Calix[4]arene-5,17-dicarboxylic acids and their interactions with aliphatic amines. Part 1. Studies in solution†

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Four tetrapropoxycalix[4]arene-5,17-dicarboxylic acids have been prepared and their structures investigated in solution with NMR. The diacids were found to form dimers with the acid groups pinched together in a non-polar solvent. Salt formation with a number of primary, secondary and tertiary aliphatic amines was found to profoundly influence the structure and to depend on the number of hydrogen interactions possible and the coulombic interactions. The binding constants for a number of amines were determined by NMR titrations. A very high binding constant was found for the natural secondary amine (−)-ephedrine in $CDCl_3$. When phenylazo groups were substituted in the 11,23-positions the titration could be followed by absorption spectroscopy indicating the possibility of preparing a sensor for ephedrine type molecules based on these calix[4]arene diacids.

Introduction

Calixarenes are large molecules with an internal cavity that can easily be prepared from simple phenol precursors.[1] They have received special interest as platforms for further synthetic elaboration into host molecules.[2] Much work has been done to modify either the lower rim with the phenolic hydroxy functions,[3] or the upper rim positions[4] to create host molecules mainly for the attraction of simple cations,[5] anions[6] and small molecules.[7]

The phenolic groups of the calix[4]arene are often etherified to fix it in a definite conformation, the most common being the so-called *cone* conformer, with all the ether groups pointing in the same direction. The *cone* conformation of the simple calix[4]arenes has been shown by dynamic NMR to exist in two so-called *pinched cone* conformers with C_{2v} symmetry[8] (see Fig. 1). They have two opposite benzene rings periplanar and the other two splayed outwards. At ambient temperature the exchange is so fast that an averaged NMR spectrum is produced indicating C_{4v} symmetry. The C_{4v} geometry has been shown by calculations to be at the energy maximum.[9]

If two positions on the upper rim‡ opposite each other (the 5 and 17 positions) are substituted by carboxylic acid groups the pinched cone conformer with the acid groups together is preferred. X-Ray structures of tetrapropoxycalix[4]arene-5,17-dicarboxylic acids have shown that they are dimers in the solid joined *via* four specific hydrogen interactions between acid groups in the two calixarene units. The dimers are also very stable in apolar solution where no change in the ^{1}H NMR can be observed upon dilution.[10] Other groups in the 5,17 positions may also tip the equilibrium between the two pinched cone conformers. Secondary amide groups are held together by dipole interactions that can be disrupted by addition of polar solvents[11] and 5,17-diaryl calixarene ethers are held together by π–π interactions if the aryl groups are large enough.[12]

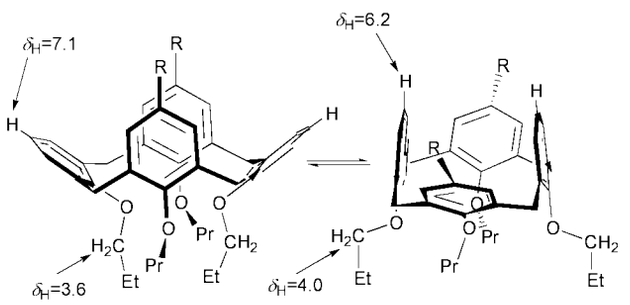

Fig. 1 Equilibrium between pinched cone conformers of calix[4]arene tetrapropoxy ether.

The starting point for the present investigation was to explore the reaction between calix[4]arene-5,17-dicarboxylic acids and amines. The acid and base strengths for aryl carboxylic acids and aliphatic amines are such that almost complete salt formation should occur. In a non-polar solution tight ion-pairs would be formed both due to the coulombic attraction, and also because of hydrogen bonds between the oxygen atoms of the carboxylate ions and the ammonium ions. A simple prediction was that as the double salt was formed the coulombic repulsion between the two carboxylate ions would force them apart favouring the other pinched cone conformer. Other work on 5,17-phenylethenylcalix[4]arene tetrapropoxy ether[13] gave the inspiration to add phenylethenyl and phenylazo groups in the remaining 11,23-positions of the calixarene dicarboxylic acids. These auxiliary groups could be used to signal the salt formation spectroscopically as well as by NMR. As will be clear later the predictions about the salt structures were far too naive and although the salts are indeed formed their interactions are much more specific making them true complexes. The overall binding strengths for the different amines also vary considerably making it possible to investigate a sensor application.

Considerable effort has also been invested in making crystals of both the neutral acids and a number of the salts that were suitable for X-ray crystallography. The resulting characterisation of the solid state structures is of course of great importance for the present investigation. These structures are

† Details of a prototype sensor device for detecting ephedrine are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/b0/b002407o/

‡ Upper rim denotes the positions on the *cone*-calix[4]arene *meta*- and *para*-to the oxygen atoms.

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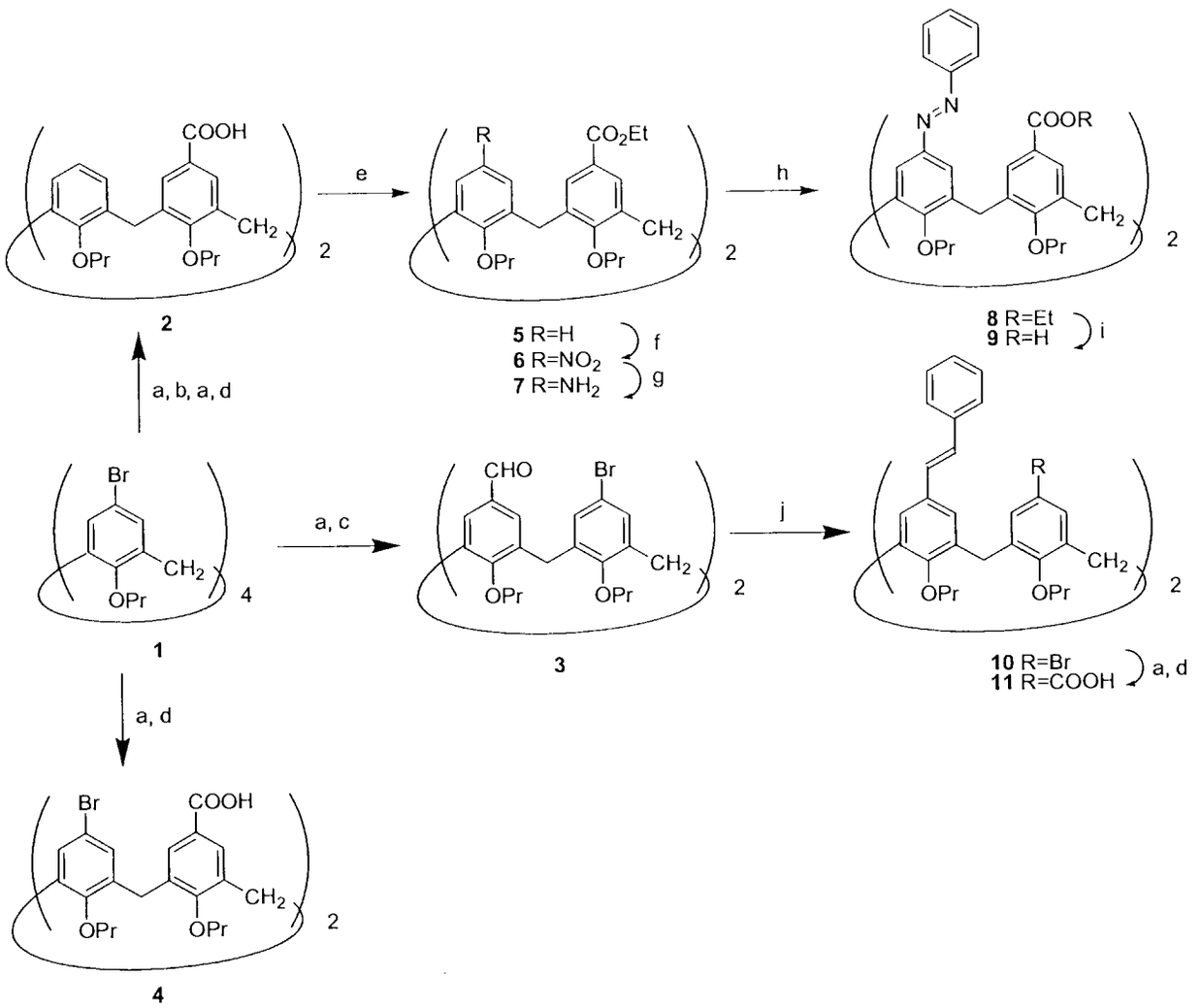

Scheme 1 *Reagents and conditions*: a: *n*-BuLi; b: MeOH; c: DMF; d, CO_2; e: $SOCl_2$ then EtOH; f: HNO_3; g: Sn, HCl; h: PhNO; i: NaOH; j: $PhCH_2P(O)(OEt)_2$, *t*-BuOK.

however not in all cases comparable to those inferred from NMR due to the subtle differences between the two states. The X-ray crystallographic work is therefore collected in a separate and adjoining paper.[14]

Results and discussion

The syntheses of the calix[4]arene dicarboxylic acids are outlined in Scheme 1.

Tetrabromotetrapropoxycalix[4]arene **1** was used a starting material to produce calix[4]arenediacids **2** and **4** and calix[4]arenedialdehyde **3,** by halogen to lithium exchange followed by quenching with electrophiles, as previously described.[15] Diacid **2** was treated with thionyl chloride and then ethanol to prepare the diester **5**. Nitration using 100% HNO_3 in methylene chloride–acetic acid gave the dinitrocalix[4]arenediester **6**. Reduction of **6** with tin powder–conc. HCl in ethanol yielded the diaminocalix[4]arene diester hydrochloride **7**. The bis(phenylazo)calix[4]arenediester **8** was prepared by condensation of **7** with nitrosobenzene in hot acetic acid (the Mills reaction).[16] Basic hydrolysis of **8** followed by acidification yielded the desired bis(phenylazo)calix[4]arene diacid **9**. The calix[4]arene dialdehyde **3** was converted to the dibromo(phenylethenyl)calix[4]arene **10** in a Horner–Wadsworth–Emmons reaction with diethyl benzylphosphonate. Carboxylic acid groups were introduced by bromine to lithium exchange followed by quenching with CO_2 to prepare the phenylethenylcalix[4]arene dicarboxylic acid **11**.

NMR studies of the solution structures and binding constants

The ^1H NMR spectra of the calixarenedicarboxylic acids can be used to determine the type of pinched cone conformation preferred.[8,11a] The protons on the phenyl groups that are pinched together will be shielded by the opposite group resulting in an upfield shift of the corresponding signals by 0.5–1 ppm. It is therefore possible to say whether it is the rings bearing the carboxylic acid groups that are pinched together or if it is the other set. At ambient temperature the equilibrium between the two conformers is rapidly established even if one is favoured. In particular, the signals from the OCH_2 groups can be used as a rough estimate of the equilibrium between the two conformations in the rapid exchange regime. If chemical shift changes due to substituents in the 5 and 17 positions can be ignored, a complete superposition of these signals indicates an equal mixture while a difference of about 0.4 ppm shows that one conformer is clearly favoured. (See Fig. 1).

The neutral forms of the calixarene diacids **2**, **4**, **9** and **11** in $CDCl_3$ showed as expected that the conformer with the carboxylic acid groups pinched together due to dimerisation was preferred. These solutions were then titrated with various primary, secondary or tertiary aliphatic amines in $CDCl_3$. The simplest cases proved to be the tertiary amines triethylamine and (−)-nicotine. As the titration proceeded the two sets of propoxy group signals interchanged places and simultaneously a downfield shift occurred for the signals due to the protons *ortho* to the carboxylic/carboxylate groups while the signals due to the protons on the other two rings moved upfield. These

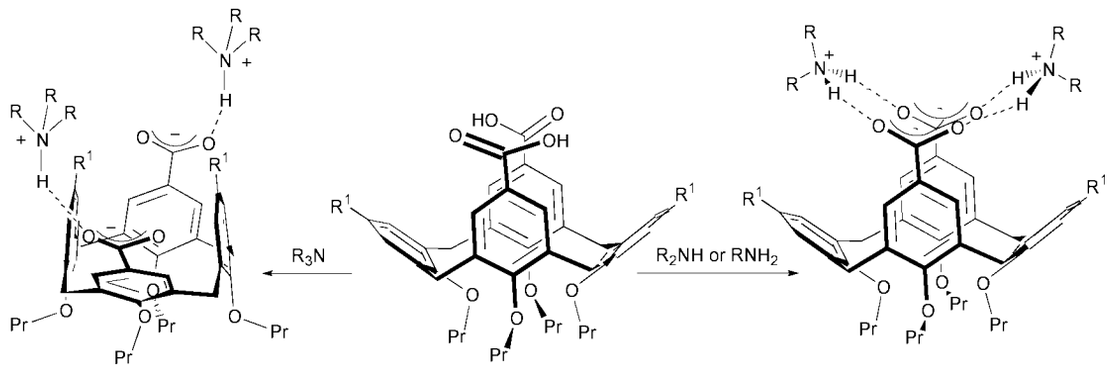

Fig. 2 Tertiary amines react with the calix[4]arene dicarboxylic acids **2**, **4**, **9** and **11** to form salts with the carboxylate groups splayed outwards, while primary and secondary amines keep them together in bridged structures, as inferred from ^{1}H NMR.

observations are in complete agreement with the prediction that the salt form of these calixarenes would prefer to have the carboxylate groups splayed outwards to minimise the coulombic repulsion. Much to our surprise titration of calixarene diacid **2** with diethylamine or propylamine did not change the spectrum significantly and hence not the conformational equilibrium. When primary or secondary amines with phenyl groups were used, *e.g.* benzylamine, significant upfield shifts were observed especially for the signals due to the protons on the phenyl rings without the acid groups. These observations can be explained considering that the corresponding ammonium ions of these amines have three or two protons respectively, available for hydrogen interactions and can therefore keep the carboxylate groups together by bridging them. The complexed benzylamine is thus kept in a position that forces its aromatic ring close to the protons of the unsubstituted aromatic nuclei of the calixarene thus shielding them; propyl- and diethylamine cannot have this same effect. The reaction between the different types of amines and calix[4]arene dicarboxylic acids are summarised in Fig. 2.

The binding of primary or secondary amines must be rather strong to overcome the repulsion between the two negatively charged carboxylate groups. Further evidence for the tight association in $CDCl_3$ was obtained from the ROESY spectra of calixarene **2** with benzylamine and that of calixarene **9** with (−)-ephedrine. In the first case clear NOE cross-peaks were observed between the phenyl and methylene protons of benzylamine and the protons *ortho* to the carboxylate groups on the calixarene **2**. In the second case a NOE cross-peak was observed between the *N*-methyl group of ephedrine and the protons *ortho* to the carboxylate groups of calixarene **9**. Since the intensities of the NOE signals fall off very rapidly with distance their observation proves that these amines are bound to the calixarenes in a complex with a definite geometry.

Overall binding constants between the calix[4]arene dicarboxylic acids **2**, **4**, **9** and **11** and various amines were determined from the titration data using the program EQNMR which performs a non-linear least squares fit.[17] It is clear that the complexation event involves several steps since dimerisation of the acids as well as acid base reactions take place. The dimerisation constants for the acids could not be determined by NMR since the ^{1}H NMR spectra of the acids remained unchanged at all accessible concentrations (see also ref. 10). No attempts to correct the binding constants for these reactions have therefore been made. The binding constants reported are therefore to be taken as the apparent values for the reaction between neutral monomeric acids and two equivalents of amine. The chemical shifts of the oxymethylene groups were followed as a function of amine concentration in the case of tertiary amines, while protons in the aromatic part of the calixarenes were used in the other cases. When the binding curves were plotted a definite inflexion point at two equivalents of amine was seen in all the cases of strong binding indicating 1:2 stoichiometry as would also be expected from the possible acid base reactions and from the X-ray structures.[14] The results are compiled in Table 1.

Table 1 Overall binding constants (log $\beta_1\beta_2$) for amines with calix[4]arenedicarboxylic acids **2**, **4**, **9** and **11** in $CDCl_3$ at 300 K [a]

Amine	2	4	9	11
Triethylamine	4.7	3.8 [b]	3.0	4.1
Benzylamine	4.6	>5	>5	>5
N-Benzylmethylamine	4.7	4.8	4.2	5.0
Dibenzylamine	<1	2.9	<1	2.8
2-Phenylethylamine	nd [c]	nd	>5	4.8 [b]
(−)-Nicotine	nd	nd	nd	1.2
(−)-Ephedrine	>5	>5	>5	>5

[a] β_1 = [Calix(COOH)COO$^-$*R_3NH^+]/([Calix(COOH)$_2$][R_3N]); β_2 = [Calix(COO^-)$_2$*(R_3NH^+)$_2$]/([Calix(COOH)COO$^-$*R_3NH^+][R_3N]). [b] At 330 K. [c] nd: not determined.

The tertiary amines, especially (−)-nicotine, have low binding constants while the primary and secondary amines form very stable complexes in $CDCl_3$. Weak bases like pyridine form no detectable complexes. The stability of the complexes is due to the coulombic attraction and the hydrogen interaction while steric hindrance in *e.g.* (−)-nicotine and dibenzylamine are destabilising. A remarkable result is the high binding constant for (−)-ephedrine. Ephedrine (Fig. 3) has a hydroxy group *vicinal* to the secondary amino group that could form an additional hydrogen interaction to the calixarene stabilising the complex. This type of hydrogen interaction has been observed previously in the structure of the 1:1 adduct between ephedrine and [2.2]paracyclophane-4-carboxylic acid.[18] Model studies indicate that this would force the phenyl ring of the ephedrine molecule to one side of the cavity. The resulting structure is depicted schematically in Fig. 3 where it can be seen that the mirror planes bisecting the neutral structure have been removed. In the ^{1}H NMR spectrum this is evidenced by the splitting of signals from the CH_2 groups between aryl groups of the calixarene and also by the splitting of the signals due to the aryl protons.

In a competition experiment calix[4]arene dicarboxylic acid **2** was first titrated with triethylamine so that the two sets of signals from the propoxy groups interchanged values (about four equivalents). Then ephedrine (about two equivalents) was added to observe the reverse interchange showing again that ephedrine forms a much stronger complex with **2**.

The stability of the complexes depends on the polarity of the solvent and its ability to form hydrogen interactions. Addition of the polar solvent [$^2H_6$]-DMSO to a solution of **2** in $CDCl_3$ forces the carboxylic acid groups outward. In pure [$^2H_6$]-DMSO no evidence of complexation with amines can be seen, but

in a mixture of 10% [$^2H_6$]-DMSO in $CDCl_3$, complexation with benzylamine occurs with a change of conformation to that observed in pure $CDCl_3$. The stability constant obtained ($\log\beta_1\beta_2 = 4.5$) is slightly lower than that observed in pure $CDCl_3$.

The dibromo-, bis(phenylazo)- and distyryl-calixarene dicarboxylic acids **4**, **9** and **11** react similarly to calixarene dicarboxylic acid **2** on titration with the various amines. The bromo, phenylazo and styryl substituents point outwards away from the calixarene cavity, but are pinched together when reacted with triethylamine. The protons in the ethylene groups of compound **11** are shielded effectively when titrated with an amine containing a phenyl group *e.g.* benzylamine. This indicates that this phenyl group is centred above the ethylene group at a short distance in the complex possibly giving rise to weak π–π interactions.

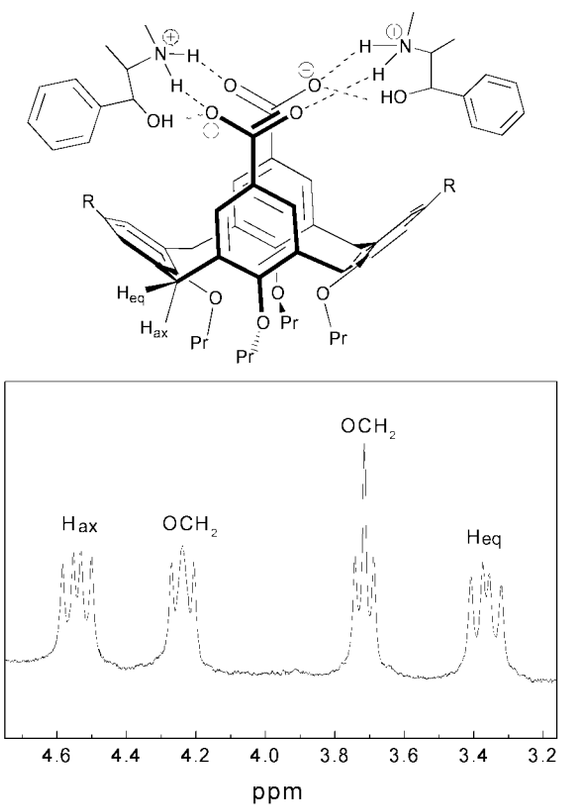

Fig. 3 Idealized structure of the salt formed between calix[4]arene-5,17-dicarboxylic acids and (−)-ephedrine (above). Splitting of the ^{1}H-NMR signals due to the binding of (−)-ephedrine (below).

Table 2 Spectroscopic properties of calixarene **9** in different solvents

	C_6H_6	$CHCl_3$	DMSO	Ethanol (99%)
λ_{max}^{ABS}	346	348	342	334
$\varepsilon/M^{-1}\,cm^{-1}$	39.700	40.900	37.400	34.600

Absorption spectroscopy

The absorption spectra of bis(phenylazo)calixarene **9** were obtained in four different solvents (benzene, chloroform, DMSO and ethanol) (Table 2). Spectra of both **9** and the reference compound 4-phenylazo-1-propoxybenzene **12** in the presence of either 0.1 M ephedrine or triethylamine in either chloroform or ethanol were also taken (Table 3).

The spectra of **9** and the monomer **12** in chloroform are nearly indistinguishable, whereas in ethanol a hypsochromic shift of 14 nm for **9** is observed while the monomer is almost unaffected by the solvent change. The absorption coefficient ε_{max} per chromophore is about the same for calixarene **9** and the monomer **12** in chloroform while it is substantially decreased for **9** in ethanol. The most reasonable explanation seen in light of the NMR evidence is that the two chromophores in calixarene **9** are preferentially splayed apart in chloroform while they are pinched together with some electronic contact when dissolved in ethanol. Addition of triethylamine to the chloroform solution of calixarene **9** leads to an even larger hypsochromic shift of 18 nm and a reduced ε_{max} in agreement with the salt formation and change of conformation evidenced from NMR. Addition of ephedrine to the chloroform solution on the other hand leads to a bathochromic shift of 8 nm with almost no change in ε_{max}. Again this can be explained by the solution structure inferred from NMR where the phenylazo chromophores are splayed away from each other and the carboxylate ions are held together and bridged by the ammonium group of ephedrine. Triethylamine or ephedrine has little or no effect on calixarene **9** in ethanol where the salts are probably dissociated and the same conformation with the chromophores pinched together.

Although the spectral changes are modest when calixarene **9** reacts with either triethylamine or ephedrine in $CHCl_3$ they can be conveniently used in titration experiments. Fig. 4 shows the results of such a titration following the absorption at 365 nm as a function of amine concentration. The opposite spectral behaviour of the two amines is evident and a much more efficient binding of ephedrine relative to triethylamine is also apparent.

Construction of a good host molecule for a biological molecule like ephedrine working in chloroform can elucidate the vital supramolecular interactions, but may have limited practical use. It therefore seemed important to demonstrate the feasibility of making an actual sensor based on the above results with the amine in water solution. Such a device was constructed with the sensor compound in a PVC membrane coated onto a glass slide as one side of an optical cell (see Supplementary Material for this article†). An interesting example of a sensor for ephedrine has been published.[19]

Conclusion

Calix[4]arene-5,17-dicarboxylic acids are bistable molecules by virtue of their dynamic interconversion between the two pinched cone conformers. We have shown that this bistability

Table 3 Spectroscopic properties of calixarene **9** and the monomer 4-phenylazo-1-propoxybenzene (**12**) in $CHCl_3$ or ethanol either pure or in the presence of ephedrine or triethylamine

	$CHCl_3$		Ethanol (99%)	
Compound	λ_{max}^{ABS}/nm	$\varepsilon/M^{-1}\,cm^{-1}$	λ_{max}^{ABS}/nm	$\varepsilon/M^{-1}\,cm^{-1}$
Calixarene **9**	348	40.900	334	34.600
+0.10 M ephedrine	356	39.800	331	33.000
+0.10 M Et_3N	330	28.600	330	31.700
Monomer **12**	349	20.600	345	22.300
+0.10 M ephedrine	348	19.900	345	23.700
+0.10 M Et_3N	348	20.500	346	24.300

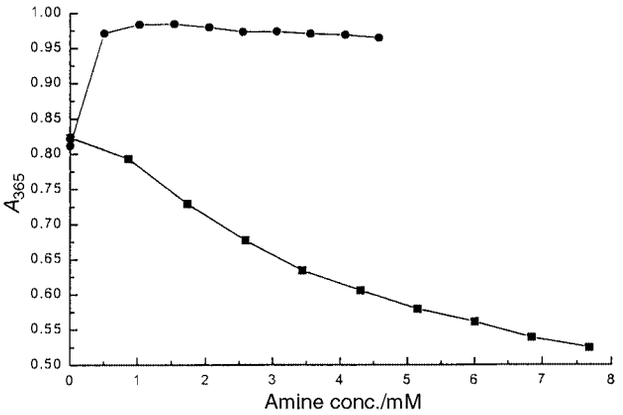

Fig. 4 Titration of bis-azo calixarene diacid **9** (2.89×10^{-5} M in $CHCl_3$) with triethylamine (squares) or (−)-ephedrine (circles) observed at 365 nm as a function of concentration.

can be utilised to differentiate how primary, secondary and tertiary amines react with the calix[4]arenedicarboxylic acids in solution. While the tertiary amines simply deprotonate the acid groups which are then splayed apart due to coulombic repulsion, the extra hydrogen bonding possibilities offered by the primary and secondary amines hold the carboxylate groups pinched together. In the case of the natural secondary amine ephedrine a fortuitously placed hydroxy group vicinal to the amine adds considerable stability to the complex *via* yet another hydrogen bond. Phenylazo or styryl groups were added to the calixarene platform as chromophores to signal the binding events by UV-VIS spectroscopy. This was investigated in the case of the phenylazo substituted calixarene dicarboxylic acid **9** where opposite (and modest) spectral changes occurred on addition of either the secondary amine ephedrine or the tertiary amine triethylamine. These spectral changes were utilised to make a simple sensor device with the calixarene diacid **9** dissolved in a PVC film mounted in a UV-VIS cell of a optical spectrometer. It was found that this device could measure the ephedrine concentration in a water solution.

Experimental

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-250 instrument with TMS as internal standard. Absorption spectra were recorded on a Cary 1E UV-VIS spectrometer from Varian. All commercially available chemicals were used without further purification. All solvents were reagent grade or better and used without further purification, except for THF which was freshly distilled from sodium–benzophenone ketyl. Calix[4]arenes **1**, **2**, **3** and **4** were prepared as described earlier.[15]

25,26,27,28-Tetrapropoxycalix[4]arene-5,17-dicarboxylic acid diethyl ester 5

Calix[4]arene dicarboxylic acid **2** (11.5 g, 16.9 mmol) was mixed with thionyl chloride (50 cm^3) and heated to reflux for 0.5 h. Excess thionyl chloride was removed *in vacuo* and the oily residue was dissolved in ethanol (200 cm^3) and heated to reflux for 0.5 h. On cooling to ambient temperature the product crystallized (7.7 g, 62%); mp 180–181 °C [Found: C, 74.31; H, 7.66. $C_{46}H_{56}O_8 \cdot \frac{1}{2}$ ethanol requires C, 74.28; H, 7.83%]; δ_H (250.1 MHz, $CDCl_3$) 0.91 (6H, t, *J* 8), 1.08 (6H, t, *J* 8), 1.41 (6H, t, *J* 8,), 1.84–1.95 (8H, m), 3.23 (d, *J* 14, 4H), 3.71 (4H, t, *J* 7), 4.06 (4H, t, *J* 8), 4.36 (4H, q, *J* 8), 4.44 (4H, d, *J* 14), 6.18–6.30 (6H, m, A_2B pattern), 7.74 (4H, s); δ_C (62.9 MHz, $CDCl_3$) 10.4, 11.2, 14.9, 23.6, 23.9, 31.4, 61.1, 77.2, 122.8, 124.3, 128.3, 130.8, 133.4, 137.1, 155.8, 162.5, 167.3.

11,23-Dinitro-25,26,27,28-tetrapropoxycalix[4]arene-5,17-dicarboxylic acid diethyl ester 6

Calix[4]arene diester **5** (5.0 g, 6.8 mmol) was dissolved in methylene chloride (400 cm^3) and acetic acid (10 cm^3). Nitric acid (100%, 5 cm^3) was added in one portion. The deep violet reaction mixture was stirred at ambient temperature for 1 h and then quenched by pouring it into water (500 cm^3). The organic phase was separated and evaporated *in vacuo* to an orange-brown solid. The product was recrystallized from ethanol and then CH_2Cl_2–CH_3CN (2.5 g, 44%); mp 227–228 °C [Found: C, 61.57; H, 6.37; N, 4.18. $C_{46}H_{54}N_2O_{12} \cdot CH_3CN \cdot CH_2Cl_2$ requires C, 61.76; H, 6.24; N, 4.41%]; δ_H (250.1 MHz, $CDCl_3$) 0.91 (6H, t, *J* 7), 1.09 (6H, t, *J* 7), 1.44 (6H, t, *J* 7), 1.86–1.92 (8H, m), 3.33 (4H, d, *J* 14), 3.80 (4H, t, *J* 7), 4.03 (4H, t, *J* 7), 4.41 (4H, q, *J* 7), 4.48 (4H, d, *J* 14), 7.10 (4H, s), 7.80 (4H, s); δ_C (62.9 MHz, $CDCl_3$) 10.2, 10.9, 14.8, 23.4, 23.8, 31.5, 61.4, 77.4, 78.0, 123.5, 125.6, 131.3, 135.4, 135.8, 143.2, 161.2, 161.5, 166.5.

11,23-Bis(phenylazo)-25,26,27,28-tetrapropoxycalix[4]arene-5,17-dicarboxylic acid diethyl ester 8

Tin powder (5 g) was added to a solution of dinitrocalix[4]arene diester **6** (3.0 g, 3.6 mmol) in hot ethanol (200 cm^3). Conc. hydrochloric acid (10 cm^3) was added over 1 h at reflux. The solution was decanted from excess tin and evaporated to dryness. The product was recrystallized from a small amount of ethanol (1.28 g, 46%) and used directly in the next step, mp 230 °C (decomp.); δ_H (250.1 MHz, $CDCl_3$) 0.83 (6H, t, *J* 7), 1.11 (6H, t, *J* 7), 1.46 (6H, t, *J* 7), 1.7–1.9 (8H, m), 3.06 (4H, d, *J* 14), 3.64 (4H, t, *J* 6), 4.00 (4H, t, *J* 8), 4.37 (4H, d, *J* 14), 4.45 (4H, q, *J* 7), 5.85 (4 + 4H, s, NH + ArH), 7.72 (4H, s); δ_C (62.9 MHz, $CDCl_3$) 10.2, 11.3, 23.5, 23.9, 31.3, 61.6, 77.1, 119.9, 124.9, 131.4, 132.0, 135.3, 137.0, 153.1, 162.8, 167.5.

Diaminocalix[4]arene diester hydrochloride **7** obtained above (1.25 g, 1.49 mmol) was dissolved in acetic acid (15 cm^3) with sodium acetate trihydrate (1.5 g) and heated to 90 °C while bubbling argon through the mixture. Nitrosobenzene (0.50 g, 4.7 mmol) was added and the heating continued for 1 h. A colour change from green to brown was observed. The reaction mixture was cooled and diluted with 3 volumes of water and stirred for 30 min. A residue formed that was filtered off and dissolved in methylene chloride. This solution was filtered through a layer of silica using an additional 200 cm^3 solvent to elute the orange product. The solvent was evaporated to give 0.83 g solid which could be purified by crystallisation from 10 cm^3 ethanol (0.793 g, 56.4%); mp 163–165 °C [Found: C, 73.86; H, 7.10; N, 5.96. $C_{58}H_{64}N_4O_8$ requires C, 73.70; H, 6.83; N, 5.93%]; δ_H (250.1 MHz, $CDCl_3$) 1.00 (6H, t, *J* 8), 1.04 (6H, t, *J* 8), 1.32 (6H, t, *J* 7), 1.98 (8H, m), 3.35 (4H, d, *J* 14), 3.87 (4H, t, *J* 8), 4.03 (4H, t, *J* 8), 4.28 (4H, q, *J* 7), 7.14 (4H, s), 7.2–7.3 (6H, m), 7.5–7.6 (8H, m); δ_C (62.9 MHz, $CDCl_3$) 10.7, 10.9, 14.8, 23.7, 23.8, 61.0, 77.4, 77.7, 122.9, 123.5, 125.1, 129.3, 130.4, 130.75, 135.3, 135.6, 148.9, 153.1, 159.4, 161.3, 166.8.

11,23-Bis(phenylazo)-25,26,27,28-tetrapropoxycalix[4]arene-5,17-dicarboxylic acid 9

Bis(phenylazo)calix[4]arene diester **8** (0.70 g) was heated in ethanol with NaOH (1 g in 10 cm^3) for 15 min then cooled and acidified with dilute HCl. The product precipitated as a light brown powder that was filtered off and washed with water and a little ethanol. It was recrystallised by dissolving it in a small amount of methylene chloride and adding acetonitrile until incipient crystallisation (0.52 g, 79%); mp >280 °C [Found: C, 72.85; H, 6.54; N, 6.26. $C_{54}H_{56}N_4O_8$ requires C, 72.95; H, 6.35; N, 6.30%]; δ_H (250.1 MHz, $CDCl_3$) 0.86 (6H, t, *J* 8), 1.10 (6H, t, *J* 8), 1.8–1.9 (8H, m), 3.29 (4H, d, *J* 14), 3.68 (4H, t, *J* 7), 4.08 (4H, t, *J* 7), 4.46 (4H, d, *J* 14), 6.86 (4H, s), 7.44–7.46 (6H, m), 7.76 (4H, s), 7.89–7.93 (4H, m), 12 (2H,

broad s); δ_C (62.9 MHz, $CDCl_3$) 10.2, 11.2, 23.4, 23.9, 31.5, 77.2, 77.9, 123.2, 124.1, 124.6, 129.3, 130.3, 130.6, 133.6, 137.5, 148.1, 153.5, 160.2, 161.2, 172.2.

5,17-Bis[(*E*)-2-phenylethen-1-yl]-11,23-dibromo-25,26,27,28-tetrapropoxycalix[4]arene 10

Compound **3** (3.83 g, 4.7 mmol) and diethyl benzylphosphonate (3.42 g, 15 mmol) were dissolved in dry THF (100 cm^3) and cooled to 5 °C. A solution of *t*-BuOK (1.68 g, 15 mmol) was added over 1 min. The yellow mixture was stirred for 1 h at ambient temperature. Then it was poured into ice cold 1 M HCl (200 cm^3) and extracted with CH_2Cl_2 (3 × 100 cm^3) (the product is not very soluble). The organic phase was washed once with brine (100 cm^3), dried over Na_2SO_4 and evaporated to dryness. The solid was dissolved in hot CH_2Cl_2 (100 cm^3) and two volumes of CH_3OH were added to precipitate the white crystalline product (4.13 g, 92%); mp >260 °C [Found: C, 70.43; H, 6.33. $C_{56}Br_2H_{58}O_4$ requires C, 70.44; H 6.12%]; δ_H (250.1 MHz, $CDCl_3$) 0.92 (6H, t, *J* 7), 1.06 (6H, t, *J* 7), 1.85–1.98 (8H, m), 3.16 (4H, d, *J* 14), 3.73 (4H, t, *J* 7), 3.97 (4H, t, *J* 8), 4.42 (4H, d, *J* 14), 6.57 (4H, s), 6.92 (2H, d, *J* 16), 7.03 (2H, d, *J* 16), 7.2–7.33 (6H, m), 7.46 (4H, d, *J* 7); δ_C (62.9 MHz, $CDCl_3$) 10.4, 11.0, 23.4, 23.7, 31.4, 77.2, 77.6, 115.6, 126.3, 126.7, 127.5, 127.7, 129.0, 129.1, 130.9, 132.2, 136.1, 136.3, 138.1, 155.3, 157.6.

11,23-Bis[(*E*)-2-phenylethen-1-yl]-25,26,27,28-tetrapropoxycalix[4]arene-5,17-dicarboxylic acid 11

Compound **10** (2.00 g, 2.1 mmol) was dissolved in dry THF (200 cm^3) and cooled on a dry ice–acetone bath to −78 °C. *n*-BuLi (6 cm^3, 9.6 mmol) was added *via* a syringe over 1 min. After 15 min CO_2 was passed rapidly through the reaction mixture and the cooling bath was removed. When the temperature had risen to 0 °C the CO_2 supply was disconnected and dilute HCl (100 cm^3) was added carefully (gas evolution). The organic solvent was removed under vacuum and the solid filtered. The raw product was washed with methanol (2 × 10 cm^3) and recrystallised by dissolving in CH_2Cl_2 (20 cm^3) and adding four volumes of methanol. The product crystallised overnight. Workup of the mother liquor gave more product (1.6 g, 86%); mp >280 °C [Found: C, 78.76; H, 7.09. $C_{58}H_{60}O_8$ requires C, 78.71; H, 6.83%]; δ_H (250.1 MHz, $CDCl_3$) 0.84 (6H, t, *J* 8), 1.10 (6H, t, *J* 8), 1.83–1.9 (8H, m), 3.17 (4H, d, *J* 14), 3.66 (4H, t, *J* 7), 4.00 (4H, t, *J* 7), 4.41 (4H, d, *J* 14), 6.81 (4H, s), 7.00 (2H, d, *J* 16), 7.12 (2H, d, *J* 16), 7.22–7.33 (10H, m), 7.53 (4H, d, *J* 7), 12.5 (2H, broad s); δ_C (62.9 MHz, $CDCl_3$) 10.1, 11.2, 31.5, 77.3, 77.9, 123.9, 126.8, 127.4, 127.8, 128.0, 128.9, 129.7, 130.1, 132.2, 133.9, 137.1, 138.4, 158.1, 160.2, 172.2.

4-Phenylazo-1-propoxybenzene 12

4-Phenylazophenol (2.0 g, 10 mmol), 1-iodopropane (3 g, 18 mmol) and K_2CO_3 (3 g) were mixed in acetonitrile, stirred vigorously and heated to reflux for two hours. The orange solution was filtered to remove the inorganic salts and evaporated under vacuum. The residue was crystallised from ethanol to give **12** as orange needle-like crystals. Yield: 1.7 g, 71%; mp 58–59 °C [Found: C, 74.87; H, 6.65; N, 11.33. $C_{15}H_{16}N_2O$ requires C, 74.97; H, 6.71; N, 11.66%]; δ_H (250.1 MHz, $CDCl_3$) 1.06 (3H, t, *J* 7), 1.8–1.9 (2H, m), 4.00 (2H, t, *J* 6), 7.00 (2H, d, *J* 9), 7.4–7.52 (3H, m), 7.85–7.93 (4H, m); δ_C (62.9 MHz, $CDCl_3$) 11.0, 23.0, 70.3, 115.2, 123.0, 125.2, 129.5, 130.8, 147.4, 153.3, 162.2.

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References

1 C. D. Gutsche and M. Iqbal, *Org. Synth.*, 1990, **68**, 234.
2 (*a*) C. D. Gutsche, *Calixarenes; Monographs in Supramolecular Chemistry*, ed. J. F. Stoddart, Royal Society of Chemistry, London, 1989; (*b*) J. Vicens and V. Böhmer, *Calixarenes: A Versatile Class of Macrocyclic Compounds*, Kluwer Academic Publishers, Dordrecht, 1990; (*c*) V. Böhmer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 713.
3 K. Iwamoto, K. Fujimoto, T. Matsuda and S. Shinkai, *Tetrahedron Lett.*, 1990, **31**, 7169; see also ref. 2.
4 (*a*) M. Almi, A. Arduini, A. Casnati, A. Pochini and R. Ungaro, *Tetrahedron*, 1989, **45**, 2177; (*b*) C. D. Gutsche and K. C. Nam, *J. Am. Chem. Soc.*, 1988, **110**, 6153; (*c*) S. Shinkai, T. Nagasaki, K. Iwamoto, A. Ikeda, G. X. He, T. Matsuda and M. Iwamoto, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 381; (*d*) C. D. Gutsche and P. F. Pagoria, *J. Org. Chem.*, 1985, **50**, 5795; (*e*) S. Shinkai, K. Araki, T. Tsubaki, T. Arimura and O. Manabe, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2297; (*f*) W. Verboom, A. Durie, R. J. M. Egberink, Z. Asfari and D. N. Reinhoudt, *J. Org. Chem.*, 1992, **57**, 1313.
5 (*a*) R. M. Izatt, J. D. Lamb, R. T. Hawkins, P. R. Brown, S. R. Izatt and J. J. Christensen, *J. Am. Chem. Soc.*, 1983, **105**, 1782; (*b*) G. Calestani, F. Ugozzoli, A. Arduini, E. Ghidini and R. Ungaro, *J. Chem. Soc., Chem. Commun.*, 1987, 344; (*c*) E. Ghidini, F. Ugozzoli, R. Ungaro, S. Harkema, A. A. El-Fadl and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1990, **112**, 6979.
6 (*a*) P. D. Beer, C. A. P. Dickson, N. Fletcher, A. J. Goulden, A. Grieve, J. Hodachova and T. Wear, *J. Chem. Soc., Chem. Commun.*, 1993, 828; (*b*) D. M. Rudkievich, W. Verboom and D. N. Reinhoudt, *J. Org. Chem.*, 1994, **59**, 3683; (*c*) J. S. M. Fochi, J. F. J. Engbersen and D. N. Reinhoudt, *J. Org. Chem.*, 1994, **59**, 7815.
7 (*a*) G. D. Andreetti, R. Ungaro and A. Pochini, *J. Chem. Soc., Chem Commun.*, 1979, 1005; (*b*) J.-D. van Loon, J. F. Heida, W. Verboom and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas*, 1992, **111**, 353; (*c*) H. Murakami and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, 1993, 828; (*d*) C. D. Gutsche and K. A. See, *J. Org. Chem.*, 1992, **57**, 4527; (*e*) P. Timmerman, E. A. Brinks, W. Verboom and D. N. Reinhoudt, *J. Chem. Soc., Chem. Commun.*, 1995, 417.
8 A. Arduini, M. Fabbi, M. Mantovani, L. Mirone, A. Pochini, A. Secchi and R. Ungaro, *J. Org. Chem.*, 1995, **60**, 1454.
9 P. D. J. Grootenhuis, P. A. Kollman, L. C. Groenen, D. N. Reinhoudt, G. J. van Hummel, F. Ugozzoli and G. D. Andreetti, *J. Am. Chem. Soc.*, 1990, **112**, 4165.
10 O. Struck, W. Verboom, W. J. J. Smeets, A. L. Spek and D. N. Reinhoudt, *J. Chem. Soc., Perkin Trans. 2*, 1997, 223.
11 (*a*) M. Jørgensen, M. Larsen, P. Sommer-Larsen, W. B. Petersen and H. Eggert, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2851; (*b*) F. C. Krebs, M. Larsen, M. Jørgensen, P. R. Rasmussen, M. Bielecki and K. Schaumburg, *J. Org. Chem.*, 1998, **63**, 9872.
12 M. Larsen, F. C. Krebs, N. Harrit and M. Jørgensen, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1749.
13 M. Larsen, F. C. Krebs, M. Jørgensen and N. Harrit, *J. Org. Chem.*, 1998, **63**, 4420.
14 F. C. Krebs and M. Jørgensen, following paper in this issue, DOI 10.1039/b002409k.
15 M. Larsen and M. Jørgensen, *J. Org. Chem.*, 1996, **61**, 6651.
16 Houben-Weyl, *Methoden der Organische Chemie*, Georg Thieme Verlag, Stuttgart, 1965, part 10/3, p. 332.
17 M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311.
18 P. G. Jones, D. Döering, T. Laue and H. Hopf, *Acta Crystallogr., Sect. C*, 1993, **49**, 1192.
19 P. S. Bates, R. Kataky and D. Parker, *J. Chem. Soc., Perkin Trans. 2*, 1994, 669.