Synthesis and inclusion properties of thiacalix[4]arene tetraamides in *cone*- and 1,3-*alternate* conformation

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Novel thiacalix[4]arene tetraamides in *cone*- and 1,3-*alternate* conformation were prepared, in which the *cone*-tetraamide shows stronger intramolecular hydrogen bonding than 1,3-*alternate*-tetraamide. The two-phase solvent extraction data indicated that tetraamides show no extractability for alkali metal cations, but small extractability for dichromate anion ($Cr_2O_7^{2-}$).

Keywords: thiacalix[4]arene, conformation, ionophores, hydrogen bond, metal complexation, anion recognition, dichromate anion

From both a biological[1] and an environmental[2] viewpoint the synthesis of anion receptors is one of the most challenging targets in supramolecular chemistry. Calixarenes[3] and more recently thiacalixarenes[4] have been widely used in molecular recognition due to their unique three-dimensional structure with almost unlimited derivatisation abilities. Despite the importance of the molecular recognition of anions, little work has been done, while that of cations has been studied intensively. Selective complexation of anions is more demanding than that of cations due to many reasons such as size, charge density, polarisability, solvation energy and pH-dependent acid-base equilibria.[5]

A number of examples of substituted calixarenes have been used for anion complexation.[6] Thus, introduction of activated amides,[7] amines,[7a] urea,[8] and thiourea[8a] into the calixarene platform, led to the receptors that interact with anions. Furthermore, such receptors are able to form ditopic systems capable of ion-pair recognition[9] which show significant relevance to the selective extraction and/or transport of metals salts across, lipophilic membranes. But receptors with multiple binding sites have not yet been reported. Resulting from our interest in the synthesis of ditopic receptors that function as not only an anion binder but also as cation binder, we introduced amide functions into the lower rim of the thiacalix[4]arene. Amide function has been used as an efficient extractant for both cations and anions due to the high stability and hydrophobicity.

We now report the synthesis and structural properties of tetraamides **4** constraining *cone*- and 1,3-*alternate* conformation. Their recognition behaviours were also investigated by ^{1}H NMR titration experiments in $CDCl_3$ and solvent extraction experiment.

Results and discussion

Synthesis

cone-Thiacalix[4]arene tetracarboxylic acid *cone*-**3** was prepared by hydrolysis of *cone*-5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene *cone*-**2**[10] with K_2CO_3 aq. in a mixture of DMSO and water, which was prepared by *O*-alkylation of **1** with ethyl bromoacetate in the presence of NaH according to the reported procedure.[11] Tetrathiacalix[4]arene tetraamide *cone*-**4** was prepared in 45% yield by condensation reaction of *cone*-**3** with *p*-toluidine in the presence of DCC and HOBt at room temperature for 15 h in CH_2Cl_2. Similarly, 1,3-*alternate*-tetrathiacalix[4]arene tetraamide 1,3-*alternate*-**4** was prepared in good yield from the corresponding 1,3-*alternate*-**2** as described above. The conformational assignments of **4** were not necessary because the tetraacetates **2** were conformationally immobilised in *cone*- and 1,3-*alternate* conformation.[11] The product structures were supported by their spectral and analytical data.[11b]

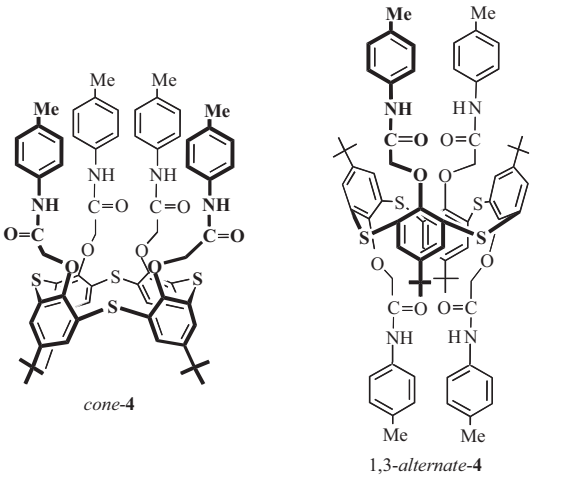

Fig.1 Structures of *cone*- and 1,3-*alternate*-**4**.

The 1,3-*alternate*-tetraamide 1,3-*alternate*-**4** has, at first glance, two possible binding sites because of the 1,3-*alternate* conformation.[12] Furthermore, the NH group can bind anions by hydrogen bonding while the carbonyl and phenolic oxygens are available for cation binding. In particular, the presence of the acetate function might provide the possibility of complexing cations and could work as a controller for the recognition of cation and/or anions by the amide function placed at the other site of the thiacalix[4]arene cavity. It is therefore possible that the two binding sites of 1,3-*alternate*-**4** could participate simultaneously and cooperatively upon ion binding producing higher forms of molecular behaviour.

Several examples of the formation of intramolecular hydrogen-bonding among opposing urea groups which can bind anionic species in calix[4]arenes have been reported.[13] Therefore, intramolecular hydrogen bonding may be foreseen between the NH and CO groups. In order to investigate the existence of intramolecular hydrogen bonding in **4** the reference compound **6** was synthesised by condensation reaction of **5**[14] with *p*-toluidine in the presence of DCC and HOBt at room temperature for 15 h in CH_2Cl_2.

The chemical shifts of the NH protons and the differences ($\Delta\delta$) in the chemical shifts of **4** from that of the reference compound **6** in both $CDCl_3$ and DMSO-d_6 are shown in Table 1. Compared with the chemical shift of the NH protons of **6** (δ 8.60 ppm) the corresponding chemical shift at δ 9.26 ppm arising from the formation of intramolecular hydrogen bonding in *cone*-**4** shows a downfield ($\Delta\delta$ = –0.66 ppm). The strong intramolecular hydrogen bonding between NH and CO groups implies a close contact of the chains OCH_2CONH

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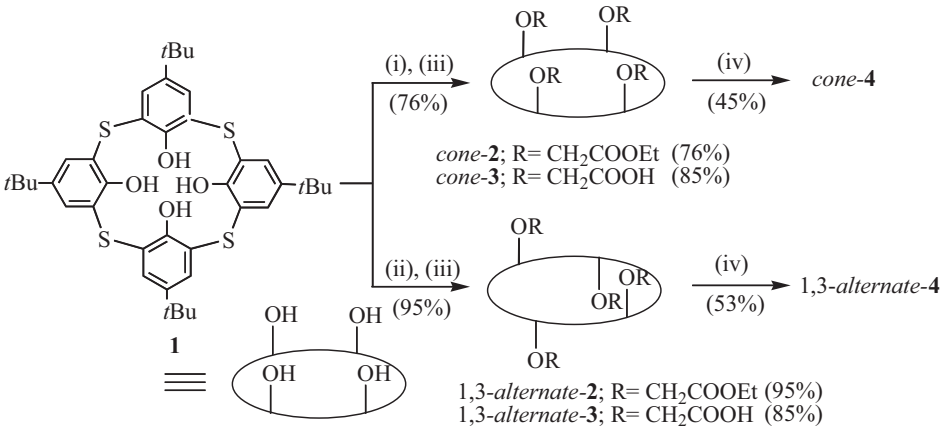
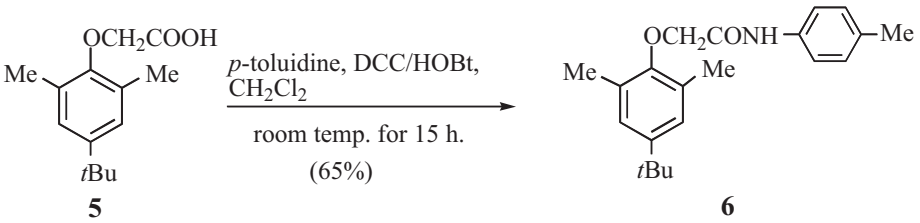


Scheme 1 *Reagents and conditions:* (i) $BrCH_2CO_2Et$, NaH, THF-DMF, reflux for 36h; (ii) $BrCH_2CO_2Et$, Cs_2CO_3, acetone, reflux for 36h; (iii) K_2CO_3, DMSO/water, 120°C for 12h; (iv) *p*-toluidine, DCC/HOBt, CH_2Cl_2, room temp. for 15h.



Scheme 2

due to the *cone* conformation. These downfield shifts are conspicuous due to several examples of the formation of intramolecular hydrogen bonding in calix[4]arene constraining *cone* conformation are well known. In contrast, the NH protons of 1,3-*alternat*e-**4**, constraining 1,3-*alternate* conformation, shows an upfield (*i.e.* $\Delta\delta$ = + 0.16 ppm). This might suggest the steric hindrance of the *tert*-butyl groups avoid the formation of intramolecular hydrogen bonding between the distal positions.

^{1}H NMR dilution studies showed no change of the chemical shift of NH protons due to the concentration-independent intramolecular hydrogen-bonding in *cone*-**4**. Due to NH, groups can also form intermolecular hydrogen-bonding based on the solvent, the compound *cone*-**4** was dissolved in the strongly hydrogen-bonding solvent DMSO-d_6. The downfield shift of NH protons of *cone*-**4** at δ 10.14 ppm (*i.e.* $\Delta\delta_{sol.}$ = –0.88 ppm) also indicates the formation of intermolecular hydrogen-bonding. By contrast, a smaller downfield shift of NH protons of 1,3-*alternate*-**4** at δ 8.74 ppm (*i.e.* $\Delta\delta_{sol.}$ = –0.30 ppm) than that of *cone*-**4** was observed, apparently from the weaker intramolecular hydrogen-bonding between the *distal*-amide moieties and then decreased formation of a new intermolecular hydrogen-bonding attributable to the steric hindrance of the *tert*-butyl groups.

Chemical shifts changes of *con*e- and 1,3-*alternat*e-**4** in $CDCl_3$ and DMSO-d_6 are shown in Fig. 2. The higher downfield shift of *tert*-butyl protons ($\Delta\delta_{sol.}$ = –0.18 ppm) in 1,3-*alternate*-**4** than that of *cone*-**4** ($\Delta\delta_{sol.}$ = –0.02 ppm) may be attributed by the conformation change of 1,3-*alternate*-**4**

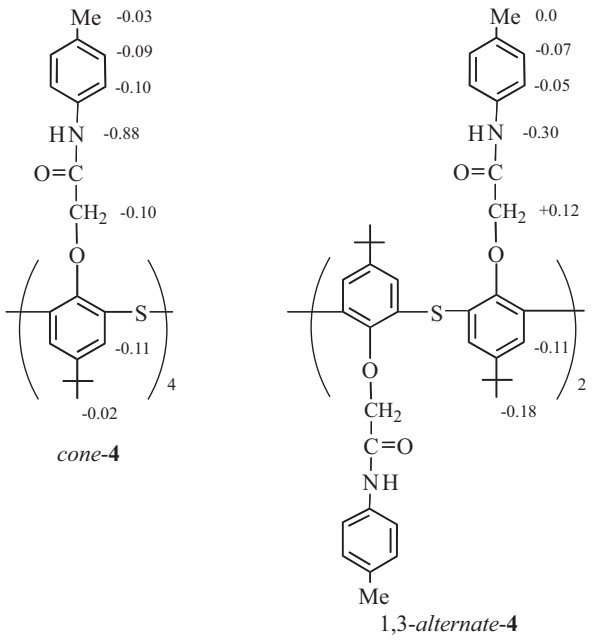


Fig. 2 Chemical shifts changes of *cone*- and 1,3-*alternate*-**4** in $CDCl_3$ and DMSO-d_6. $\Delta\delta = \delta$ [in $CDCl_3$] - δ [in DMSO-d_6].

in DMSO-d_6. It was also found that in the cases of *cone*-**4** the chemical shift of the methylene protons of OCH_2CONH shifted to a lower field ($\Delta\delta_{sol.}$ = –0.10 ppm) in DMSO-d_6, whereas

Table 1 Chemical shifts (δ) of the NH protons of *cone*- and 1,3-*alternate*-**4**[a]

Compound	$CDCl_3$ δ_{NH} ($\Delta\delta_{ref.NH}$[b])	DMSO-d_6 δ_{NH} ($\Delta\delta_{ref.NH}$[b])	$\Delta\delta_{sol.\ NH}$[c]
cone-**4**	9.26 (-0.66)	10.14 (-0.25)	–0.88
1,3-*alternate*-**4**	8.44 (+0.16)	8.74 (+1.14)	–0.30
reference **6**	8.60	9.88	–1.28

[a]Determined in $CDCl_3$ or DMSO-d_6 by using $SiMe_4$ as a reference and express δ in ppm; [b]$\Delta\delta_{ref.} = \delta$ [reference **6**] – δ [thiacalixarene **4**]; [c]$\Delta\delta_{sol.} = \delta$ [in $CDCl_3$] – δ [in DMSO-d_6]

an upper field shift ($\Delta\delta_{sol.}$ = + 0.12 ppm) was observed in 1, 3-*alternate*-**4**, which might be attributable to being to locate in the area of the ring current effect[15] arising from the two inverted calixarene benzene rings.

Binding studies

The recognition properties of receptors **4** were investigated by ^{1}H NMR titration experiments in $CDCl_3$ toward selected anions (tetrabutylammonium (TBA) chloride and bromide) and cations (silver and potassium trifluoromethanesulfonate). In general, the titration experiments were carried out by the increasing addition of ion (0.1 mol dm^{-3}) into 5 × 10^{-6} mol of the receptor in 0.5 cm^3 of $CDCl_3$. Addition of 1 equiv of KSO_3CF_3 into either *cone*- and 1,3-*alternate*-**4** solutions did not cause significant chemical shift (*i.e.* greater than 0.01 ppm) even in the presence of an excess of K^+ ion. Similar titration of *cone*- and 1,3-*alternate*-**4** with 1 equiv or an excess of $AgSO_3CF_3$ did not caused chemical shift.

Disappointingly, in the titration of *cone*- and 1,3-*alternate*-**4** with 1 equiv or excess of TBACl or TBABr no significant shifts were observed indicating that there is little interaction or no interaction between these molecules and the anionic species. This implies that the two hydrogen-bonding systems in 1,3-*alternate*-**4** is not strong enough to form tight complexes with anion species such as Cl^- or Br^-.

Solvent extraction

Recently a number of chemically modified calixarenes have been synthesised that can be used as host for simple anions.[16] Dichromate anions in particular are important because of their high toxicity[17] and their presence in soils and waters.[18] For this purpose we have preliminary evaluation of the binding efficiencies of the extractant **4** which has been carried out by solvent extraction of alkali metal picrates and dichromate from aqueous into dichloromethane. As expected from the titration experiment described above, both *cone*- and 1,3-*alternate*-**4** hardly extracted alkali metal cations (Na^+, K^+) and Ag^+ in the present experimental system. Interestingly, small extractability for dichromate ($Cr_2O_7^{2-}$) [extraction% ($Na_2Cr_2O_7$): 5.0% for *cone*-**4** and 8.3% for 1,3-*alternate*-**4**] and higher extractability for 1,3-*alternate*-**4** than that of *cone*-**4** was observed. Although an explanation for the different extractabilities from those of metal cations is not clear in the present stage, one might assume the larger size of dichromate to construct the intermolecular hydrogen bondings between NH protons of amide moieties and two oxyanions of dichromate. It was also found the decreased extractability for $K_2Cr_2O_7$ (extraction%: 4.1 for *cone*-**4** and 1.2% for 1,3-*alternate*-**4**. The larger size of the K^+ than Na^+ might affect the present dichromate extraction, but this is also awaiting confirmation.

Conclusions

The two novel thiacalix[4] arene amide derivatives in *cone*- and 1,3-*alternate* conformation were prepared, in which the *cone*-tetraamide shows stronger intramolecular hydrogen bonding than 1,3-*alternate*-tetraamide. Even though there is a presence of intramolecular hydrogen bonding in *cone*-**4,** their affinity for K^+ and anion species is quite small. In the case of 1,3-*alternate*-**4**, the complexation of K^+ does not induce any enhancement for anion complexation. The very low affinity of all thiacalix[4]arene amide derivatives can be ascribe to both no suitable preorganisation and the two or four intramolecular hydrogen bonding system. At present, only a dichromate extraction phenomenon has been observed for *cone*- and 1,3-*alternate*-**4**; variation of the solvent extraction experiment conditions and the introduction of the further binding units to the amide moieties could lead to the new type of dichromate anion extractants.

Experiment

All melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on a Nippon Denshi JEOL FT-300 NMR spectrometer in deuteriochloroform with Me_4Si as an internal reference. IR spectra were measured as KBr pellets on a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-HX110A Ultrahigh Performance Mass Spectrometer at 75 eV using a direct-inlet system. Elemental analyses were performed by Yanaco MT-5.

Materials

cone-(*cone*-**2**) and 1,3-*alternate*-5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-*alternate*-**2**) were prepared in 76 and 95% by *O*-alkylation of **1** with ethyl bromoacetate according to the reported procedure.[11]

cone-5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[carboxymethoxy]-2,8,14,20-tetrathiacalix[4]arene **(***cone*-**3)**: A solution of *cone*-**2** (1.07 g, 1.0, mmol), K_2CO_3 (2.76 g, 20 mmol) in DMSO-water (6:1, 35 cm^3) was heated at 120°C for 12 h and then 2 M HCl (60 cm^3) was added to the cooled mixture in an ice-water bath. The precipitate was collected by filtration and washed with water, then dissolved in chloroform. After filtering off the solid residue, the filtrate was evaporated to dryness to obtain *cone*-**3**, which was recrystallised from water–acetone to obtain a pure sample as a white solid (750 mg, 85%) as colourless prisms, m.p. 333–335°C; IR ν (KBr)/cm^{-1} 3480 (OH), 1758 (CO); δ_H ($CDCl_3$) 1.11(36H, s, *t*Bu), 5.07 (8H, s, O*CH*$_2$), 7.38 (8H, s, ArH); *m/z*: 975.1 [M + Na]$^+$. (Found: C, 60.23; H, 5.70. $C_{48}H_{56}O_{12}S_4$ (953.22) requires C, 60.48; H, 5.92%).

1,3-*alternate-5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis [carboxymethoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-*alternate-**3**)*:* A similar procedure to that of *cone*-**2** was carried out to give 1,3-*alternate*-**3** (85%) as an off-white solid, m.p. 325–326°C; IR ν (KBr)/cm^{-1} 3421 (OH), 1695 (CO); δH ($CDCl_3$) 1.25 (36H, s, tBu), 4.66 (8H, s, O*CH*$_2$), 7.39 (8H, s, Ar*H*); *m/z:* 975.1 [M + Na]$^+$. (Found: C, 60.32; H, 5.86. $C_{48}H_{56}O_{12}S_4$ (953.22) requires C, 60.48; H, 5.92%).

cone-5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(p-methylphenylamino)carbonylmethoxy]-2,8,14,29-tetrathiacalix[4]arene (*cone*-**4**): To a solution of *cone*-**3** (100 mg, 0.105 mmol), *p*-toluidine (108 mg, 1.14 mmol) and 1-hydroxybenzotriazole (HOBt) (26 mg, 0.17 mmol) in CH_2Cl_2:DMF (4:1, 25 cm^3) was added dropwise a solution of dicyclohexylcarbodiimide (DCC) (190 mg, 0.92 mmol) in CH_2Cl_2 (5 cm^3) at 0°C. After the mixture was stirred for 20 h at room temperature, it was condensed under reduced pressure. The residue was extracted with ethyl acetate (2 × 30 cm^3). The combined extracts were washed with 10% citric acid (2 × 20 cm^3), 5% sodium bicarbonate (20 cm^3), water (20 cm^3), saturated brine (20 cm^3), dried ($MgSO_4$) and condensed under reduce pressure. The residue was recrystallised from methanol affording pure compound *cone*-**4** (62 mg, 45%) as colourless prisms, m.p. 245–247°C; IR ν (KBr)/cm^{-1} 3721 (NH), 1680 (CO); δ_H ($CDCl_3$) 1.13 (36H, s, tBu), 2.23 (12H, s, Ph-*CH*$_3$), 4.94 (8H, s, O*CH*$_2$), 6.96 (8H, d, *J* = 8.4 Hz, Ph-*H*), 7.38 (8H, s, Ar*H*), 7.42 (8H, d, *J* = 8.4 Hz Ph-*H*), 9.26 (4H, t, *NH*); δ_H (DMSO-d_6) 1.15 (36H, s, *t* Bu), 2.26 (12H, s, Ph-*CH*$_3$), 5.04 (8H, s, O*CH*$_2$), 7.06 (8H, d, *J* = 8.4 Hz, Ph-*H*), 7.49 (8H, s, Ar*H*), 7.51 (8H, d, *J* = 8.4 Hz Ph-*H*), 10.14 (4H, t, *NH*); *m/z:* 1308 (M$^+$). (Found: C, 69.64; H, 6.72; N, 4.05. $C_{76}H_{84}N_4O_8S_4$ (1309.78) requires C, 69.69; H, 6.46; N, 4.28%).

*1,3-alternate-5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis [(p-methylphenylamino)carbonylmethoxy]-2,8,14,29-tetra-thiacalix [4]arene (1,3-*alternate-**4**)*: A similar procedure to that of *cone*-**4** was carried out to give 1,3-*alternate*-**4** as colourless prisms in 53% yield. m.p. 230–232°C; IR ν (KBr)/cm^{-1} 3393 (NH), 1685 (CO); δ_H ($CDCl_3$) 0.70 (36H, s, *t*Bu), 2.32 (12H, s, Ph-*CH*$_3$), 4.75 (8H, s, O*CH*$_2$), 7.14 (8H, d, *J* = 8.4 Hz, Ph-*H*), 7.39 (8H, d, *J* = 8.4 Hz Ph-*H*), 7.46 (8H, s, Ar*H*), 8.44 (4H, t, *NH*); δ_H (DMSO-d_6) 0.88 (36H, s, *t*Bu), 2.32 (12H, s, Ph-*CH*$_3$), 4.63 (8H, s, O*CH*$_2$), 7.19 (8H, d, *J* = 8.4 Hz, Ph-*H*), 7.46 (8H, d, *J* = 8.7 Hz Ph-*H*), 7.57 (8H, s, Ar*H*), 8.74 (4H, t, *NH*); *m/z*: 1308.50 (M$^+$). (Found: C, 69.64; H, 6.45; N, 4.27. $C_{76}H_{84}N_4O_8S_4$ (1309.78) requires C, 69.69; H, 6.46; N, 4.28%).

4-tert-Butyl-2,6-dimethyl[(4-methylphenylamino)carbonylmethoxy] benzene **(6)**: To a solution of (4-*tert*-butyl-2,6-dimethyl)phenoxyacetic acid **5**[14] (100 mg, 0.43 mmol), *p*-toluidine (137 mg, 1.28 mmol) and HOBt (75 mg, 0.17 mmol) in CH_2Cl_2 (12 cm^3) was added dropwise a solution of DCC (560 mg) in CH_2Cl_2 (5 cm^3) at 0°C. After the mixture was stirred for 15 h at room temperature, it was condensed under reduced pressure. The residue was extracted with ethyl acetate (2 × 30 cm^3). The combined extracts were washed with 10% citric

acid (2 × 20 cm^3), 5% sodium bicarbonate (20 cm^3), water (20 cm^3), saturated brine (20 cm^3), dried (Na_2SO_4) and condensed under reduce pressure. The residue was recrystallised from methanol gave the *title compound* **6** (95 mg, 65%) as colourless prisms; m.p. 204–206°C; IR ν (KBr)/cm^{-1} 3277(NH), 1667 (CO); δ_H ($CDCl_3$) 1.30 (9H, s, *t*-Bu), 2.30 (6H, s, Ph-CH_3), 2.35 (3 H, s, Ph-CH_3), 4.39 (2H, s, ArOCH_2), 7.05 (2H, s, ArH), 7.18 (2H, d, J = 8.8, Ph-H_a), 7.52 (2H, d, J = 8.8, Ph-H_b), 8.60 (1H, s, *NH*); δ_H (DMSO-d_6) 1.24 (9H, s, *t*Bu), 2.26 (9H, s, Ph-CH_3, Ar-CH_3), 4.35 (2H, s, ArOCH_2), 7.05 (2H, s, Ar*H*), 7.13 (2H, d, J = 8.3, Ph-H_a), 7.59 (2H, d, J = 8.8, Ph-H_b), 9.88 (1H, s, *NH*); *m/z*: 325 (M^+). (Found: C, 77.36; H, 8.33; N, 4.27. $C_{21}H_{27}O_2N$ (325.45) requires C, 77.50; H, 8.36; N, 4.3%).

^1H NMR complexation experiments

To a $CDCl_3$ solution (4×10^{-3} M) of **4** in the NMR tube was added 1 molar to 2 molar solution of KSO_3CF_3 or $AgSO_3CF_3$. The spectrum was registered after addition and the temperature of NMR probe kept constant at 27°C.

Solvent extraction

Picrate and/or dichromate extraction experiments were performed following Pedersen's procedure.[19] 5 cm^3 of a 2.5×10^{-4} M aqueous solution or 1×10^{-4} M aqueous dichromate solution and 5 cm^3 of 1×10^{-4} M solution of calixarene in CH_2Cl_2 were vigorously agitated in a stoppered glass tube with a mechanical shaker for 2 min then magnetically stirred in a thermostated water-bath at 25°C for 12 h, and finally left standing for an additional 30 min. Blank experiments showed that no metal picrate or dichromate extraction occurred in the absence of thiacllix[4]arene derivative **4**. The percent extraction (E%) has been calculated as:

$$(E\%) = (A_0 - A/A_0) \times 100,$$

where A_0 and A are the initial and final concentrations of the metal picrate/dichromate before and after the extraction respectively.

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