at -0.28 ppm. This conclusion was confirmed by the presence of relevant cross-peaks in the 2D NOESY spectrum between the shielded *t*-Bu signal at -0.28 ppm and those of the remaining four equivalent *t*-Bu groups at 0.99 ppm (36H) (Figure 9(a)) and of proximal calixarene aromatic protons at 7.05 and 7.06 ppm (AB system, $J = 1.9$ Hz, 8H) (Figure 9(b)).

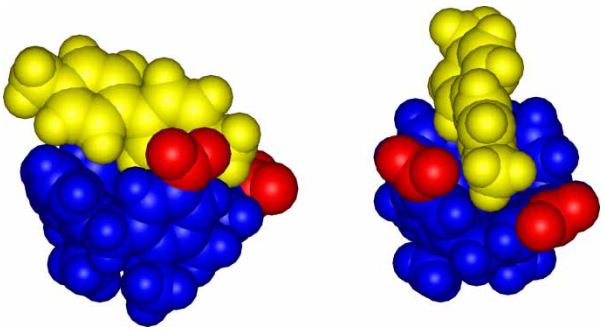
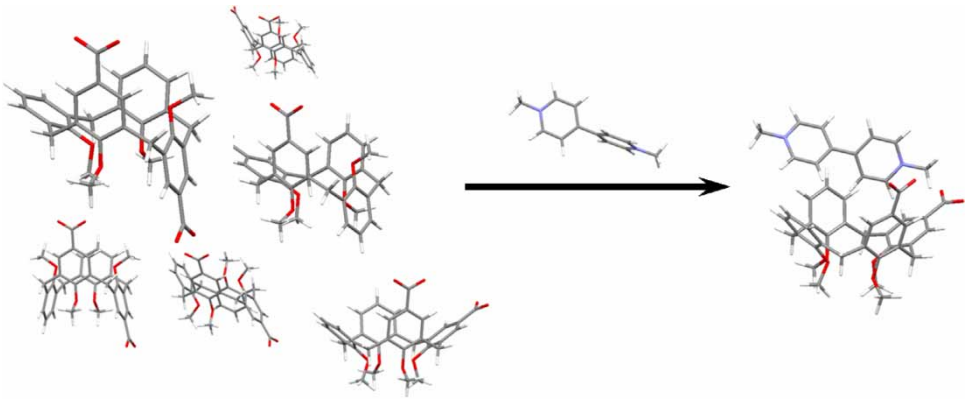


Figure 6. Side (left) and top (right) views of the lowest OPLS-energy structure of the **3**·**4** complex.

Therefore, the most abundant conformation of **5** present in CD_3OD can be described as *1,2,3-alternate* with an *inward* inclination of the central ring of each 3/4-cone subunit (Figure 10), which gives rise to a self-filling of the cavity.

A VT ^{1}H NMR study indicated the absence of conformational interconversions upon lowering the temperature of a sample of **5** from 298 to 258 K. Instead, upon heating, a coalescence at 333 K was ascertained for



Scheme 2. The conformational templation of *p*-carboxylatocalix[4]arene derivative **4** induced by dicationic paraquat guest **3**.

the $ArCH_2Ar$ AB system, which led to an energy barrier of 16.5 kcal/mol, which could be determined for the rotation of carboxylato-bearing rings.

The complexation ability of derivative **5** towards dicationic paraquat guest **3** was investigated by ^1H NMR experiments (400 MHz) in CD_3OD at 298 K (Figure 11). Upon addition of a solution of paraquat dichloride **3** (1.0 M in CD_3OD) to a CD_3OD solution of host **5** (0.013 M), a new set of signals emerged due to the formation of a **3**·**12** complex (Figure 11) slowly exchanging in the NMR time scale. In particular, two $ArCH_2Ar$ AX systems appeared at 3.38/4.83 ppm (8H, $J = 16.0$ Hz) and 3.12/4.17 ppm (4H, $J = 16.0$ Hz), which correlates in the 2D HSQC spectrum (298 K, 400 MHz, CD_3OD) with ^{13}C signals at 30.3 and 30.0 ppm, respectively. The observed ^1H $\Delta\delta$ (1.45 and 1.05) and ^{13}C δ values for each $ArCH_2Ar$ group clearly indicated a *syn* orientation between all the adjacent aromatic rings. Therefore, the addition of paraquat dichloride **3** induces the change of the prevalent *1,2,3-alternate* conformation of calix[6]arene host **5** to a *cone* one, which is blocked in the NMR time scale. In accordance with this conformational change, the shielded *t*-Bu group of carboxylato-bearing ring A (and D) now resonates at the normal value of 1.18 ppm (Figure 11). An association constant value of $2.7 \times 10^4\ M^{-1}$ and a 1:1 stoichiometry were determined

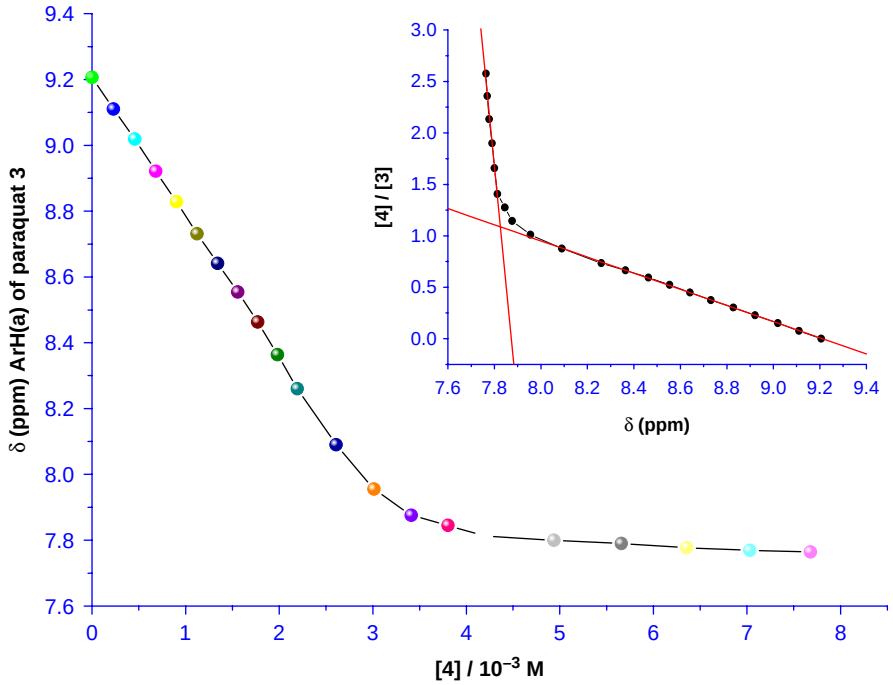


Figure 7. Plot of chemical shift δ of ArH protons of **3** as a function of the concentration of *p*-carboxylatocalix[4]arene **4** [$CDCl_3/CD_3OD$ (1/8, v/v), 25°C, 400 MHz]. Inset: corresponding molar ratio plot.

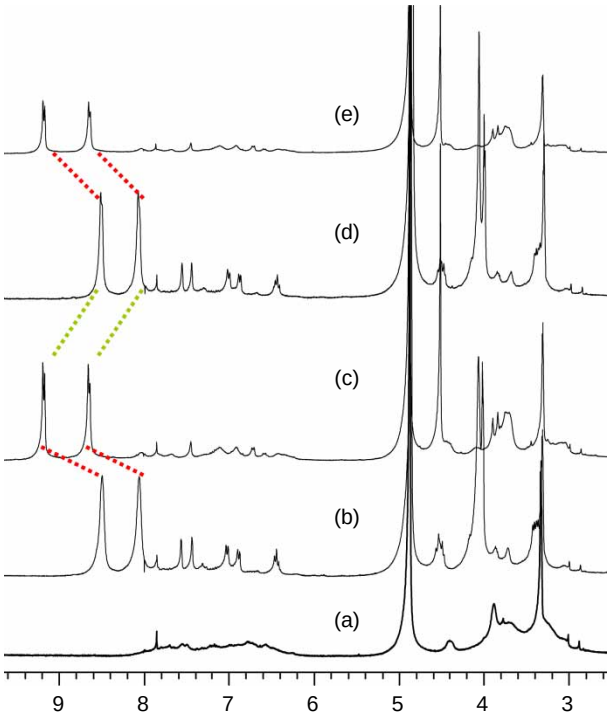


Figure 8. ^{1}H NMR spectra [400 MHz, in $CDCl_3/CD_3OD$ (1/8, v/v), 298 K] recorded on proximal dicarboxylatocalix[4]arene **4** (9.6 mM) before (a) and after the successive addition of (b) 1.5 equiv. of paraquat dichloride **3**, (c) 2.0 equiv. of DCl, (d) 2.5 equiv. of NaOD and (e) 2.5 equiv. of DCl.

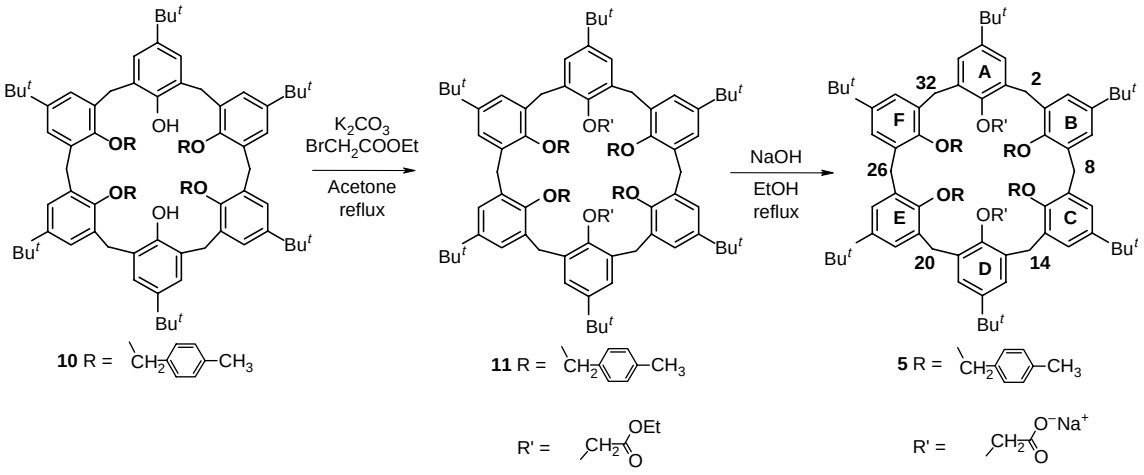
for the slowly exchanging **3·5** complex by integration of pertinent ^{1}H NMR signals.

The two aromatic protons of paraquat guest in the **3·5** complex were accidentally isochronous and resonate at 8.87 ppm reflecting only minor shifts upon complexation. This indicates that guest **3** is not included inside the calix[6]arene cavity, because very large shifts are usually observed in such cases (*18b*, *18c*, *24*). Therefore, the guest most likely has to be located in the lower rim region to give a better electrostatic interaction with the appended *syn* carboxylate groups. This binding mode was confirmed by the lowest OPLS-energy calculated structure of **3·5** complex (Figure 12), in which paraquat dicationic guest templates the calix[6]arene cone conformation by means of electrostatic interactions with anionic carboxylato groups at the lower rim.

3. Conclusion

In summary, we have shown that calixarene carboxylate derivatives **4** and **5** are able to complex dicationic paraquat guest **3** through an induced-fit mechanism, which originates from the conformational flexibility of calixarene macrocycle. In particular, in the case of proximal *p*-carboxylatocalix[4]arene **4**, an oxygen-through-the-annulus rotation of the inverted $ArCOO^-$ ring of the prevalent *anti-partial-cone* conformer occurs to 'wrap' the guest. Larger adaptive structural changes are observed for distal calix[6]arene carboxylate **5**, in which a half of the molecule rotates from the most abundant *1,2,3-alternate* conformation to give a *cone* structure upon guest templation at the lower rim.

In addition, we have also shown that the complexing abilities of calixarene carboxylate hosts are strongly dependent on the pH of the medium. Therefore, a switching system was realised in which the inclusion of dicationic paraquat guest in/out of the cavity of *p*-carboxylatocalixarene host **4** can be controlled through an acid/base external stimulus. This process is reversible and consequently the acid/base addition cycle can be iterated several times.



Scheme 3. Synthesis of distal dicarboxylatocalix[6]arene **5**.

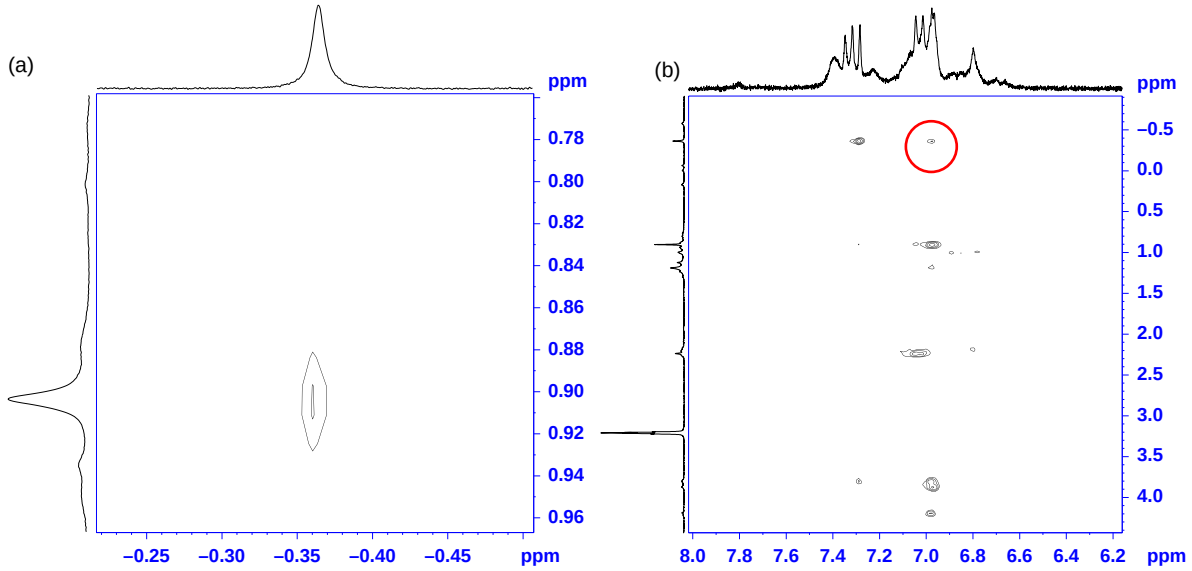


Figure 9. Expansion of 2D NOESY spectrum of dicarboxylatocalix[6]arene **5** (250 MHz, CD_3OD, 298 K).

4. Experimental section

4.1 General comments

ESI-MS measurements were performed on a Micromass Bio-Q triple quadrupole mass spectrometer equipped with electrospray ion source. Flash chromatography was performed on silica gel (60, 40–63 μm). All chemicals were reagent grade and were used without further purification. Anhydrous DMF and THF were purchased and used without further purification. Reaction temperatures were measured externally; reactions were monitored by TLC on silica gel plates (0.25 mm) and visualised by UV light and spraying with H_2SO_4–$Ce(SO_4)_2$. Compounds **6** (*12*) and **10** (*18*) were prepared following literature procedures. All 1D and 2D NMR spectra were recorded at 400 (^{1}H) and 100 MHz (^{13}C) on Bruker Avance-400 spectrometer, or at 300 (^{1}H) and 75.5 MHz (^{13}C) on a Bruker Avance-300 spectrometer, or at 250 (^{1}H) and 62.8 MHz (^{13}C) on a Bruker Avance-250 spectrometer; chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: δ 7.26; $CDCl_3$: δ 77.23; CH_3OD: δ 4.87; CD_3OD: δ 49.15). Standard pulse programs, provided by the manufacturer, were used for DEPT, HSQC and NOESY multipulse sequences.

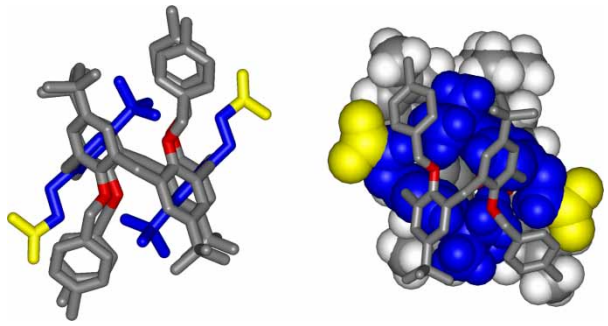


Figure 10. Different views of the lowest OPLS-energy ($CHCl_3$ solvent, GB/SA implicit model solvent) *inward-1,2,3-alternate* conformation of free **5**. Hydrogen atoms are omitted for clarity.

4.2 Synthesis of sodium 5,11-dicarboxylato-25,26,27,28-tetramethoxycalix[4]arene (4)

4.2.1 5,11-Dibromo-25,26-dimethoxy-27,28-dihydroxycalix[4]arene (7)

Br_2 (1.0 g, 8.0 mmol) was added dropwise to a solution of derivative **6** (0.7 g, 1.5 mmol) (*12*) in $CHCl_3$. The reaction mixture was stirred for 2 h at room temperature, and the solid product was filtered and triturated with aqueous 1 M solution of sodium bisulphite. The precipitate was dissolved in CH_2Cl_2, dried on Na_2SO_4, filtered and the solvent was removed under reduced pressure to obtain **7** (0.58 g, 64% yield). ESI(+) MS: $m/z = 633$ (MNa^+); ^{1}H NMR ($CDCl_3$, 298 K, 400 MHz, mixture of *cone* conformer and a minor one* in a 10:4 ratio): δ 8.31 (s, 2H, OH *cone* conformer), 7.73 (s, 0.4 × 2H*, OH minor conformer), 7.20–6.87 (overlapped, 10H, ArH *cone* conformer and 0.4 × 10H*, ArH minor conformer), 4.40–3.23 (overlapped, 8H, $ArCH_2Ar$ *cone* conformer; 0.4 × 8H*, $ArCH_2Ar$ minor conformer), 4.05 (s, 6H, OCH_3 *cone* conformer), 3.44 (s, 0.4* × 6H, OCH_3 minor conformer); ^{13}C NMR ($CDCl_3$, 390 K, 400 MHz): δ 115.2, 154.6, 150.9, 150.6, 134.5, 133.6, 133.5, 131.6, 131.3, 131.1, 131.0, 130.6, 129.6, 125.7, 112.7, 62.9, 59.9, 37.9, 34.4, 31.8, 31.6, 31.0, 30.7. Anal. calcd for $C_{30}H_{26}Br_2O_4$: C 59.04; H 4.29. Found: C, 59.14; H, 5.50.

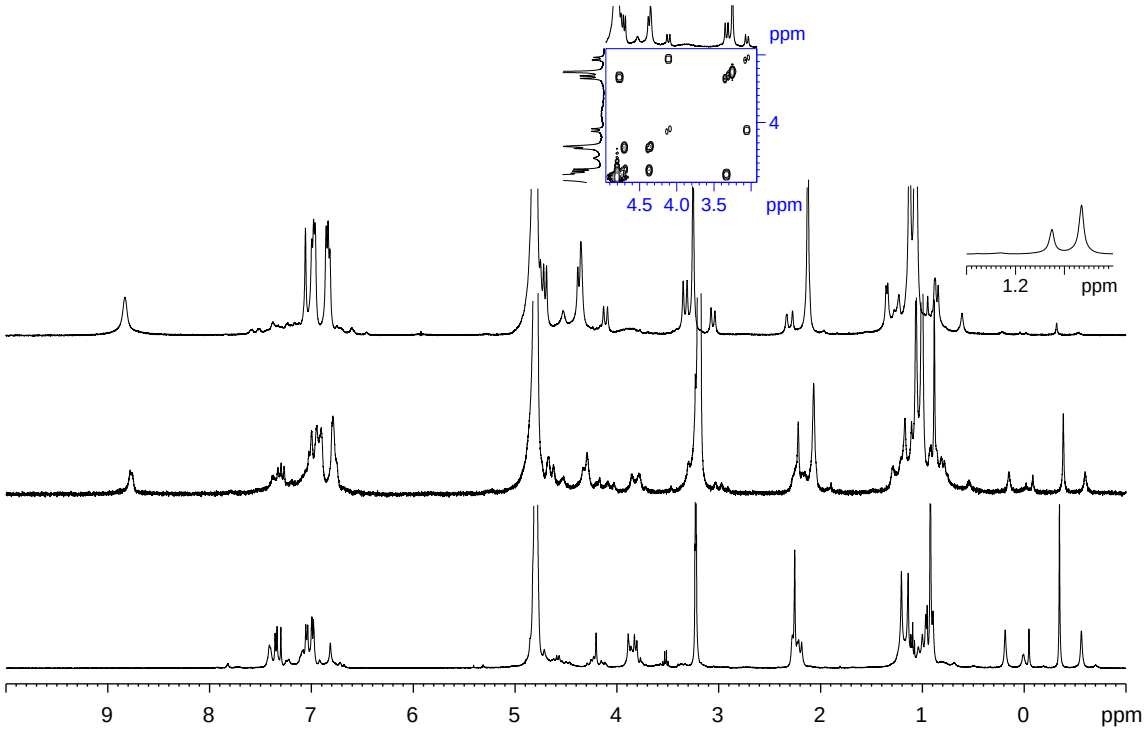


Figure 11. ^{1}H NMR spectra (400 MHz, 298 K, CD_3OD) of (bottom) free **5** and after the addition of (middle) 0.5 or (top) 1 equiv. of guest **3**. Inset: Expansion of the methylene region of COSY-45 spectrum of **3**·**5** complex in CD_3OD (400 MHz, 298 K).

*4.2.2 5,11-Dibromo-25,26,27,28-tetramethoxycalix[4]arene (**8**)*

To a solution of derivative **7** (0.6 g, 0.1 mmol) in dry DMF (10 ml) was added NaH (mineral oil 60%, 0.48 g, 19.9 mmol), and the mixture was kept under stirring at 70°C for 15 min. CH_3I (2.8 g, 19.9 mmol) was added and the mixture was kept under stirring at 70°C for 12 h, under nitrogen. The reaction was quenched with aqueous 1 M HCl (50 ml) and the product was extracted with CH_2Cl_2 (2 × 50 ml). The organic layer was washed with aqueous 1 M HCl (3 × 50 ml) and brine (50 ml). The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was subjected to flash chromatography on silica gel (petroleum ether/chloroform, 8/3, v/v) to give **8** (15 mg, 24%). ESI(+) MS: $m/z = 661.2$ (MNa^+). ^{1}H NMR (1,1,2,2-tetrachloroethane-d_2 (TCDE), 390 K, 300 MHz): δ 7.15–6.67 (broad, 10H, ArH), 3.66 (overlapped, 20H, $ArCH_2Ar$ and OCH_3). ^{13}C NMR (TCDE, 390 K, 75 MHz): δ 160.9, 160.1, 134.8, 134.3, 132.1, 131.6, 125.4, 117.9, 63.4, 34.8. Anal. calcd for $C_{32}H_{30}Br_2O_4$: C 60.21; H 4.74. Found: C, 59.30; H, 4.64.

*4.2.3 5,11-Dicarboxy-25,26,27,28-tetramethoxycalix[4]arene (**9**)*

Derivative **8** (0.10 g, 0.16 mmol) was dissolved in dry THF (6 ml) under nitrogen atmosphere. The reaction mixture was stirred at −78°C for 15 min, then *n*-BuLi was added

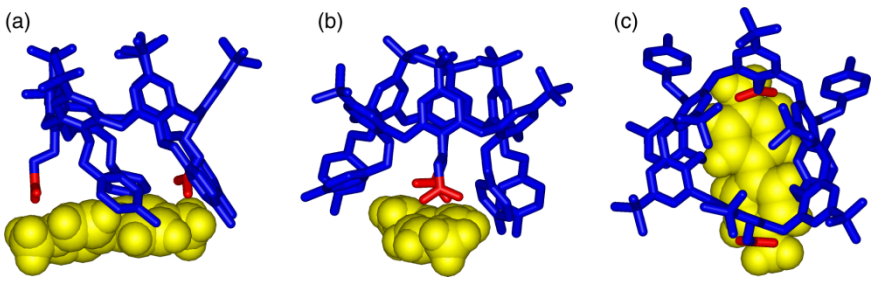


Figure 12. Different views of the lowest OPLS-energy ($CHCl_3$ solvent, GB/SA implicit model solvent) structure of **3**·**5** complex. Hydrogen atoms of the calix[6]arene host (blue) are omitted for clarity. Dicationic paraquat guest, in close contact with anionic carboxylato groups (red), is represented as yellow CPK model.

(0.6 ml, 2.5 M in hexane solution). The mixture was stirred for 30 min at −78°C and then dry CO_2 was bubbled for 30 min. The reaction was quenched with ice cold water (20 ml) and the product was extracted with CH_2Cl_2 and washed with aqueous 1 M HCl (2 × 20 ml) obtaining pure derivative **9** (0.046 g, 51%). ESI(−) MS: *m/z* = 567.42 ($M - H^-$); ^{1}H NMR (TCDE, 390 K, 300 MHz): δ 7.46–6.40 (10H, ArH), 3.48 (overlapped $ArCH_2Ar$ and OCH_3, 20H); ^{13}C NMR (TCDE, 390 K, 75 MHz): δ 166.8, 160.8, 129.7, 129.2, 127.4, 126.9, 121.3, 120.5, 58.5, 30.4. Anal. calcd for $C_{34}H_{32}O_8$: C 71.82; H 5.67. Found: C, 71.72; H, 5.77.

*4.2.4 Sodium 5,11-dicarboxylato-25,26,27,28-tetramethoxycalix[4]arene (**4**)*

Derivative **9** (0.10 g, 0.18 mmol) was dissolved in EtOH (5 ml), a 1.0 M solution of NaOH in EtOH was added (1.8 ml) and the mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the product was washed with water and filtered to give derivative **4** as a colourless solid in quantitative yield. ^{1}H NMR (TCDE, 390 K, 300 MHz): δ 7.40–6.38 (10H, ArH), 3.53 (overlapped $ArCH_2Ar$ and OCH_3, 20H); ^{13}C NMR (TCDE, 390 K, 75 MHz): δ 165.0, 160.0, 130.3, 129.2, 127.0, 126.9, 120.9, 120.2, 57.2, 30.4.

*4.3 Synthesis of sodium 5,11,17,23,29,35-hexa-*tert*-butyl-39,42-bis(carboxylato-methoxy)-37,38,40,41-tetrakis[(4-methylbenzyl)oxy]calix[6]arene (5)*

*4.3.1 5,11,17,23,29,35-Hexa-*tert*-butyl-39,42-bis(ethoxycarbonylmethoxy)-37,38,40,41-tetrakis[(4-methylbenzyl)oxy]calix[6]arene (**11**)*

To a solution of **10** (1.0 g, 0.7 mmol) (*20*) in acetone (75 ml) was added K_2CO_3 (6.0 g, 43.2 mmol), and the mixture was kept under stirring at the refluxing temperature for 1 h. $BrCH_2COOEt$ was added (7.2 g, 43.2 mmol) and the reaction mixture was kept under stirring at the refluxing temperature for 96 h. The solvent was removed under reduced pressure and the product was dissolved in CH_2Cl_2 (50 ml) and washed with aqueous 1 M solution of HCl (50 ml) and H_2O (50 ml). The organic phase was dried on Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was subjected to flash chromatography on silica gel (petroleum ether/CH_2Cl_2 6/4, v/v) to give derivative **11** as a white solid, 0.17 g, 15% yield. ESI(+) MS: *m/z* = 1563 (MH^+); ^{1}H NMR (TCDE, 373 K, 250 MHz), δ 0.87 (s, *t*-Bu, 18H), (s, overlapped, *t*-Bu and OCH_2CH_3, 42H), 0.90 (s, *t*-Bu, 54H), 2.20 (s, $OCH_2C_6H_4CH_3$, 12H), 3.79 (overlapped, $ArCH_2Ar$ and OCH_2CH_3, 16H), 4.06 (s, OCH_2COOEt, 4H), 4.55 (s, $OCH_2C_6H_4CH_3$, 8H), 6.74 (s, ArH, 4H), 6.84 (overlapped, ArH, 8H), 6.94 (d, ArH, *J* = 7.6 Hz, 8H), 7.08 (bd, ArH, *J* = 7.6 Hz, 8H). ^{13}C NMR (TCDE, 62.5 MHz, 373 K): δ 12.2, 19.1, 29.6, 32.1, 58.5, 68.5, 73.2, 124.2, 124.5, 126.5, 127.0, 131.1, 131.3, 131.4, 133.6, 135.1, 143.9, 144.2, 151.2, 167.2. Anal. calcd for $C_{106}H_{128}O_{10}$: C, 81.50; H, 8.26. Found: C, 81.43; H, 8.34.

*4.3.2 Sodium 5,11,17,23,29,35-hexa-*tert*-butyl-39,42-bis(carboxylato-methoxy)-37,38,40,41-tetrakis[(4-methylbenzyl)oxy]calix[6]arene (**5**)*

To a solution of derivative **11** (0.27 g, 0.17 mmol) in EtOH (10 ml) was added an aqueous 1 M solution of NaOH (3.5 ml). The reaction mixture was kept under stirring at the refluxing temperature overnight, and the solvent was removed under reduced pressure. H_2O (20 ml) was added and, after 1 h, the solid was filtered and washed with MeOH (2 × 20 ml) to obtain derivative **5** as a colourless solid, 0.24 g, quantitative yield. ^{1}H NMR (DMSO-d_6, 373 K, 300 MHz), δ 1.27 (br s, *t*-Bu, 54H), 2.30 (br s, $OCH_2C_6H_4CH_3$, 12H), 4.04 (broad, $ArCH_2Ar$, 12H), 4.08 (br s, OCH_2COO^-, 4H), 4.79 (br s, $OCH_2C_6H_4CH_3$, 8H), 7.09–7.32 (overlapped ArH, 28H); ^{13}C NMR (toluene, 75.0 MHz, 320 K): δ 30.3, 30.5, 30.9, 31.7, 31.9, 34.4, 74.9, 76.37, 133.6, 133.7, 134.1, 135.3, 145.8, 152.2, 155.0, 175.1.

4.4 Complexation studies

^{1}H NMR titrations were performed at 298 K (400 MHz) in $CDCl_3/CD_3OD$ (1/8, v/v). Chemical shifts were externally referenced to the residual solvent peak ($CHCl_3$: δ 7.26; CH_3OD: δ 4.87). The Paraquat dichloride **3** concentration (2.98 mM) was kept constant while the host concentration was varied (0–8 mM). The signals of guest **3** were followed and the data were analysed by nonlinear regression analysis using the WinEQNMR program.

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