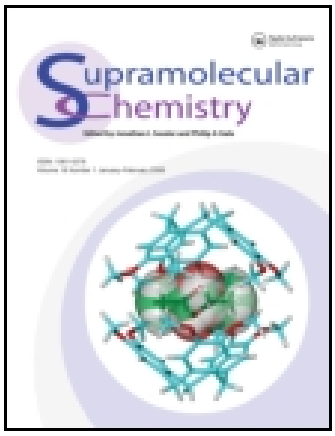

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Calix[3]amide-based anion receptors: high affinity for fluoride ions and a twisted binding model

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Tris-phenylurea-substituted calix[3]amides (**3a**, **3b**) and tris-phenylthiourea-substituted calix[3]amides (**4a**, **4b**) were synthesised by the reaction of amine with isocyanates and thioisocyanate, respectively. Single crystal X-ray analysis revealed that the cyclic trimers adopt a *syn* conformation with all of the urea groups on the same side. The binding affinities of these compounds towards anions were measured using ^{1}H NMR titrations in DMF-d_7, DMSO-d_6 or $CDCl_3$. Each receptor was observed to bind halogen anions in a 1:1 stoichiometry, exclusively through hydrogen bonding, and the anion selectivity was in the order $F^- > Cl^- \gg Br^- > I^-$. DFT calculations revealed that the fluoride anion is anchored in the centre of the six N—H hydrogen atoms of **3a** through H···F interactions.

Keywords: calix[3]amide; anion receptor; DFT calculations

Introduction

In recent years, the development of anion receptors has become a major area of supramolecular chemistry because anion receptors serve as models of biological processes and have potential uses in the design of sensors for medical applications (*1*). In the design of anion receptors, macrocyclic structures were utilised because they provide a well-defined host environment for guest inclusion (*2*). During the last two decades, calixarenes have been widely used in the field of host–guest chemistry as building blocks or molecular scaffolds for the construction of various receptors (*3–5*). Anion receptors that are based on the calixarenes have recognition sites such as amides (*6*), urea/thiourea (*7*) and pyrroles (*8*), which establish hydrogen-bonding (H-bonding) interactions with anions that bind these receptors. In particular, urea and thiourea are promising functional groups for designing anion receptors because they have two N—H fragments, which can bind a single atom anion with a six-membered chelate ring (*7*). In the course of our studies on cyclic aromatic amides (calixamides), we found that the calix[3]amides were obtained with larger ring sizes by macrocyclisation reactions of 3-*N*-alkylaminobenzoic acids (*9*). Moreover, these produced calix[3]amides have a small bowl-shaped cavity which should bind anions if appropriate functional groups are present. In a previous paper, we reported the synthesis and the crystal structures of calix[3]amides with nitro or amino groups. The structures of these calix[3]-amides were dimers, in which the cavity of one molecule was filled with the functional group of the other molecule (*9*), suggesting that the cavity would act as a binding site for guest molecules. Herein we report the synthesis of tris-urea/thiourea-substituted calix[3]amides (**3a**, **3b**, **4a** and **4b**) which function as anion receptors. Furthermore, a binding model of **3a**-F^- was determined by DFT calculations.

Results and discussion

Synthesis

The syntheses of tris-phenylurea-substituted calix[3]a-mide **3** and tris-phenylthiourea-substituted calix[3]amide **4** are shown in Scheme 1. Details of calix[3]amides (**1a**, **1b**) syntheses were reported previously. The reaction of **2a** and **2b** with phenyl isocyanate in $CHCl_3$ at 80°C led to the tris-phenylurea-substituted calix[3]amide **3a** and **3b** in 94% and 88% yields, respectively. Similarly, the tris-phenylthioura-substituted calix[3]amides **4a** and **4b** were obtained by the reaction of phenyl thioisocyanate with **2a** and **2b**, respectively.

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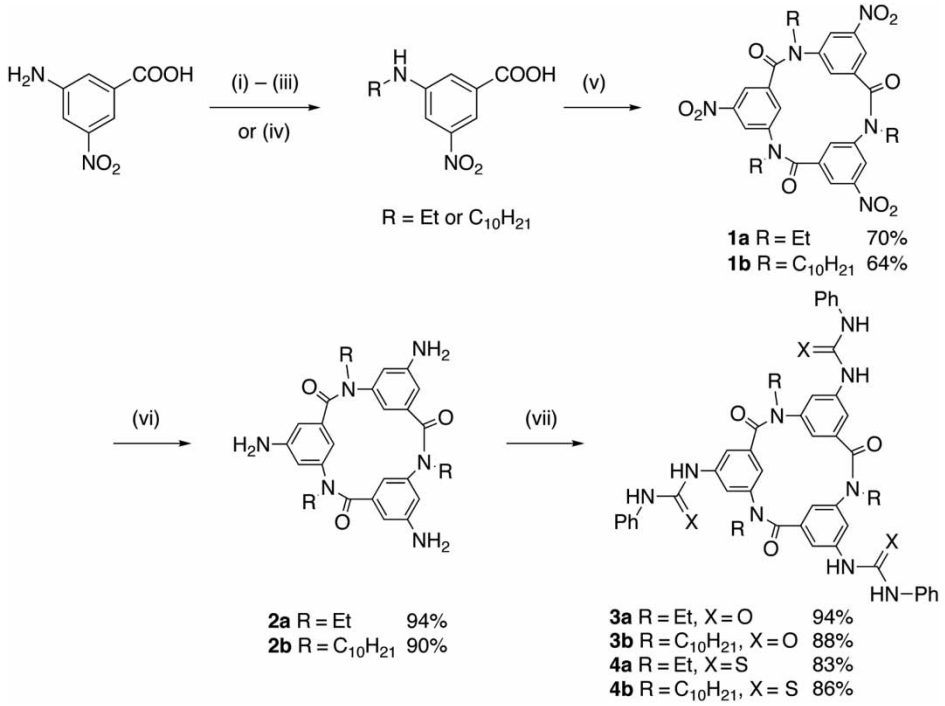

Scheme 1. Syntheses of ureido and thioureidocalix[3]amides **3**, **4**. (i) H_2SO_4, EtOH, 80°C, 6 h, 98%; (ii) EtI, HMPA, 80°C, 6 h, 85%; (iii) 4 M NaOHaq., EtOH, 90°C, 6 h, 94%; (iv) $C_{10}H_{21}I$, HMPA, 120°C; 6 h, 52%; (v) Ph_3PCl_2; 1,1,2,2-tetrachloroethane, 120°C, 6 h; (vi) Pd/C, H_2, EtOH, rt, 18 h and (vii) PhNCX, $CHCl_3$, 50°C, 7 h.

X-ray analysis

X-Ray crystallography was performed on a single crystal of ureidocalix[3]amide **3a**, which was obtained from a mixture of chloroform, methanol and toluene by slow evaporation of the solvent.[1] Single crystals of **3a** crystallised in a monoclinic system, space group $P2_1/n$, and included four molecules of **3a**, four molecules of toluene and four molecules of water in the unit cell (Figure 1). The cyclic trimer **3a** exists in the *syn* conformation in the solid state with three terminal phenyl groups located in the same direction. Based on the direction of the amide bonds, **3a** adopts a *syn* conformation. The unit cell has the same number of enantiomeric conformers, which results in the crystal having no chiral property (Figure 1(b)). These enantiomeric conformers exist as dimers in the crystal, where the cavity of one **3a** molecule was filled with the backside of an enantiomeric molecule of **3a** through H bonds between the nitrogen atoms of urea and the oxygen atom of the carbonyl group in the neighbouring molecule (the distances of N···O are 2.800(2) and 2.938(3)Å).

Complexation abilities

The addition of anions, in the form of tetrabutylammonium (TBA) salts, to the DMF-d_7, DMSO-d_6 and $CDCl_3$ solutions of each calix[3]amide, **3** or **4**, caused significant downfield shifts of the —NH— (urea) signals in the ^{1}H NMR spectra, indicating the formation of N—H···X ($X = F^-$, Cl^-, Br^-, I^-) H bonds and also the fast equilibrium between the complexed and free forms of the hosts. Increasing the concentration of the chloride anion in the host–guest mixture solution induced a ~ 1 ppm downfield shift of the NH peak (Figure 2). Typical titration curves are shown in Figure 3(a). Binding constants calculated by curve-fitting 1:1 binding isotherms to these data are presented in Table 1. The host molecules bind strongly to F^- and high selectivity between Cl^- and Br^-. The Job plots of the **3a**-X^-, **3b**-X^-, **4a**-X^- and **4b**-X^- interactions displayed maxima of mole fraction χ of 0.5, which is consistent with 1:1 binding stoichiometries (Figure 3(b)) (*10*). The electro-spray ionisation mass spectrometry provided additional support for the formation of 1:1 stoichiometric complexes ($[\mathbf{3a} + F]^-$ (*m/z* 862.4), $[\mathbf{3a} + Cl]^-$ (*m/z* 878.4), $[\mathbf{3a} + Br]^-$ (*m/z* 922.4 and 924.4) and $[\mathbf{3a} + I]^-$ (*m/z* 970.3); see the Supporting Information). The *syn* conformation is a requirement for this type of very strong complexation through H-bonding interactions. Although the calix[3]amides show conformational conversion through the sequence *syn-anti-anti-syn* ring inversion (*9*), the major conformation of **3a** is *syn* in DMF-d_7 (Figure S14). The selectivity for halogen anions can be understood on the basis of the guest basicity and the anion size (*7*, *11*). In our system, the binding constants of F^- and Cl^- were much higher than those of

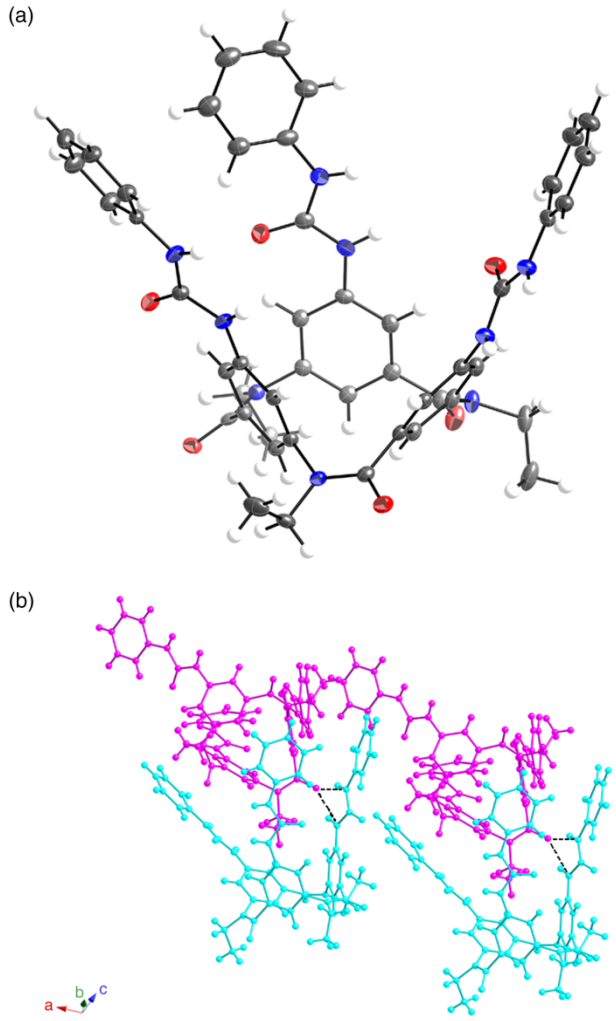

Figure 1. (a) Thermal ellipsoid models of the crystal structure of **3a.** (b) Enantiomeric dimer of **3a** in a ball-and-stick model. The enantiomeric conformers are shown in cyan and magenta. H bonds are indicated by black dashed lines. The solvent molecules are omitted for clarity.

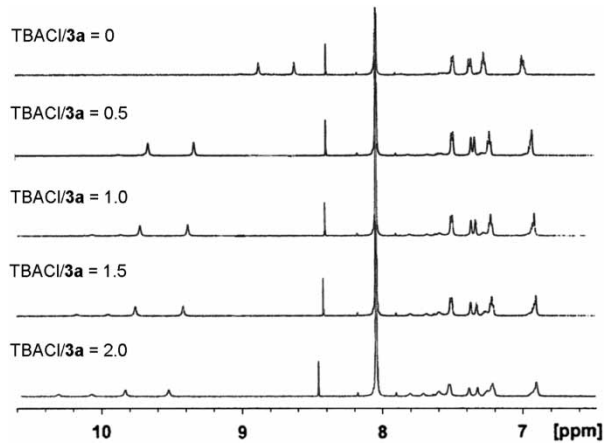

Figure 2. ^{1}H NMR spectral changes observed for the NH protons of **3a** upon the addition of TBACl (0–2.0 equiv.) to a DMF-d_7 solution.

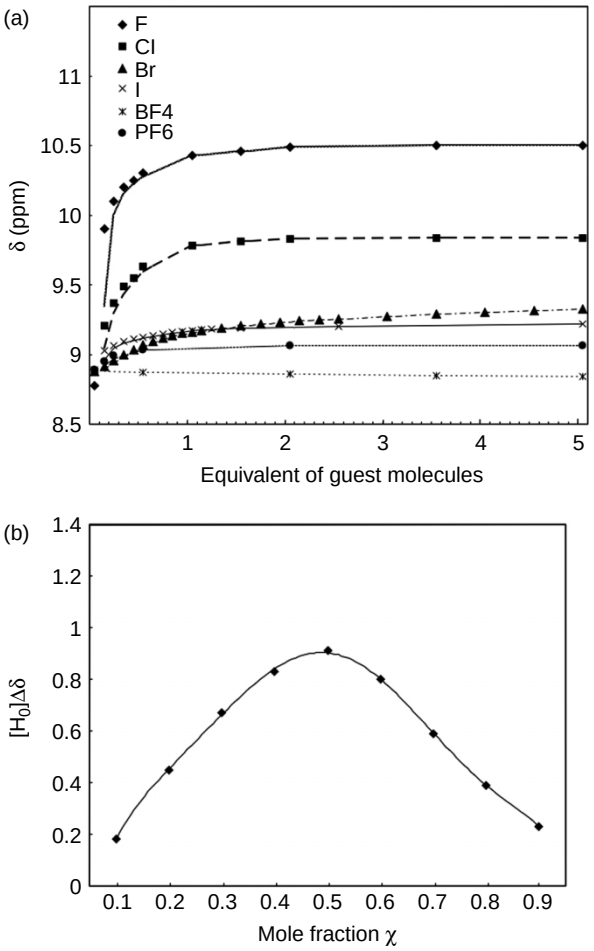

Figure 3. (a) ^{1}H NMR titration curves of **3a** with various anions; F^-, Cl^-, Br^-, I^-, BF_4^- and PF_6^-. (b) Job plot for the binding of **3a** to F^- in DMF-d_7.

Br^- and I^-. These results suggest that F^- and Cl^- have the proper size for the binding site surrounded by the three urea/thiourea groups. On the other hand, the fact that the binding constant of F^- was higher than that of Cl^- would be attributed to the basicity of anions.

Theoretical calculations

A binding mode of **3a** with a fluoride anion (**3a**-F^-) was calculated using a DFT calculation. The initial model structure was constructed by combining a fluoride anion and the host molecule **3a** with all N—H protons directed towards the centre of the cavity, which was based on the coordinate data of cyclic triamide **3a** determined by X-ray crystallography. The DFT calculation was performed on the model structure to obtain an accurate position of F^- in the binding site and the stable conformation of host molecule when the F^- anion is bound. An optimised structure of the **3a**-F^- complex is shown in Figure 4. The fluoride anion was anchored in the centre of the six N—H

Table 1. Binding constants of **3a**, **3b**, **4a** and **4b** with TBA^+X^- (298 K).

X^-	**3a** (in DMF-d_7) K_a $[M^{-1}]^a$	**3b** (in $CDCl_3$) K_a $[M^{-1}]^a$	**4a** (in DMSO-d_6) K_a $[M^{-1}]^a$	**4b** (in DMSO-d_6) K_a $[M^{-1}]^a$
F^-	29,800	49,660	23,840	25,700
Cl^-	9,550	15,910	7,600	9,720
Br^-	920	1,540	700	1,080
I^-	170	280	<100	<100
BF_4^-	–[b]	<100		
PF_6^-	<100	<100		

[a] $(\Delta\delta_{max}-\Delta\delta)K_a = \Delta\delta\Delta\delta_{max}/(\Delta\delta_{max}[H]_0-\Delta\delta\,[G]_0)$ (*10*)
[b] Cannot be estimated from the titration curve.

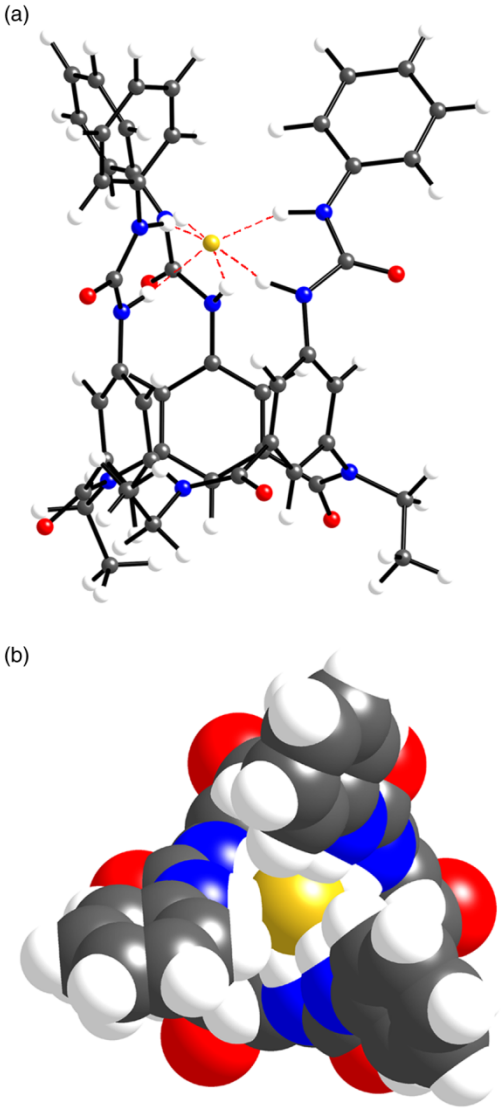

Figure 4. (a) The calculated structure of **3a**-F^- in the ball-and-stick model (side view). The fluoride anion is located in the centre of the six N—H hydrogen atoms of all the urea groups. H-bonds are indicated by red dashed lines. (b) The calculated structure of **3a**-F^- in the space-filling model (top view). The terminal phenyl groups are shown to adopt a twisted structure.

hydrogen atoms through H···F interactions. Remarkably, the terminal phenyl groups of **3a** are shown to adopt a twisted structure.

Conclusion

Calix[3]amide-based anion receptors that bind halogen anions have been synthesised. Tris-phenylurea-substituted calix[3]amide and tris-phenylthiourea-substituted calix[3]amide were observed to recognise halogen anions in a 1:1 stoichiometry, exclusively through H-bonding interactions. The anion selectivity was in the order of $F^- > Cl^- \gg Br^- > I^-$. Using a DFT calculation, the F^- anion was found to be anchored in the centre of the six N—H hydrogen atoms through H···F interactions which formed a helical structure. Due to their distinct selectivity, the substituted calix[3]amides hold significant potential for use in a number of applications, including anion sensors and anion selective switching devices.

Experimental

General procedures

Melting points were determined using AS ONE (ATM-01). ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker AV-700 spectrometer (700 MHz) or Bruker AV-400 spectrometer (400 MHz) at 298 K. High- and low-mass spectra were obtained on a JEOL MStation JMS-700 spectrometer or JEOL AccuTOF JMS-T100LC spectrometer. IR spectra were determined using a JASCO FT-IR-6300 spectrometer with ATR PR0410-S. X-ray data were collected on a Bruker SMART Apex II CCD detector. The crystal structures were solved by direct methods SHELXS-97 (Sheldrick 1996) and refined by full-matrix least-squares SHELXL-97 (Sheldrick 1997) (*12*). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included at their calculated positions. Column chromatography was performed using Wakogel C200, and thin-layer chromatography was carried out on 0.25 mm Merck precoated silica gel glass

plates. Elemental analyses were within ± 0.3% of the theoretical values.

Tris-phenylurea-substituted calix[3]amide 3a

To a suspension of cyclic trimer **2a** (0.338 g, 0.70 mmol) in $CHCl_3$ (7 ml), phenyl isocyanate (0.38 ml, 3.48 mmol) was added. The mixture was heated under reflux for 5 h. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ (5 ml) and the white powder was filtered. The filtrate was purified by gel permeation chromatography (GPC) to give tris-phenylurea-substituted calix[3]amide **3a** (0.56 g, 0.63 mmol) as a white powder. Yield: 94%; mp > 300°C; ^{1}H NMR (DMF-d_7, 400 MHz, 25°C) δ 8.86 (s, 1H), 8.60 (s, 1H), 7.47 (d, 2H, $J = 7.7$ Hz), 7.36 (s, 1H), 7.35 (s, 1H), 7.25 (t, 2H, $J = 7.7$ Hz), 6.98 (s, 1H), 6.97 (t, 1H, $J = 7.0$ Hz) 3.76 (q, 2H, $J = 7.7$ Hz) and 1.15 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (DMF-d_7, 100 MHz, 25°C) δ 169.69, 152.65, 142.69, 140.91, 140.08, 139.85, 128.75, 122.18, 121.26, 118.90, 118.79, 115.52, 44.33 and 12.43; IR (ATR, in DMF) 3648, 3524, 1698 and 1628 cm^{-1}; FAB-MS: *m/z* 845 ([M + H]$^+$); HRMS: *m/z* ([M + Na]$^+$) Calcd for $C_{48}H_{25}N_9O_6Na$: 866.33905. Found 866.33477; Elemental Analysis Calcd for $C_{48}H_{45}N_9O_6 \cdot 1/2C_7H_8$: C, 69.50; H, 5.55; N, 14.16. Found: C, 69.48; H, 5.55; N, 14.15.

Tris-phenylurea-substituted calix[3]amide 3b

To a suspension of cyclic trimer **2b** (0.576 g, 0.70 mmol) in $CHCl_3$ (7 ml), phenyl isocyanate (0.38 ml, 3.48 mmol) was added. The mixture was heated under reflux for 5 h. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ (5 ml) and the white powder was filtered. The filtrate was purified by GPC to give tris-phenylurea-substituted calix[3]amide **3b** (0.726 g, 0.62 mmol) as a white powder. Yield: 88%; mp > 300°C; ^{1}H NMR (DMSO-d_6, 400 MHz, 25°C) δ 8.72 (s, 1H), 8.60 (s, 1H), 7.42 (d, 2H, $J = 7.7$ Hz), 7.37 (s, 1H), 7.35–7.19 (m, 3H), 7.02–6.92 (m, 2H), 3.63 (t, 2H, $J = 6.8$ Hz), 1.51 (br, 3H), 1.24 (br, 10H) and 0.84 (br, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz, 25°C) δ 169.86, 152.62, 142.79, 140.59, 139.82, 129.23, 129.15, 128.97, 122.44, 118.79, 116.06, 114.31, 49.47, 31.77, 29.46, 29.28, 29.18, 27.56, 26.68, 22.56, 14.40 and 10.36; IR (ATR, in $CDCl_3$) 2926, 2855, 1709, 1648 and 1593 cm^{-1}; FAB-MS: *m/z* 1181 ([M + H]$^+$); HRMS: *m/z* ([M + H]$^+$) Calcd for $C_{72}H_{94}N_9O_6$: 1180.7249. Found 1180.7235.; Elemental Analysis Calcd for $C_{72}H_{93}N_9O_6$: C, 73.25; H, 7.94; N, 10.68. Found: C, 73.22; H, 7.93; N, 10.70.

Tris-phenylthiourea-substituted calix[3]amide 4a

To a suspension of cyclic trimer **2a** (0.338 g, 0.70 mmol) in $CHCl_3$ (7 ml), phenyl thioisocyanate (0.41 ml, 3.48 mmol) was added. The mixture was heated under reflux for 5 h. After cooling to room temperature the solvent was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ (5 ml) and the white powder was filtered. The filtrate was purified by GPC to give tris-phenylthiourea-substituted calix[3]amide **4a** (0.52 g, 0.58 mmol) as a white powder. Yield: 83%; mp > 300°C; ^{1}H NMR (DMSO-d_6, 400 MHz, 25°C) δ 10.03 (s, 1H), 9.94 (s, 1H), 7.47 (d, 2H, $J = 8.0$ Hz), 7.39 (s, 1H), 7.25–7.20 (m, 3H), 7.11 (s, 1H), 6.96 (s, 1H), 3.70 (br, 2H,) and 1.11 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (DMSO-d_6, 100 MHz, 25°C) δ 188.39, 140.27, 139.95, 142.07, 135.64, 135.35, 132.15, 130.29, 129.28, 128.88, 128.50, 126.43, 124.78, 123.95, 116.11, 13.21 and 13.09; FAB-MS ([M + H]$^+$): *m/z* 892; HRMS: *m/z* ([M + H]$^+$) Calcd for $C_{48}H_{46}N_9O_3S_3$: 891.2807. Found 891.2711; Elemental Analysis Calcd for $C_{48}H_{45}N_9O_3S_3$: C, 64.62; H, 5.08; N, 14.13; S, 10.78. Found: C, 64.28; H, 5.21; N, 14.00; S, 10.74.

Tris-phenylthiourea-substituted calix[3]amide 4b

To a suspension of cyclic trimer **2b** (0.576 g, 0.70 mmol) in $CHCl_3$ (7 ml), phenyl thioisocyanate (0.41 ml, 3.48 mmol) was added. The mixture was heated under reflux for 5 h. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ (5 ml) and the white powder was filtered. The filtrate was purified by GPC to give tris-phenylthiourea-substituted calix[3]amide **4b** (0.71 g, 0.60 mmol) as a white powder. Yield: 86%; mp > 300°C; ^{1}H NMR (DMSO-d_6, 400 MHz, 25°C) δ 9.89 (s, 1H), 9.69 (s, 1H), 7.46 (d, 2H, $J = 8.0$ Hz), 7.30 (br, 2H), 7.20 (s, 1H), 7.14–7.09 (m, 2H), 6.96 (brs, 1H), 3.70 (br, 2H,), 1.51 (br, 3H), 1.24 (br, 10H) and 0.84 (brt, 6H, $J = 6.4$ Hz); ^{13}C NMR (DMSO-d_6, 100 MHz, 25°C) δ 169.61, 150.71, 143.99, 142.07, 139.60, 130.23, 129.01, 128.90, 123.93, 123.83, 121.60, 119.61, 47.73, 31.76, 29.45, 29.17, 27.48, 26.70, 22.56, 17.30, 14.41 and 13.63; FAB-MS ([M + H]$^+$): *m/z* 1229; HRMS: *m/z* ([M + H]$^+$) Calcd for $C_{48}H_{46}N_9O_3S_3$: 1227.6563. Found 1227.6521; Elemental Analysis Calcd for $C_{72}H_{93}N_9O_3S_3$: C, 70.38; H, 7.63; N, 10.26; S, 7.83. Found: C, 70.44; H, 7.66; N, 10.40; S, 7.99.

Note

1. Crystal data for **3a**: $C_{55}H_{55}N_9O_7$; $M = 954.08$ gmol^{-1}, Monoclinic, $P21/n$, colourless prismatic, measuring $0.10 \times 0.10 \times 0.05$ mm^3, $T = 90$ K, $a = 13.8775(13)$, $b = 23.609(2)$, $c = 15.5704(15)$ Å, $\alpha = 90$, $\beta = 109.216(2)$, $\gamma = 90$°, $V = 4817.1(8)$ Å^3, $Z = 4$, $D_c = 1.316$ Mg m^{-3}, $\mu = 0.089$ mm^{-1}, $T_{max} = 0.9956$, $T_{min} = 0.9912$, GOF on $F^2 = 1.050$, $R_1 = 0.0553$, $wR_2 = 0.1416$ ($[I > 2\sigma(I)]$), $R_1 = 0.0986$, and $wR_2 = 0.1787$ (all data). CCDC − 678149

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