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Synthesis and capsule formation of upper rim substituted tetra-acrylamido calix[4]arenes

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Received 15th February 2005, Accepted 14th April 2005
First published as an Advance Article on the web 4th May 2005

Upper rim substituted tetraiodo calix[4]arenes are coupled to a variety of acrylamides using the palladium catalysed Heck reaction. Tetra-acrylamido upper rim substituted calix[4]arenes are obtained in good yields with exceptionally high stereoselectivity, to produce the all-*trans* isomers. Tetra-acrylamido calix[4]arenes derived from secondary acrylamides are shown to dimerise *via* eight hydrogen bonds to form dimeric capsules, which are able to include small organic molecules.

Introduction

The main factor contributing to the stability of secondary protein structure is hydrogen bonding. In α-helical structures and β-sheet structures *trans*-amide moieties form regular hydrogen bond arrays between amide C=O and adjacent amide N–H bonds.[1] In order to achieve a sufficient degree of stability, several hydrogen bonds within a single strand (α-helical) or between two and more strands (β-sheet) are necessary to maintain structural integrity.[2] A transverse section through both an α-helix (parallel to the axis isolating a quarter of amide bonds) or a β-sheet (orthogonal to the strands) reveals a topologically similar chain of hydrogen bonded amides. This chain motif is, to our knowledge, not found without the structural context of a helix or sheet in any structurally characterised peptide or protein. Thus, we wondered whether such a motif of single hydrogen bonds forming a chain of isolated interstrand amide hydrogen bonds would be stable in a synthetic system. Amide substituted calix[*n*]arenes could display such an unusual hydrogen bonding motif by dimerisation, although in a cyclic form, by using the structural complementarity of their C=O and N–H moieties. Similar hydrogen bonding motifs have been described by the groups of Rebek[3–5] and Böhmer[6] using a self complementary non-covalent assembly *via* 16 hydrogen bonds of tetra-ureido calix[4]arenes. A related dimerisation between calix[6] substituted dipeptides has recently been described by de Mendoza *et al*.[7] In this assembly 18 hydrogen bonds are formed between three sets of dipeptides linked to the calix[6]arene scaffold. It should be noted that both *N*-linked and *C*-linked peptide calix[4]arenes introduced by the Ungaro group[8,9] did not show dimerisation by self complementary assembly, possibly due to unfavourable stereoelectronic effects or lack of secondary interactions stabilising the assembly. Related resorcinarene molecular capsules have been reported by Atwood and co-workers.[10] Dimeric capsules formed by electrostatic interactions have been reported by the groups of Reinhardt and Schrader.[11,12] In this contribution we like to describe in detail the synthesis and supramolecular chemistry of tetra-acrylamido calix[4]arenes. Part of this work has been reported as a short communication.[13]

Results and discussion

Synthesis of tetra-acrylamido calix[4]arenes

Within our research programme aimed at the synthesis of macrocyclic libraries[14,15] we have recently reported on the palladium catalysed Heck reaction of tetra-iodo calix[4]arenes to produce tri- and tetra-olefinic calix[4]arenes.[14] In order to expand the scope of the C–C bond formation process, we became interested in coupling acrylamides to the broader rim of the calix[4]arene. Using our standard reaction conditions we were able to obtain a small selection of tertiary tetra-acrylamido calix[4]arenes **3a–d** (Fig. 1) in good yields using $Pd(OAc)_2$ and dppp as the catalytic system, with NEt_3 as the base, in DMF. Yields and selected spectroscopic data are given in Table 1. All reactions proceed completely stereoselectively to produce the all-*trans* tetra-olefinic calix[4]arenes as a single stereoisomer, as indicated by the large $^3J_{HC=CH}$ olefinic coupling constant between 15.5 and 16 Hz (see Table 1). All products are additionally found exclusively in the cone conformation. It has to be stressed that this highly chemo- and stereoselective outcome of the reaction is remarkable indeed, keeping in mind that a total of 120 reaction products are possible in this reaction including stereoisomers.[16] Furthermore, it is worth noting that only very few examples of Heck coupling reactions with acrylamides have been reported.[17]

Secondary acrylamides **4a–d** could be coupled successfully under similar conditions used for the tertiary acrylamides (Fig. 2). Similar to the tertiary acrylamides **3a–d** and acrylate series,[14] the all-*trans* isomers of **5a–d** could be obtained exclusively. The structures can be directly deduced from their NMR spectra. As discussed earlier,[14,18] the difference in chemical shift $\Delta\delta$ for the two calx[4]arene methylene protons are a good indication of a close to parallel arrangement of the four olefinic substituents. Calix[4]arenes found in this particular type of conformation have been referred to as deep cavity calix[4]arenes.[14] All compounds were found in the cone conformation, exhibiting NMR spectra in polar solvents with one set of signals for the four repeating units as expected for a C_{4V}-symmetric molecule. In all tetra-olefinic substituted derivatives the stereochemical relationship across the

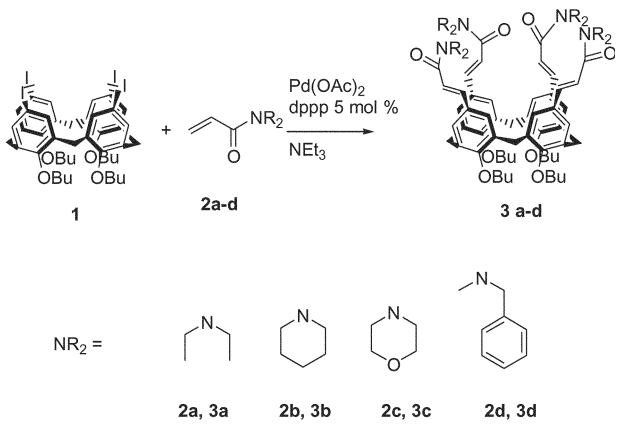

Fig. 1 Heck coupling of tertiary acrylamides.

DOI:10.1039/b502378e

Table 1 Yields and selected spectroscopic data tetra-acrylamido calix[4]arenes **3a–d**, **5a–d**, **8** and **9**

Compound	NR_2	Yield (%)	Coupling constant $^3J_{HC=CH}$/Hz	Coupling constant $^2J_{HCH}$/Hz	Molecular ion *m/z*
3a	NEt_2	60	16.0	13.4	1149
3b	*N*-Cyclo-C_5H_{10}	74	15.1	13.2	1198
3c	*N*-Cyclo-*i*C_4H_8O	50	15.5	13.5	1206
3d	NMeBn	65	NA	13.4	1342
5a	NH(4-$NO_2C_6H_4$)	75	15.5	13.5	1409
5b	NH(4-CNC_6H_4)	70	15.5	12.8	1329
5c	NH(4-$CF_3C_6H_4$)	65	15.1	13.8	1525
5d	NHBn	65	15.5	13.9	1286
8	NH(4-$NH_2C_6H_4$)	33	15.5	11.8	1289
9	NH(4-$NHAcC_6H_4$)	49	15.9	12.1	1481 [M + Na]

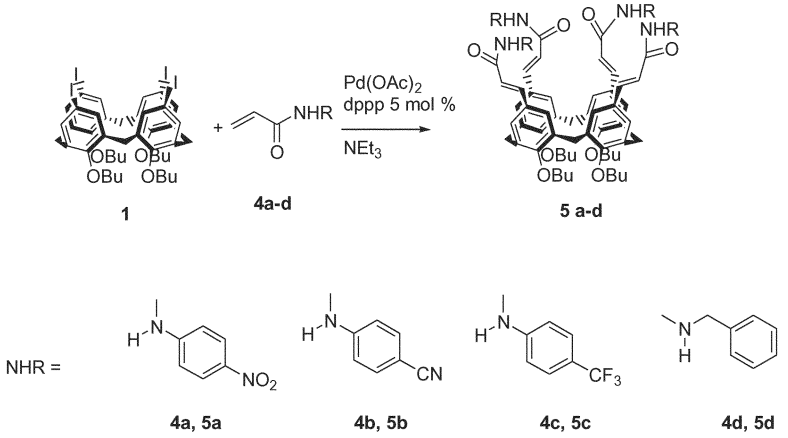

Fig. 2 Heck coupling of secondary acrylamides.

double bond is *trans*, as indicated by their large $^3J_{HC=CH}$ olefinic coupling constants between 14.9 to 15.5 Hz. Yields and selected spectroscopic data are given in Table 1.

Hydrogen bonding and dimerisation

In solvents competing for hydrogen bonding, such as DMSO and acetone, the ^{1}H-NMR spectra of compounds **3a–d** and **5a–d** revealed one set of signals per repeating unit in agreement with their overall C_{4v}-symmetry. In non-polar solvents, such as $CDCl_3$, CD_2Cl_2, $C_2D_2Cl_4$ and C_6D_6, however, the spectra changed completely for compounds **5a–c**. For compounds **5a**, **5b** and **5c** in $CDCl_3$ two sets of signals for the aromatic calix[4]arene protons were apparent. For a detailed description we limit ourselves to compound **5b**. A new sharp set of signals displaying two aromatic signals at unusual high-fields at 5.88 ppm and 6.76 ppm and a N–H proton signal at 11.20 ppm was observed. This observation is indicative of a dimerisation process involving hydrogen bonding that reduces the rotational barrier around the C_{Ar}–C=C bond, hence giving rise to a pair of non-equivalent aromatic protons (see Fig. 3). Both ^{1}H^{1}H-COSY and ^{1}H^{13}C-HMQC spectra confirmed this assignment. The ^{1}H^{15}N-HMQC revealed one cross peak corresponding to the H-bonded N–H of **5b**·**5b** at 136 ppm. Compounds **3a–d**, as tertiary amides lacking the ability to form hydrogen bonds, and compound **5d**, lacking the ability to form a dimer presumably due to a lack of favourable aromatic π–π interactions that further stabilise a dimeric structure, did not show the behaviour described above. Experimental evidence for aromatic π–π interactions can be found in the chemical shifts in the ^{1}H-NMR spectra of the dimeric species in $CDCl_3$. The ESI-mass spectra for the dimeric compounds **5a**·**5a**, **5b**·**5b** and **5c**·**5c** in methanol recorded in the negative ion mode show the dimeric compound with one molecule of methanol included, presumably in the centre of the capsule. As a representative example, the ESI spectra of **5b**·**5b**·**MeOH** with a molecular ion at *m/z* 2689.2 is shown in Fig. 4. In contrast, the FAB mass spectra show the molecular ion of the monomeric calix[4]arene exclusively.

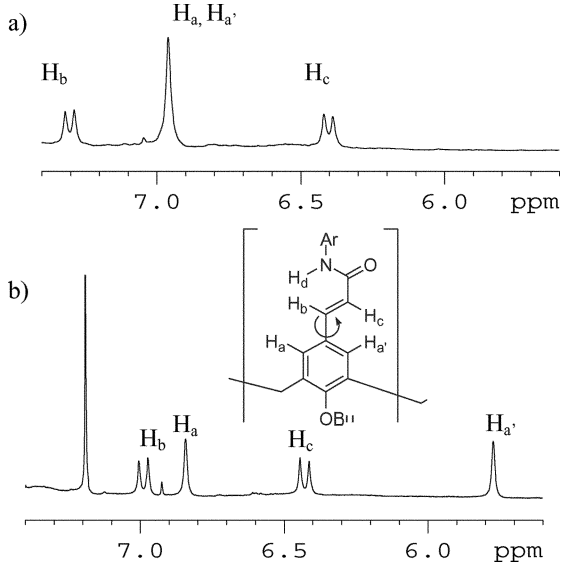

Fig. 3 Expanded 500 MHz ^{1}H-NMR spectra of (a) **5b** (in DMSO) with low barrier of rotation around C_{Ar}–C=C; (b) **5b**·**5b** (in $CDCl_3$) restricted around C_{Ar}–C=C.

We propose structure **5b**·**5b** (Fig. 5 and Fig. 6) for the hydrogen bonded dimer, that is in full agreement with semi-quantitative NOE data and the ASIS effects based on the McConnell equation.[20] The detailed hydrogen bonding is shown in Fig. 6. Dimerisation occurs *via* only eight hydrogen bonds, half the number reported for most previous examples,[4–6] between C=O and N–H moieties of opposing acrylamides. The amide occupies the *trans* geometry in all cases. The capsule geometry resembles topologically the tetra-ureido hydrogen bonded capsules reported by Böhmer and Rebek,[4,6] with a seam of hydrogen bonds in the "equatorial" position. The two halves of the capsules are enantiomeric and the hydrogen bond array forms a cyclic stereogenic element. The electron deficient *p*-CN–aryl

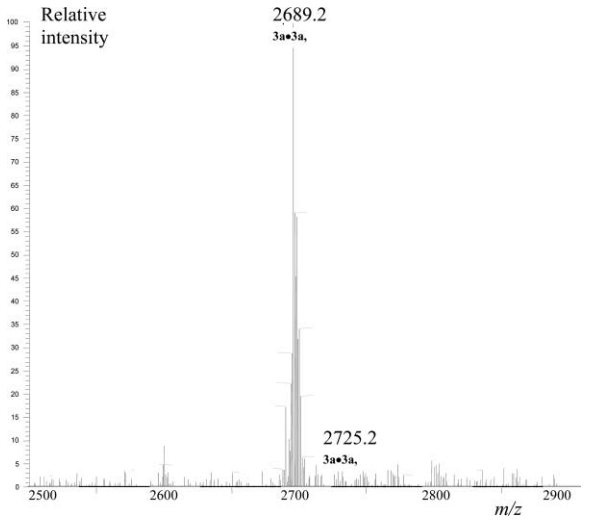

Fig. 4 Expanded region of ESI-mass spectrum of **5b·5b·MeOH** (recorded in the negative ion mode).

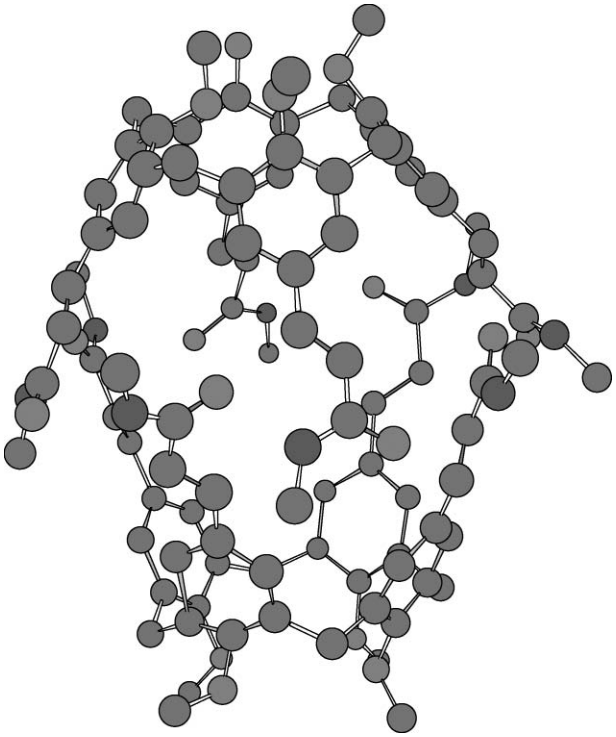

Fig. 5 Proposed 3D structure of dimeric capsule **5b·5b** obtained by ASIS and NOE data (Hs, *n*-Bu and aromatic residues have been omitted for clarity).[13]

group interacts "face to face" with the electron rich aromatic moiety of the calix[4]arene, adding a further element of stability. This interaction follows from the ASIS shift induced on to the high field aromatic calix[4]arene proton $H_{a'}$ at 5.89 ppm (see Fig. 3). The hydrogen bonding array resembles topologically a transverse slice through a β-sheet structure, as discussed above, in which a single amide in one strand binds to a single amide in a second strand in a cyclic manner.

Further evidence for the dimeric capsule structure comes from two classic experiments devised by the Böhmer group.[19,20] The addition of benzene to a $CDCl_3$ solution of **5b·5b** results in the appearance of a high field signal at 4.52 ppm in the ^{1}H-NMR spectrum. A signal at a comparable chemical shift was assigned to a benzene molecule encapsulated in a tetra-ureido calix[4]arene dimer by Böhmer and Cohen.[21] A similar inclusion complex could be observed with the pesticides tetramethyl-thiuram-disulfide **6** or triazine **7** as a guest (Fig. 7). The two methyl resonances of **6** are shifted towards higher field on encapsulation, from *e.g.* 3.52 ppm to 3.21 ppm. The uptake of this guest is relatively slow ($t_{1/2} \sim 36$ h in $CDCl_3$ at 4.1 mM of **6** and **5b·5b**) as estimated by ^{1}H-NMR spectroscopy. Further evidence for the encapsulation of **6** results from diffusion NMR experiments. On encapsulation the diffusion coefficient of **6** changes from 2.08×10^{-10} m^2 s^{-1} to 7.89×10^{-11} m^2 s^{-1}. The latter diffusion coefficient corresponds to the value found for **5b·5b**. Similar changes in diffusion coefficient, along with chemical shift changes in the ^{1}H-NMR spectrum, are observed for the inclusion complex with triazine **5b·5b·7** accompanied by a change of diffusion coefficient from 2.2×10^{-10} m^2 s^{-1} to 7.90×10^{-11} m^2 s^{-1} on encapsulation. Change in a diffusion coefficient is in line with encapsulation, as discussed by Cohen *et al*.[21,22] Encapsulation appears to be irreversible. If inclusion complex **5b·5b·7** is treated with an excess of **6** no exchange of the included guest is apparent after 400 h by ^{1}H-NMR spectroscopy and the same was observed for the reverse experiment, in which inclusion complex **5b·5b·6** was treated with an excess of **7**.

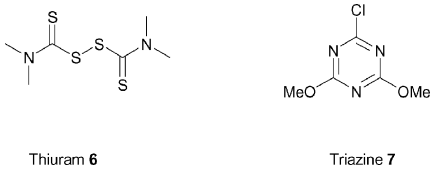

Fig. 7 Encapsulated guest molecules.

Heterodimerisation

Finally, and most importantly, an equimolar mixture of **5a** and **5b** in $CDCl_3$ gives rise to the formation of heterodimeric capsules. In the ^{1}H-NMR spectrum four N–H signals corresponding to the four different N–H protons of the three species present in solution **5a·5a**, **5a·5b** and **5b·5b** are observed in a statistical ratio

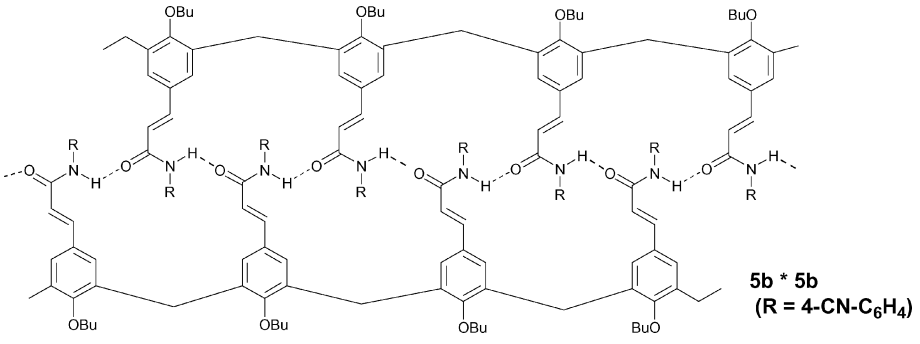

Fig. 6 2D representation of schematic hydrogen-bonding array in dimeric capsule **5b·5b** (note that C–C bonds completing the macrocyclic structure have been omitted for clarity).

of 1 : 2 : 1 at 8.2 mM concentration of a mixture of **5a** and **5b** in $CDCl_3$ (see Fig. 8). The three required molecular ions for the three heterodimeric species can also be observed in the ESI spectra of the mixture of **5b·5b** in methanol in the negative ion mode. Similar heterodimers are observable for mixtures of **5b** and **5c** as well as **5a** and **5c**.

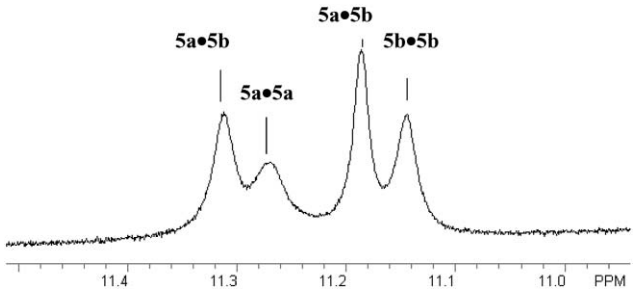

Fig. 8 Expanded 500 MHz ^{1}H-NMR spectrum in $CDCl_3$ of the amide region showing four N–H signals corresponding to **5a·5a**, **5a·5b** and **5b·5b**.

Aggregation in $C_2D_2Cl_4$

Suprisingly, in addition to the dimeric capsule **5b·5b** (in this section referred to as a **5b·5b** (**A**)) we observed a second calix[4]arene species (referred to here as **5b·5b** (**B**)) in CD_2Cl_4, showing almost identical spectral data as compared to **5b·5b** in $CDCl_3$. The second calix[4]arene aggregate displays a full set of broad ^{1}H- and ^{13}C-signals required for a calix[4]arene (see Fig. 9). Regarding the second calix[4]arene assembly **5b·5b** (**B**), we have no unambigious definite structural information but a vast amount of further data that allows some careful suggestions with regard to its chemical nature.

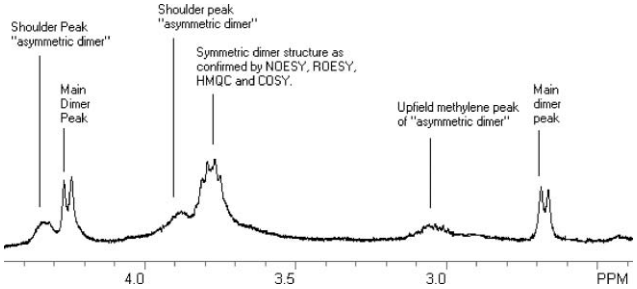

Fig. 9 ^{1}H-NMR spectrum of **5b·5b** (**A**) and **5b·5b** (**B**) in $C_2D_2Cl_4$ (500 MHz).

It has been argued by Rebek and Böhmer[3–5,19] that dimerisation *via* hydrogen bonds of tetraureido calix[4]arenes is templated by small guests and that in the absence of these guests loose hydrogen bonded aggregates are formed, resulting in ill defined, broad NMR spectra. Careful addition of chloroform to the mixture did, however, reveal that the ratio of **5b·5b** (**A**) to **5b·5b** (**B**) remained largely unaffected at low chloroform concentrations. Only by using a chloroform excess of >1000, the concentration of **5b·5b** (**B**) was significantly reduced and the signal intensity of **5b·5b** (**A**) increased. We also considered that an impurity in our $C_2D_2Cl_4$ might affect the dimerisation process, however, no impurities could be detected by GC–MS and NMR spectroscopy. From the ^{1}H-^{1}H-NOESY spectra we can conclude that due to the absence of any exchange peaks between of **5b·5b** (**A**) and **5b·5b** (**B**) the exchange between these species is very slow on the NMR time scale. The signals in the ^{1}H-NMR spectrum corresponding to **5b·5b** (**B**) are broad. Possible explanations for this include a high molecular weight, a dynamic exchange process or both. At lower temperature (−60 °C) the lines of **5b·5b** (**B**) broaden considerably, suggesting approaching coalescence and a dynamic exchange process.

A further calix[4]arene assembly spectroscopically similar to **5b·5b** (**B**), characterised by broad signals at roughly identical chemical shifts can be observed on addition of $\frac{1}{8}$ mol eq. of acrylamide or *p*-CN–Ar–acrylamide to the dimeric structure **5b·5b** in $CDCl_3$ producing **5b·5b·H$_2$NC=OHC=CH$_2$**. Similarily, addition of acrylamide to the two aggregates in $C_2D_2Cl_4$ resulted in the disappearance of the signals corresponding to **5b·5b** (**A**) and a new set of signals corresponding to **5b·5b·H$_2$NC=OHC=CH$_2$** appeared.

A diffusion NMR experiment of **5b·5b** (**B**) in $CDCl_3$ and $C_2D_2Cl_4$ using two well separated high field CH_2 multiplets of the two aggregates revealed the following diffusion constants: 5.3×10^{-9} m^2 s^{-1} for **5b·5b**, 5.3×10^{-9} m^2 s^{-1} for **5b·5b·4b** and 5.4×10^{-9} m^2 s^{-1} for **5b·5b** (**B**). These data clearly indicate that the hydrodynamic radius of all three components is virtually identical. All three aggregates must therefore be dimeric calix[4]arene species, although **5b·5b** (**B**) and **5b·5b·4b** with a reduced symmetry induced by host–guest chemistry.

The nature of the guest molecule interacting with the hydrogen bond motif is subject to some speculation.

^{1}H-NMR spectra of **5b·5b** (**A**) in $C_2D_2Cl_4$ change considerably with increasing temperature. The non-equivalent two singlets of the aromatic protons in the **5b·5b** (**A**) dimeric capsule seem to coalesce into one singlet. Coalescence temperature can be observed around 320 K. This process can be explained by the rupture of the dimeric structure at higher temperatures giving two monomeric **5b**. Alternatively, this NMR behaviour can be rationalised by assuming rapid rotation around Ar–CH= in an intact dimeric structure. Similarly, increasing the temperature of **5b·5b** (**A**) in $C_2D_2Cl_4$ results in the steady collapse of the methylene doublet at δ 2.70 ppm and the growth of a doublet at δ 3.2 ppm, suggesting the adoption of a more pinched cone conformation.

Estimation of dimerisation constant

In any supramolecular system the estimation of the dimerisation constant is important. In the case presented this is not a straightforward task. In the NMR spectra the chemical shift for the monomer in the solvents of interest is unknown and, therefore, a NMR shift titration not feasible. Due to the success of our diffusion NMR experiments we decided to use diffusion NMR to estimate the dimerisation constant. It has been reported that in supramolecular systems the diffusion constant is dependent on the relative concentration of monomer and dimer.[23] The diffusion constant D was determined for compound **5b·5b** for five different concentrations in $CDCl_3$, using a ^{1}H-cryoprobe at 500 MHz with *z*-field gradients. Indeed, a difference in diffusion constant larger than the estimated error of the experiment could be observed. The data obtained are shown in Fig. 10. From the data a dimerisation constant, using standard curve fitting of the appropriate binding model,[23] of 4600 ± 900 M^{-1} was estimated. Due to the relatively large error of the diffusion constant measurements (±10–15%), in particular at low concentrations, an error of 20% was estimated for the dimerisation constant.

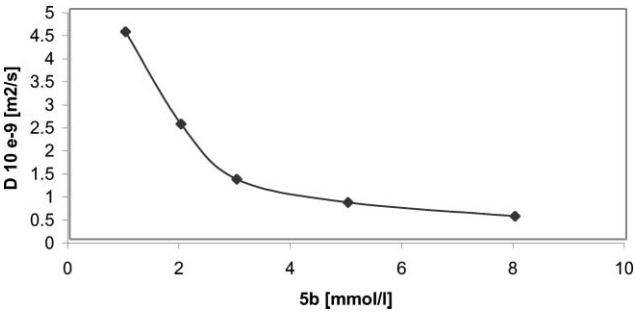

Fig. 10 Plot of diffusion constant D *versus* concentration of **5b** in $CDCl_3$.

Extended Acrylamides

Following the observation that tetra-acrylamido calix[4]arenes derived from secondary acrylamides form dimeric capsules in solution, we decided to synthesise compounds that display two such hydrogen bonding motifs. In this case it might be possible to obtain dimeric capsules of different sizes from the same monomer and eventually control the size by judicious choice of conditions. Hence, we reduced nitro compound **5a** using stannous chloride to give tetra-amine **8** in moderate yield. Acetylation of **8** gave octa-amide **9**, displaying two distinct sets of hydrogen bonding motifs (Fig. 11). However, the purity of **9** was unsatisfactory and we obtained **9** in an alternative synthetic approach using a direct Heck coupling strategy as before, this time to obtain **9** in satisfactory purity. The spectroscopic data of **8** and **9** are as expected and mirror those of **3a–d** and **5a–d**. Unfortunately, **9** is only soluble in DMSO and not in unpolar solvents such as chloroform, which thus prevents any detailed analysis of the dimerisation process in less polar solvents as discussed above.

Conclusion

We have synthesised tetra-acrylamido upper rim calix[4]arene derivatives and applied the Heck reaction to the synthesis of functionalised calix[4]arenes. All reactions proceed in good yield and give stereoselectively the all-*trans* tetra-olefinic calix[4]arenes.

Calix[4]arenes derived from secondary acrylamides have been shown to dimerise in non polar solvents to give molecular capsules using eight N–H–O=C hydrogen bonds and a series of aromatic aromatic interactions.

Experimental

^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL GSX 270 MHz and a Bruker Avance 500 MHz spectrometer, δ values are quoted relative to teramethylsilane (δ_H 0.00 ppm) or chloroform (δ_H 7.23 ppm) for ^{1}H-NMR and relative to chloroform (δ_C 77.0 ppm) for ^{13}C-NMR. Coupling constants J are in Hz. Microanalysis were carried out using a Leeman CE 440 automatic elemental analyser. Due to the hygroscopic nature of the calix[4]arenes, water inclusion molecules are incorporated into the microanalytical data. Infrared spectra were determined on a Perkin Elmer 200 Spectrometer. The FAB and CI mass spectra were recorded using a ThermoQuest Finnigan MAT 95 XL spectrometer. ESI-MS spectra were recorded on a ThermoFinnigan DECA CQXP Plus.

Thin layer chromatography (TLC) was carried out on commercially available precoated plates (Merck Kieselgel 60 F254 silica) using 1 : 3 ethylacetate–hexane as a solvent sysytem. Flash column chromatography at a pressure of 1 bar was carried out on Merck Kieselgel 60 (230–400 mesh) silica. All chemicals/reagents were purchased from the Aldrich Chemical Company. Solvents were dried using the usual procedures and reagents used without further purification unless stated otherwise. Calix[4]arenes **1** were prepared according to the literature procedure.[14]

General procedure for the preparation of acrylamides

Et_3N (8.23 ml) and the amine (27 mmol) were stirred in DCM 75 ml for 10 min at rt. Acryloyl chloride (2.66 ml) was very slowly added with the temperature being maintained at rt. The reaction was monitored *via* TLC or NMR. Upon completion, the reaction was quenched with iced water (200 ml) and the organic component extracted with DCM (3 × 50 ml). The combined organic extracts were washed with HCl (3 × 40 ml, 3 M), water (2 × 50 ml) NaOH (3 × 30 ml, 2 M) and again with water (2 × 50 ml). The organic extract was dried (Na_2SO_4), filtered and evaporated under a reduced pressure. Solid acrylamides could be recrystalised from hot methanol and all acrylamides were stored below 0 °C or used immediately.

Diethylacrylamide 2a[24]. Pale yellow oil (78%); δ_H(270 MHz; $CDCl_3$) 6.25 (1H, dd, J 17.4, 10.2 H_c), 7.40 (1H, d, J 17.4, H_c), 5.62 (1H, d, J 10.2, H_d), 3.32 (4H, q, J 5.8, H_h), 1.10 (6H, t, J 5.8, H_a).

Benzylacrylamide 4d[24]. Pale orange shards (78%); δ_H(500 MHz; $CDCl_3$) 7.32–7.24 (5H, m, H_a, H_b, H_c), 6.52 (1H, s (broad), H_g), 6.28 (1H, dd, J 17.8, 1.4 H_e), 7.40 (1H, dd, J 17.8, 10.3, H_d), 5.62 (1H, dd, J 10.3, 1.4, H_f), 4.46 (2H, d, J 5.6, H_h).

5,11,17,23-Tetrakis[(*E*)-*N*-(diethyl)-acrylamido]-25,26,27,28-tetra-*n*-butoxycalix[4]arene 3a. Triethylamine (0.335 ml, 0.157 g, 1.56 mmol) and diethylacrylamide **2a** (0.264 g, 2.08 mmol) was added to a stirred solution of 5,11,17,23-tetraiodocalixarene-25,26,27,28-tetra-*n*-butylether (0.3 g, 0.26 mmol) **1** in DMF (20 ml). After 10 min of vigorous stirring at 25 °C, palladium acetate (0.006 g, 0.026 mmol) and diphenylphosphinopropane (0.011 g, 0.026 mmol) were added, the mixture heated to 100 °C and stirred for 300 h.

After addition of 50 ml diethylether the mixture was washed with HCl (3 × 20 ml, 3 M). The organic extract was dried (Na_2SO_4), filtered and evaporated under a reduced pressure. The residue was further dried in a desiccator (SiO_2) under a reduced pressure for 12 h and purified *via* column chromatography (SiO_2, EtOAc–hexane 1 : 1) to give the calix[4]arene **3a** (0.15 g, 51%) as off-white cubes; mp 120–122 °C; ν_{max} (Nujol)/cm^{-1} 1620 (C=C), 1645 (C=O); δ_H(270 MHz; $CDCl_3$) 7.31 (4H, d, J 16.0, Ar–CH=), 6.81 (8H, s, Ar–H), 6.39 (4H, d, J 16.0, Ar–CH=CH–C=O), 4.41 (4H, d, J 13.4, CH_AH$_B$Ar), 3.83 (8H, t, J 6.4, CH_2O), 3.4–3.2 (16H, m, NCH_2), 3.19 (4H, d, J 13.4, CH$_A$$H_B$Ar), 1.90 (8H, m, C$H_2CH_2$O), 1.50–1.35 (8H, m, OCHCH$_2$CH_2), 1.05–1.20 (24H, m NCH$_2$CH_3), 1.00 (12H, t, J 8.3, CH_3CH$_2$); δ_c ($CDCl_3$) 164.7, 159.4, 142.6, 126.3, 124.5, 123.2, 119.8, 72.2, 45.6, 40.3, 32.3, 31.2, 19.4, 14.1, 13.2; m/z (EI) 1149 [M+].

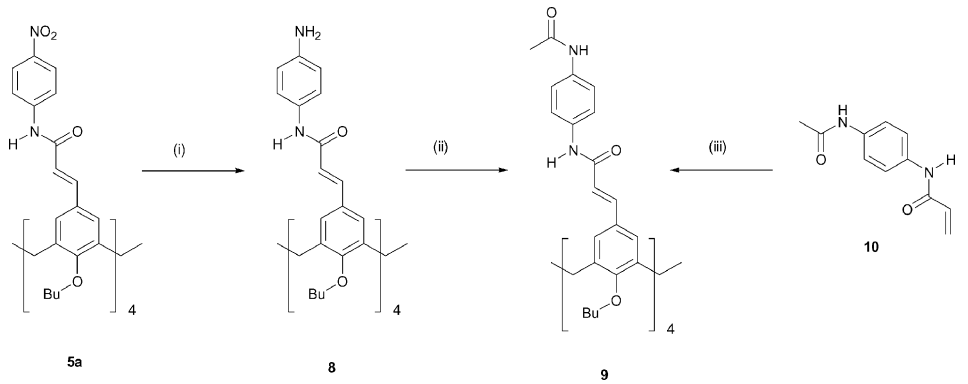

Fig. 11 *Reagents and conditions*: (i) $SnCl_2$–HCl; (ii) Ac_2O, NEt_3; (iii) **1**, NEt_3–15% $Pd(OAc)_2$, dppp, DMF, 100 °C, 275 h.

Found C, 68.95; H, 8.37; N, 4.56% $C_{72}H_{100}O_8N_4{\cdot}6H_2O$ requires C, 68.76; H, 8.98; N, 4.50%.

5,11,17,23-Tetrakis[(*E*)-*N*-(piperidyl)-acrylamido]-25,26,27,28-tetra-*n*-butoxycalix[4]arene 3b. Triethylamine (0.335 ml, 0.157 g, 1.56 mmol) and piperidylacrylamide **2b** (0.289 g, 2.08 mmol) were added to a stirred solution of 5,11,17,23-tetraiodocalixarene-25,26,27,28-tetra-*n*-butylether (0.3 g, 0.26 mmol) **1** in DMF (20 ml). After 10 min of vigorous stirring at 25 °C, palladium acetate (0.006 g, 0.026 mmol) and diphenylphosphinopropane (0.011 g, 0.026 mmol) were added, the mixture heated to 100 °C and stirred for 325 h.

After addition of 50 ml diethylether the mixture was washed with HCl (3 × 20 ml, 3 M). The organic extract was dried (Na_2SO_4), filtered and evaporated under a reduced pressure. The residue was further dried in a desiccator (SiO_2) under a reduced pressure for 12 h and recrystalised from hot methanol to give the calix[4]arene **3b** (0.17 g, 55%) as off-white cubes; mp 88–90 °C; ν_{max} (Nujol)/cm^{-1} 1646 (C=O), 1605 (C=C); δ_H(270 MHz; $CDCl_3$) 7.28 (4H, d, *J* 15.1, Ar–CH=), 6.82 (8H, s, Ar–H), 6.49 (4H, d, *J* 15.1, Ar–CH=C*H*–C=O), 4.41 (4H, d, *J* 13.2, CH_AH$_B$Ar), 3.90 (8H, t, *J* 7.4, CH_2O), 3.6–3.4 (16H, m, CH_2NCH_2), 3.20 (4H, d, *J* 13.2, CH_AH_BAr), 1.90 (8H, m, CH_2CH_2O), 1.70–1.40 (32H, m, $OCHCH_2CH_2$ and $CH_2CH_2CH_2CH_2NCH_2$), 1.00 (12H, t, *J* 8.3, CH_3CH_2); δ_C ($CDCl_3$) 165.9, 158.2, 142.3, 136.1, 130.1, 128.8, 115.9, 75.5, 47.1, 43.3, 32.5, 30.8, 26.7, 24.7, 19.5, 14.1; *m/z* (EI) 1198 [M+]. Found C, 75.10; H, 8.23; N, 4.52% $C_{76}H_{100}N_4O_8{\cdot}H_2O$ requires C, 75.09; H, 8.46; N, 4.61%.

5,11,17,23-Tetrakis[(*E*)-*N*-(morpholinyl)-acrylamido]-25,26,27,28-tetra-*n*-butoxycalix[4]arene 3c. Triethylamine (0.335 ml, 0.157 g, 1.56 mmol) and acryloylmorpholine **2c** (0.294 g, 2.08 mmol) were added to a stirred solution of 5,11,17,23-tetraiodocalixarene-25,26,27,28-tetra-*n*-butylether (0.3 g, 0.26 mmol) **1** in DMF (20 ml). After 10 min of vigorous stirring at 25 °C, palladium acetate (0.006 g, 0.026 mmol) and diphenylphosphinopropane (0.011 g, 0.026 mmol) were added and the mixture heated to 100 °C and stirred for 275 hrs.

After addition of 50 ml diethylether the mixture was washed with HCl (3 × 20 ml 3 M HCl). The organic extract was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was further dried in a desiccator (SiO_2) under reduced pressure for 12 hrs and recrystalised from methanol to give the calix[4]arene **3c** (0.14 g, 40%) as light brown cubes; mp 254–256 °C; ν_{max} (Nujol)/cm^{-1} 1645 (C=C) 1620 (C=O); δ_H(270 MHz; $CDCl_3$) 7.32 (4H, d, *J* 15.5, Ar–CH=), 6.82 (8H, *J* 13.4, s, Ar–H), 6.46 (4H, d, *J* 15.5, Ar–CH=C*H*–C=O), 4.42 (4H, d, *J* 13.5, CH_AH$_B$Ar), 3.90 (8H, t, *J* 7.5, CH_2O), 3.73–3.56 (16H, m, H_2COCH_2), 3.72–3.70 (16H, m, $H_2CN(CO)CH_2$), 3.19 (4H, d, *J* 13.5, CH_AH_BAr), 1.90–1.88 (8H, m, CH_2CH_2O), 1.50–1.44 (8H, m, $OCHCH_2CH_2$), 1.00 (12H, t, *J* 8.3, CH_3CH_2); δ_C ($CDCl_3$) 165.7, 158.3, 143.1, 135.3, 129.4, 128.0, 114.3, 75.2, 66.8, 45.5, 42.1, 32.3, 30.9, 19.3, 14.1; *m/z* (EI) 1206 [M+]. Found C, 65.49; H, 7.35; N, 4.13% $C_{72}H_{92}N_4O_{12}{\cdot}6H_2O$ requires C, 65.83; H, 7.98; N, 4.27%.

5,11,17,23-Tetrakis[(*E*)-*N*-(methylbenzyl)-acrylamido]-25,26,27,28-tetra-*n*-butoxycalix[4]arene 3d. Triethylamine (0.335 ml, 0.157 g, 1.56 mmol) and methylbenzylacrylamide **2d** (0.364 g, 2.08 mmol) were added to a stirred solution of 5,11,17,23-tetraiodocalixarene-25,26,27,28-tetra-*n*-butylether (0.3 g, 0.26 mmol) **1** in DMF (20 ml). After 10 min of vigorous stirring at 25 °C, palladium acetate (0.006 g, 0.026 mmol) and diphenylphosphinopropane (0.011 g, 0.026 mmol) were added, the mixture heated to 100 °C and stirred 325 h. After addition of 50 ml diethylether the mixture was washed with HCl (3 × 20 ml, 3 M). The organic extract was dried (Na_2SO_4), filtered and evaporated under a reduced pressure. The residue was further dried in a desiccator (SiO_2) under a reduced pressure for 12 h and purified *via* column chromatography (1 : 5 EtOAc–Hexane, SiO_2) to give the calix[4]arene **3d** (0.19 g, 55%) as brown cubes; mp 98–100 °C; ν_{max} (Nujol)/cm^{-1} 1607 (C=C), 1648(C=O); δ_H(270 MHz; $CDCl_3$) 7.50–7.16 (24H, m, Ar–CH= and Ar–H (benzyl)), 6.80–6.62 (8H, s, Ar–H), 6.41–6.5 (4H, m, Ar–CH=C*H*–C=O), 4.69 (4H, m, CH_AH$_B$Ar), 4.35 (8H, m, CH_2Ar), 4.0–3.6 (8H, m, CH_2O), 3.19 (4H, d, *J* 13.4, CH_AH_BAr), 3.01 (12H, s, CH_3N), 1.90 (8H, m, CH_2CH_2O), 1.50–1.35 (8H, m, $OCHCH_2CH_2$), 1.00 (12H, t, *J* 8.3, CH_3CH_2). δ_C ($CDCl_3$) 167.5, 158.1, 143.0, 142.8, 137.2, 129.6, 128.4, 127.7, 127.6, 122.6, 115.3, 75.1, 53.6, 32.7, 32.4, 30.9, 19.4, 14.1; *m/z* (EI) 1342 [M+]. Found C, 73.20; H, 7.71; N, 3.75% $C_{88}H_{100}N_4O_8{\cdot}5H_2O$ requires C, 73.82; H, 7.74; N, 3.91%.

5,11,17,23-Tetrakis[(*E*)-*N*-(4-nitrophenyl)-acrylamido]-25,26,27,28-tetra-*n*-butoxycalix[4]arene 5a. Triethylamine (0.335 ml, 0.157 g, 1.56 mmol) and 4-nitrophenylacrylamide **4a** (0.399 g, 2.08 mmol) were added to a stirred solution of 5,11,17,23-tetraiodocalixarene-25,26,27,28-tetra-*n*-butylether (0.3 g, 0.26 mmol) **1** in DMF (20 ml). After 10 min of vigorous stirring at 25 °C, palladium acetate (0.006 g, 0.026 mmol) and diphenylphosphinopropane (0.011 g, 0.026 mmol) were added, the mixture heated to 100 °C and stirred for 48 hrs.

After addition of 50 ml DCM the mixture was washed with HCl (3 × 20 ml, 3 M). The organic extract was dried (Na_2SO_4), filtered and evaporated under a reduced pressure. The residue was further dried in a desiccator (SiO_2) under a reduced pressure for 12 h and recrystalised from hot methanol to give the calix[4]arene **5a** (0.15 g, 51%) as off-white cubes; mp 151–154 °C; ν_{max} (Nujol)/cm^{-1} 3384 (N–H), 1748 (C=O), 1615 (C=C); δ_H(270 MHz; d_6-DMSO) 10.65 (4H, s, NH), 8.05 (8H, d, *J* 9.0, Ar–H (nitrobenzene)), 7.36 (8H, d, *J* 9.0, Ar–H (nitrobenzene), 7.37 (4H, d, *J* 15.5, Ar–CH=), 7.00 (8H, s, Ar–H), 6.48 (4H, d, *J* 15.5, Ar–CH=C*H*–C=O), 4.44 (4H, d, *J* 13.5, CH_AH$_B$Ar), 3.96 (8H, t, *J* 6.8, CH_2O), 3.37 (4H, d, *J* 13.5, CH_AH_BAr), 1.90 (8H, m, CH_2CH_2O), 1.50–1.47 (8H, m, $OCHCH_2CH_2$), 1.02 (12H, t, *J* 8.3, CH_3CH_2); δ_c (d_6-DMSO) 165.0, 158.9, 146.3, 142.6, 142.3, 135.8, 129.1, 128.8, 125.6, 126.1, 119.7, 75.2, 36.2, 32.5, 19.2, 14.2; *m/z* (EI) 1409 [M+]; found C, 66.88; H, 5.52; N, 7.60% $C_{80}H_{80}N_8O_{16}{\cdot}2H_2O$ requires C, 66.47; H, 5.86; N, 7.75%.

5,11,17,23-Tetrakis[(*E*)-*N*-(4-cyanophenyl)-acrylamido]-25,26,27,28-tetra-*n*-butoxycalix[4]arene 5b. Triethylamine (0.335 ml, 0.157 g, 1.56 mmol) and 4-cyanophenylacrylamide **4b** (0.33 g, 2.08 mmol) were added to a stirred solution of 5,11,17,23-tetraiodocalixarene-25,26,27,28-tetra-*n*-butylether **1** (0.3 g, 0.26 mmol) in DMF (20 ml). After 10 min of vigorous stirring at 25 °C, palladium acetate (0.006 g, 0.026 mmol) and diphenylphosphinopropane (0.011 g, 0.026 mmol) were added, the mixture heated to 100 °C and stirred for 24 h. After addition of 50 ml DCM the mixture was washed with HCl (3 × 20 ml, 3 M). The organic extract was dried (Na_2SO_4), filtered and evaporated under a reduced pressure. The residue was further dried in a desiccator (SiO_2) under a reduced pressure for 12 h and purified *via* column chromatography (SiO_2, EtOAc–hexane 1 : 2) to give the calix[4]arene **5b** (0.19 g, 55%) as off-white cubes; mp 180–183 °C; ν_{max} (Nujol)/cm^{-1} 3312 (N–H), 2228 (CN), 1686 (C=O), 1604 (C=C); δ_H(500 MHz; d_6-DMSO) 10.43 (4H, s, NH), 7.72 (8H, d, *J* 8.8, Ar–H (benzenenitrile)), 7.61 (8H, d, *J* 8.8, Ar–H (benzenenitrile)), 7.32 (4H, d, *J* 15.5, Ar–CH=), 6.97 (8H, s, Ar–H), 6.42 (4H, d, *J* 15.5, Ar–CH=C*H*–C=O), 4.41 (4H, d, *J* 13.8, CH_AH$_B$Ar), 3.93 (8H, t, *J* 6.4, CH_2O), 3.31 (4H, d, *J* 13.8, CH_AH_BAr), 1.90 (8H, m, CH_2CH_2O), 1.50–1.38 (8H, m, $OCHCH_2CH_2$), 1.00 12H, t, *J* 8.3, CH_3CH_2); δ_H (500 MHz; $CDCl_3$) 11.20 (8H, s, NH), 8.21 (8H, d, *J* 8.7, Ar–H (benzenenitrile)), 7.72 (8H, d, *J* 8.7, Ar–H (benzenenitrile)), 7.05 (4H, d, *J* 15.5, Ar–CH=), 6.84 (4H, s, Ar–H), 6.42 (4H, d, *J* 15.5, Ar–CH=C*H*–C=O), 5.77 (4H, s, Ar–H), 4.22 (4H, d, *J* 11.8, CH_AH$_B$Ar), 3.74 (8H, dd, *J* 12.7 *J* 8.1, CH_2O), 2.63 (4H, d, *J* 11.8, CH_AH_BAr), 1.92 (8H, m,

CH_2CH_2O), 1.44–1.20 (8H, m, $OCHCH_2CH_2$), 1.00 (12H, t, *J* 8.3, CH_3CH_2); δ_c (d_6-DMSO) 167.4, 155.2, 139.9, 139.2, 134.6, 133.9, 127.1, 122.7, 120.3, 119.9, 116.2, 96.3, 76.6, 32.5, 33.0, 19.7, 15.1; *m/z* (LSIMS) 1329 [M+]; *m/z* (ESI, negative ion mode in MeOH) 2689.2 [M_2^- + CH_3OH] $C_{165}H_{164}N_{16}O_{17}$; found C, 75.79; H, 6.37; N, 8.29% $C_{84}H_{80}N_8O_8$ requires C, 75.88; H, 6.06; N, 8.43%.

5,11,17,23-Tetrakis[(*E*)-*N*-(4-trifluoromethylphenyl)-acrylamido]-25,26,27,28-tetra-*n*-butoxycalix[4]arene 5c. Triethylamine (0.335 ml, 0.157 g, 1.56 mmol) and 4-trifluoromethylphenylacrylamide **4c** (0.399 g, 2.08 mmol) were added to a stirred solution of 5,11,17,23-tetraiodocalixarene 25,26,27,28-tetra-*n*-butylether (0.3 g, 0.26 mmol) **1** in DMF (20 ml). After 10 min of vigorous stirring at 25 °C, palladium acetate (0.006 g, 0.026 mmol) and diphenylphosphinopropane (0.011 g, 0.026 mmol) were added, the mixture heated to 100 °C and stirred for 175 h.

After cooling to rt and addition of HCl (50 ml, 2 M) the mixture was filtered and the residue washed with water (100 ml) and methanol (100 ml). The organic extract was dried (Na_2SO_4), filtered and evaporated under a reduced pressure. The residue was further dried in a desiccator (SiO_2) under a reduced pressure for 12 h and recrystalised from methanol to give the calix[4]arene **5c**; mp 235–240 °C; δ_H(300 MHz; d_6-DMSO) 10.34 (4H, s, HNCO), 7.69 (8H, d, *J* 10.0, Ar–H (triflouromethylaniline)), 7.43 (8H, d, *J* 10.0, Ar–H (triflouromethylaniline), 7.25 (4H, d, *J* 15.10, Ar–CH=), 6.92 (8H, s, Ar–H), 6.27 (4H, d, *J* 15.20, CH–C=O), 4.35 (4H, d, *J* 13.8, CH_AH_BAr), 3.89 (8H, q, *J* 6.3, OCH_2CH_2), 3.30 (4H, d, *J* 13.8, CH_AH_BAr), 1.89–1.72 (8H, m, CH_2CH_2O), 1.47–1.37 (8H, m, $OCH_2CH_2CH_2$), 0.94 (12H, t, *J* 8.2, CH_3CH_2); δ_C (d_6-DMSO) 164.5, 143.3, 141.4, 136.7, 135.7, 129.3, 129.1, 128.1, 126.7, 126.4, 126.3, 119.2, 74.9, 32.0, 30.5, 18.9, 14.0; *m/z* (LSIMS) 1525 [M + 1H + Na)]; found C, 64.63; H, 5.53; N, 4.59% $C_{84}H_{80}F_{12}O_8N_4\cdot 2DMF$ requires C, 65.60; H, 5.75; N, 5.10%.

5,11,17,23-Tetrakis[(*E*)-*N*-(benzyl)-acrylamido]-25,26,27,28-tetra-*n*-butoxycalix[4]arene 5d. Triethylamine (0.314 ml, 0.210 g, 2.083 mmol) and benzylacrylamide **4d** (0.251 g, 1.56 mmol) were added to a stirred solution of 5,11,17,23-tetraiodocalixarene-25,26,27,28 tetra-*n*-butylether (0.3 g, 0.26 mmol) **1** in DMF (20 ml). After 10 min of vigorous stirring at 25 °C, palladium acetate (0.006 g, 0.026 mmol) and diphenylphosphinopropane (0.011 g, 0.026 mmol) were added, the mixture heated to 100 °C and stirred for 48 h.

After addition of 50 ml DCM the mixture was washed with HCl (3 × 20 ml, 3 M). The organic extract was dried (Na_2SO_4), filtered and evaporated under a reduced pressure. The residue was further dried in a desiccator (SiO_2) under a reduced pressure for 12 h and recrystalised from hot methanol to give the calix[4]arene **5d** (0.21 g, 65%) as pale brown cubes; mp 151–154 °C; ν_{max} (Nujol)/cm^{-1} 3275 (N–H), 1656 (C=O), 1542 (C=C); δ_H(270 MHz; $CDCl_3$) 7.31–7.19 (24H, m, Ar–CH= & Ar–H (benzyl)), 6.74 (8H, s, Ar–H), 6.09 (4H, d, *J* 15.5, Ar–CH=C*H*–C=O), 4.51 (8H, d, 5.7, CH_2NH), 4.41 (4H, d, *J* 13.9, CH_AH_BAr), 3.88 (8H, t, *J* 7.8, CH_2O), 3.12 (4H, d, *J* 13.9, CH_AH_BAr), 1.90 (8H, m, CH_2CH_2O), 1.46–1.39 (8H, m, $OCHCH_2CH_2$), 1.00 (12H, t, *J* 8.3, CH_3CH_2); δ_C ($CDCl_3$) 165.0, 157.2, 138.3, 134.7, 128.9, 128.2, 128.1, 128.0, 127.5, 127.3, 126.6, 76.6, 43.7, 32.2, 30.1, 19.7, 14.1. *m/z* (EI) 1286 [M+]; found C, 75.95; H, 7.17; N, 4.26% $C_{84}H_{92}N_4O_8\cdot 2H_2O$ requires C, 76.33; H, 7.32; N, 4.24%.

5,11,17,23-Tetrakis[(*E*)-*N*-(4-aminophenyl)-acrylamido]-25,26,27,28-tetra-*n*-butoxycalix[4]arene 8. $SnCl_2\cdot 2H_2O$ (0.478 g, 2.2 mmol) was added to a stirred solution of 5,11,17,23-tetranitrophenylacrylamidocalixarene-25,26,27,28-tetra-*n*-butylether **5a** (0.15 g, 0.12 mmol) in ethanol (25 ml). After 6 h of vigorous reflux, the mixture was poured onto ice 100 g and the pH adjusted to 8 with NaOH (2 M). The product was extracted with DCM (2 × 100 ml) and the organic layer stirred with distilled water (300 ml) for 5 h. Separation of the organic layer preceded the removal of the solvent under a reduced pressure. The residue was further dried in a desiccator (SiO_2) under a reduced pressure for 12 h to give the calix[4]arene **8** (60 mg, 33%) as light brown shards; mp 120–123; ν_{max} (Nujol)/cm^{-1} 3501 (N–H), 3384 (N–H (amide)), 1748 (C=O), 1615 (C=C); δ_H(270 MHz; d_6-DMSO) 9.62 (4H, s, NH), 7.33 (8H, d, *J* 7.8, Ar–H (aminobenzene)), 7.22 (4H, d, *J* 15.5, Ar–CH=), 7.04 (8H, s, Ar–H), 6.48 (8H, d, *J* 7.8, Ar–H (aminobenzene)), 6.39 (4H, d, *J* 15.5, Ar–CH=C*H*–C=O), 4.80 (8H, s, NH_2), 4.38 (4H, d, *J* 11.8, CH_AH_BAr), 3.92 (8H, t, *J* 6.4, CH_2O), 3.22 (4H, d, *J* 11.8, CH_AH_BAr), 1.90 (8H, m, CH_2CH_2O), 1.46–1.39 (8H, m, $OCHCH_2CH_2$), 1.00 (12H, t, *J* 8.3, CH_3CH_2); δ_c (d_6-DMSO) 151.4, 143.9, 143.5, 138.1, 134.7, 127.1, 126.9, 122.7, 120.7, 120.3, 113.9, 75.2, 36.2, 32.5, 19.2, 14.2; *m/z* (LSMIS) 1289 [M+]; found C, 71.75; H, 6.95; N, 8.00% $C_{80}H_{88}N_8O_8\cdot 2H_2O$ requires C, 72.48; H, 7.00; N, 8.45%.

5,11,17,23-Tetrakis[(*E*)-*N*-(4-acetamidophenyl)-acrylamido]-25,26,27,28-tetra-*n*-butoxycalix[4]arene 9. Triethylamine (0.335 ml, 0.157 g, 1.56 mmol) and 4-acrylamidephenylacetamide (0.428 g, 2.10 mmol) were added to a stirred solution of 5,11,17,23-tetraiodocalixarene-25,26,27,28-tetra-*n*-butylether (0.3 g, 0.26 mmol) **1** in DMF (20 ml). After 10 min of vigorous stirring at 25 °C, palladium acetate (0.006 g, 0.026 mmol) and diphenylphosphinopropane (0.011 g, 0.026 mmol) were added, the mixture heated to 100 °C and stirred for 275 h.

After addition of 50 ml HCl (2 M) the mixture was filtered and washed with water (100 ml) and methanol (100 ml). The organic extract was dried (Na_2SO_4), filtered and evaporated under a reduced pressure. The residue was further dried in a desiccator (SiO_2) under a reduced pressure for 12 h and recrystalised from hot methanol to give the calix[4]arene **9** (0.15 g, 49%) as dark brown microcrystals; mp 219–221 °C; ν_{max} (Nujol)/cm^{-1} 3398 (N–H), 3384 (N–H), 1748 (C=O), 1732 (C=O), 1615 (C=C); δ_H(300 MHz; d_6-DMSO) 10.33 (4H, s, CH_3CONH), 9.89 (4H, s, C=CHCON*H*), 7.50 (8H, d, *J* 8.3, Ar–H (anilide)), 7.40 (8H, d, *J* 8.3, Ar–H (anilide)), 7.38 (4H, d, *J* 15.9, Ar–CH=), 7.00 (8H, s, Ar–H), 6.49 (4H, d, *J* 15.9, Ar–CH=C*H*–C=O), 4.39 (4H, d, *J* 12.1, CH_AH_BAr), 3.93 (8H, t, *J* 6.8, CH_2O), 3.37 (4H, d, *J* 12.1, CH_AH_BAr), 2.02 (12H, s, CH_3CON), 1.90 (8H, m, CH_2CH_2O), 1.50–1.47 (8H, m, $OCHCH_2CH_2$), 1.02 (12H, t, *J* 8.3, CH_3CH_2); δ_c (d_6-DMSO) 169.2, 165.0, 158.9, 146.3, 142.6, 135.8, 129.1, 129.0, 128.8, 125.6, 126.1, 119.7, 75.2, 36.2, 32.5, 24.8, 19.2, 14.2; *m/z* (EI) 1481[M + Na]; found C, 69.86; H, 6.20; N, 6.61% $C_{88}H_{96}N_8O_{12}\cdot 4H_2O$ requires C, 69.09; H, 6.85; N, 7.32%.

Diffusion NMR spectra

Diffusion NMR spectra were obtained following the procedure of: E. J. Cabrita and S. Berger, *Magn. Reson. Chem.*, 2001, **39**, 142. Typical conditions for diffusion NMR spectra using a Bruker AMX 500 Avance instrument with standard Bruker diffusion software were as follows: δ = 3 ms, Δ = 35 ms, ten gradients from 98% to 2% using 256 scans each, using a field gradient tritium/proton cryoprobe.

Acknowledgements

We would like to thank the EPSRC for a studentship for A. L. G. and the European Union for further financial support (project "Pesticide"; No. ICA2-CT-2000-10002). Furthermore, N. K. would like to thank Prof. A. Danil de Namor, Prof. P. Sammes and Dr S. Faulkner for helpful discussions and Ms J. Peters, Mr R. Chaundy, Ms N. Walker and Mr J. Bloxsidge for their excellent technical support. We acknowledge the excellent service of the EPSRC National Mass Spectrometry Service in Swansea.

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