Synthesis of calix[4]crowns containing soft donor atoms and a study of their metal–cation binding properties: highly selective receptors for Cu^{2+}

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Two new calix[4]arenethiacrown derivatives **1** and **2** in the *cone* conformation were synthesized by two different pathways in good yield. Their complexation properties toward alkali, alkaline earth and transition metal cations were studied in acetonitrile at 298.15 K using a conductometric titration technique. The selectivity for Cu^{2+} over other cations with these novel ligands was excellent.

Introduction

Many macrocyclic ligands possessing different donor atoms have been developed and their complexation properties have been extensively studied.[1,2] Those macrocycles containing hard donor atoms such as O atoms or N atoms mainly complex alkali or alkaline earth metal ions, whereas those containing soft donor atoms such as thioether S atoms or phosphine P atoms bind transition metal ions.[1,2] Interest in the study of the complexation of heavy metals with macrocycles is mainly due to the importance of such ions in biological and environmental processes. An important parameter in the study of macrocyclic ligand–metal complexes is the stability constant, K_{assoc}. The magnitudes of these stability constants depend on several factors, including the relative size of the cation and the macrocyclic cavity, the number and the nature of binding sites, the acid–base character of metal ions and the nature of the solvent.[3] All of these factors also affect the selectivity of the macrocyclic ligands towards cations. A group of such compounds that are currently under intensive study are the calixarenes, and calix[4]arenes in particular.[4] More commonly, however, calixarenes modified on their lower rims represent simple, though effective and versatile means of producing receptors with very selective cation binding properties. Most calixarene derivatives with pendant ether,[5] ester,[6] ketone,[7] carboxylic acid,[8] amide[9] or crown ether[10] groups complex alkali and alkaline earth metal cations. Calixarene ligands which are better for "softer" transition metals can be derived by incorporating "softer" N and/or S atoms into the lower rim. Schiff base,[11] thioamide[12] and thioether[13] derivatives are able to extract Ag^{+}, Pb^{2+}, $Cu^{2+}$and Hg^{2+} ions for example, but among such calix[4]arene derivatives that have been reported, the selectivity for these transition metals was not very pronounced.

In order to enhance the selectivity toward transition metal ions by controlling the cavity size of the calix[4]arene crown derivatives, and also the rigidity of the crown tether we report herein the synthesis of two new calix[4]thiacrown derivatives. These derivatives, calix[4]dithiadioxadibenzocrown **1** and calix[4]trithiadioxadibenzocrown **2** were shown to exist in *cone* conformations, and a preliminary investigation of their metal ion binding properties is also reported herein.

Results and discussion

Synthesis

The synthesis of *p-tert*-butylcalix[4]trithiadioxadibenzocrown **2** was carried out by following two different pathways (Schemes 1 and 2) while *p-tert*-butylcalix[4]dithiadioxadibenzocrown **1** was obtained as shown in Scheme 1. Salicylaldehyde was reacted with an equimolar amount of ethyl bromoacetate in the presence of one equiv. of anhydrous K_2CO_3 in refluxing CH_3CN (3–4 h) to afford a yellow oily mixture of compounds **3** and **4** (Scheme 1). With longer reaction times, the benzofuran **4**[14] was obtained exclusively. When salicylaldehyde was treated with ethyl bromoacetate in the presence of K_2CO_3 in refluxing anhydrous acetone for 3–4 h however, **3** could be obtained in 88% yield. Trace amounts of remaining starting material could easily be removed by washing the ether solution of the crude product with aqueous 5% NaOH. Reduction of **3** using $NaBH_4$ in MeOH at room temperature afforded a mixture of **5** and **6**. With longer reaction times (6–7 h) **3** was completely converted to **6**. However, when the reduction was conducted at −5–0 °C for only 10–15 min, **5** was obtained in 95% yield. Treatment of **5** with freshly distilled $SOCl_2$ at 0 °C for 15 min produced **7** (92%) which, under basic conditions with ethanedithiol or 2-mercaptoethyl sulfide, afforded **8** and **9** respectively, in quantitative yields. Lithium aluminium hydride reduction of **8** or **9** in THF at room temperature afforded **10** and **11** respectively, in 98% yield. Reaction of **10** or **11** with *p*-TsCl and KOH in ether at 0 °C successfully produced **12** and **13** respectively, also in good yields, after column chromatographic purification. *p-tert*-Butylcalix[4]dithiadioxadibenzocrown **1** and *p-tert*-butylcalix[4]trithiadioxadibenzocrown **2** were prepared by coupling of *p-tert*-butylcalix[4]arene with an equimolar amount of **12** or **13** respectively, in the presence of excess anhydrous K_2CO_3 in refluxing anhydrous CH_3CN for 7 d. Each of the resulting reaction products was purified by column chromatography to give **1** or **2** as colourless solids, in 30 and 39% yields, respectively. Further purification was achieved by washing the solids with diethyl ether. Compounds **1** and **2** were fully characterized, and established to be in *cone* conformations by the presence of two sets of doublet signals in their ^1H NMR spectra at δ 3.31 and 4.38 ppm, and at δ 3.31 and 4.45 ppm respectively, due to the methylene bridge protons ($ArCH_2Ar$), as well as by the presence of two singlet signals due to the *tert*-butyl groups at δ 0.98 and 1.30 ppm and at δ 0.8 and 1.30 ppm, respectively.

Alternatively, **2** could also be prepared in 74% yield using the shorter reaction pathway shown in Scheme 2. Alkylation of salicylaldehyde with an excess of 1,2-dibromoethane in the presence of 2 equiv. of anhydrous K_2CO_3 in refluxing anhydrous CH_3CN afforded, after column chromatographic purification, **14** as a pale yellow solid in 66% yield, along with a

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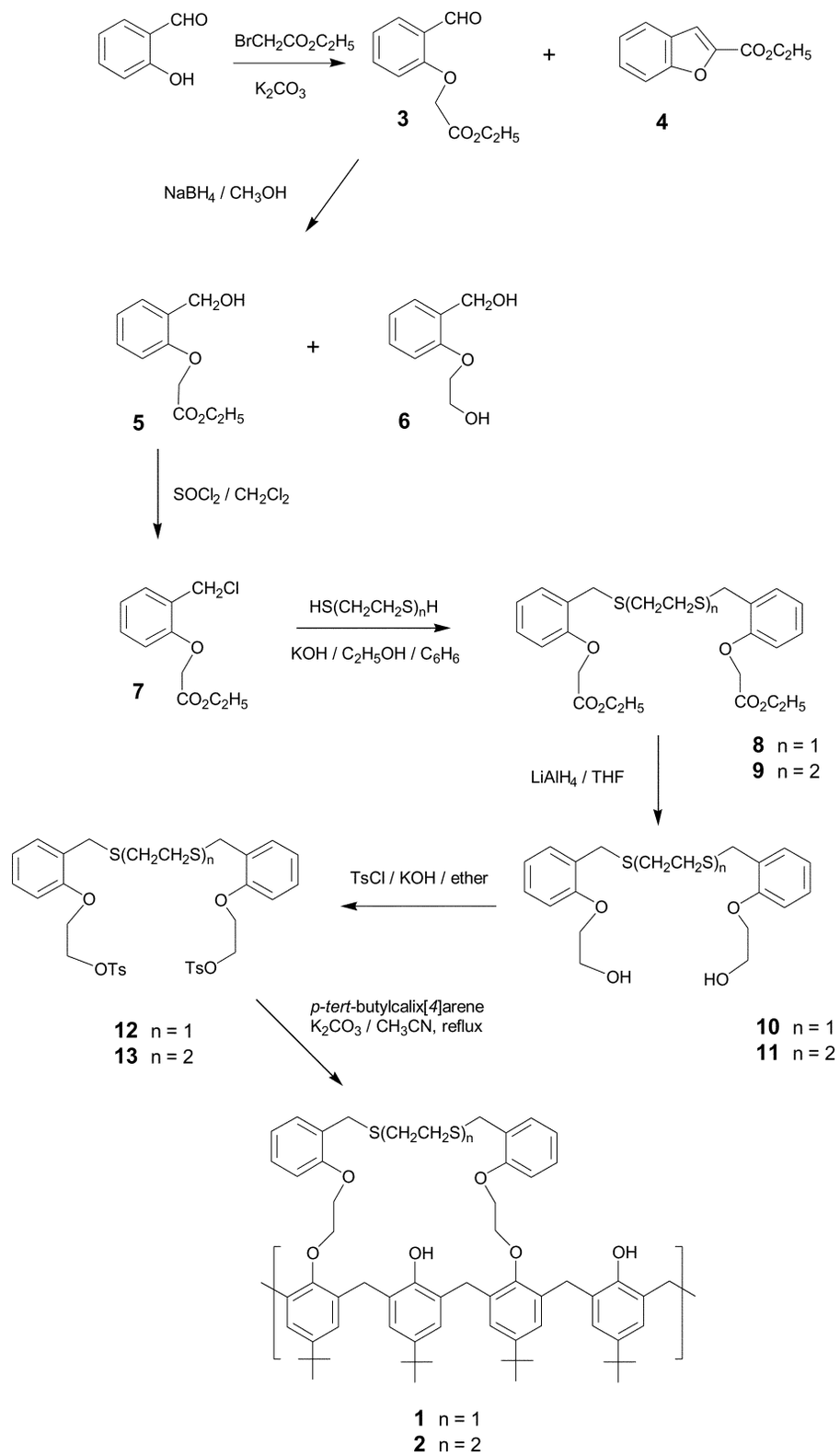
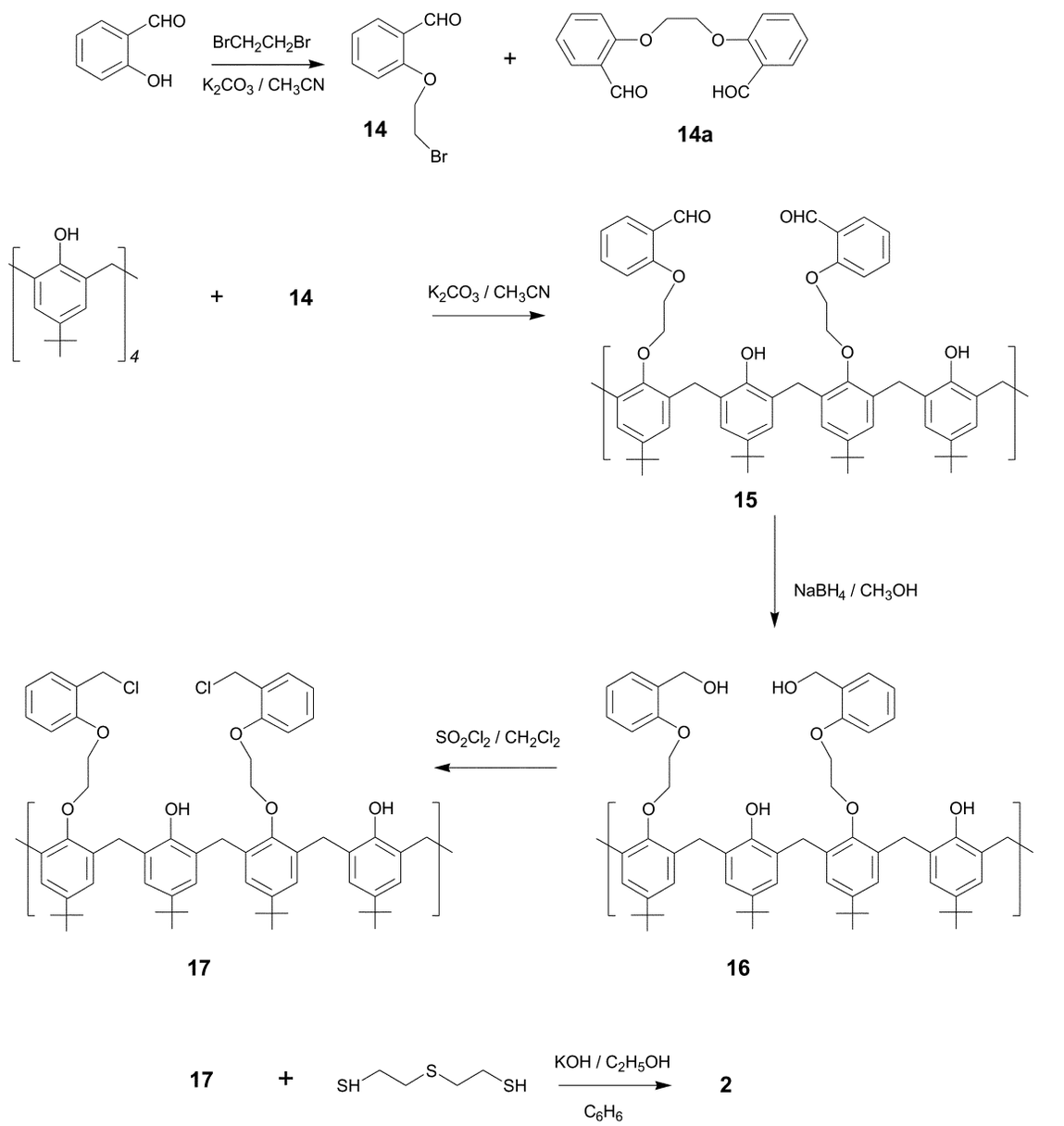


Scheme 1

minor product (<10%) **14a** whose melting point was identical to that reported in the literature.[15] The 1,3-dialdehyde **15** was prepared by alkylation of *p-tert*-butylcalix[4]arene with 2 equiv. of compound **14** in refluxing anhydrous CH_3CN containing 1 equiv. of anhydrous K_2CO_3. Compound **15** was formed as a colourless solid in 75% yield after washing the crude product with diethyl ether. Reduction of **15** using $NaBH_4$ in MeOH at room temperature afforded **16** in quantitative yield. Treatment of **16** with freshly distilled $SOCl_2$ at room temperature in anhydrous benzene or CH_2Cl_2 for 15 min afforded, after column chromatographic purification, **17** in 58% yield. Base-mediated coupling of equimolar amounts of **17** and 2-mercaptoethyl sulfide afforded **2** in 74% yield.

Conductometric titrations

In principle, measurements of the variation of electrical conductance with the concentration of metal salts and receptors can be used to determine the strength, stoichiometry and stability constants of complex formation and to assess the



Scheme 2

nature of the interactions taking place.[16,17] We employed such measurements to establish the stoichiometry of the complexes formed between several individual metal cations and **1** and **2**, and to assess qualitatively the strength of the complexes from the shape of the conductometric titration curves, and also to determine the stability constants of these complexes. Plots showing no or very slight slopes indicate very little or no complexation at any given mole ratio. For complexes of moderate stability, plots with well-defined changes in curvature at the stoichiometric ratios of the reaction were obtained. Plots in which two straight lines intersect at the stoichiometric ratios of the reaction are indicative of strong complexation. The molar conductance *versus* $[L]_T/[M]_T$ plots in acetonitrile at 25 °C are given in Figs. 1 and 2. $[L]_T$ and $[M]_T$ are the total concentrations of the ligands **1** or **2** and of the metal cations respectively. As can be seen, in Fig. 1 the addition of calixthiacrown **1** to solutions of Cu^{2+} or Ag^+, but not of Mg^{2+} or Cs^+, result in continuous decreases in the molar conductances of the resulting solutions. Also, as shown in Fig. 2, addition of calixthiacrown **2** to solutions of Cu^{2+} or Ag^+, but not of Mg^{2+} or Cs^+, result in continuous decreases in the molar conductances of the resulting solutions. These decreases indicate lower mobilities of the metal–ligand complexes as compared to the solvated cations alone. The decreases in molar conductances for

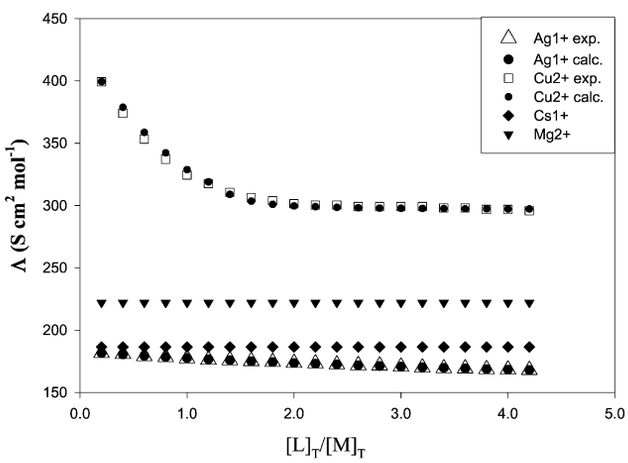


Fig. 1

Cu^{2+} and Ag^+, which are shown in Figs. 1 and 2 start to level off at a mole ratio of 1. The corresponding slopes of the plots for these cations also change at the point where the calixthiacrown-to-cation mole ratio is 1, implying the formation of 1 : 1 complexes. It is noteworthy that the sharp decreases of the

Table 1 K_{assoc} (in $dm^3\ mol^{-1}$) for complexation of Cu^{2+} and Ag^+ with **1** and **2** in acetonitrile at 25 °C

Compound	Cu^{2+}	Ag^+
1	5.77 ± 0.28	3.39 ± 0.16
2	5.58 ± 0.27	4.50 ± 0.22

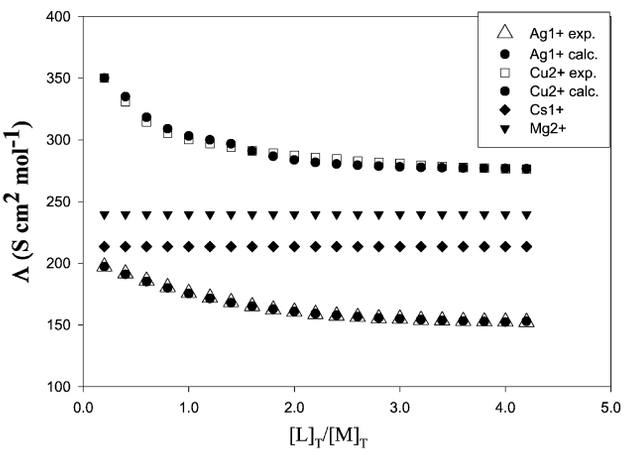


Fig. 2

slopes for calixthiacrown–Cu^{2+} complexes of **1** or **2** indicate that these complexes are more stable than the corresponding calixthiacrown–Ag^+ complexes and that the stability constants of the calixthiacrown–Cu^{2+} complexes of **1** or **2** are higher than those of the Ag^+–calixthiacrown complexes (Table 1). Furthermore, it can also be seen that the strength of the calixthiacrown **1**–Cu^{2+} complex is higher than that of the calixthiacrown **2**–Cu^{2+} complex, while that of the calixthiacrown **2**–Ag^+ complex is higher than that of the calixthiacrown **1**–Ag^+ complex. Figs. 1 and 2 also reveal that despite increases in the calixthiacrown concentrations of **1** or **2**, no detectable changes in molar conductances were found for Mg^{2+} and Cs^+, for example. Similar negligible changes in molar conductances were also found for M^{n+} = Na^+, K^+, Rb^+, Cr^{3+}, Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+} and Cd^{2+}. Determinations of their complex formation constants with calixthiacrowns **1** and **2** were therefore not possible. Such behavior can indicate that no complexation takes place between calixthiacrowns **1** or **2** and the above mentioned metal cations other than Cu^{2+} and Ag^+.

In conclusion, two new calix[4]thiacrowns **1** and **2** have been synthesized in good yields by two different pathways. These two receptors showed highest complexation ability and selectivity for Cu^{2+} among all of the metal cations studied. Conductance data indicated well-defined breaks in the titration curves for Cu^{2+} and Ag^+ with **1** and **2**, indicative of the formation of 1 : 1 complexes in acetonitrile at 25 °C. Since no detectable changes were observed in the shapes of the conductance titration curves determined for various metal cations, other than Cu^{2+} and Ag^+, no complexation apparently occurred with these cations. A follow-up study on other thermodynamic parameters and the effect of solvent changes on these parameters will be reported in due course.[18]

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a 200 MHz spectrometer. In all cases, samples were dissolved in $CDCl_3$ using TMS as internal standard. Infrared (IR) spectra were determined on an FT-IR spectrometer. All materials were analytical grade and used without further purification. For conductivity experiments, acetonitrile (HPLC grade, GCC, assay 99.8%) was dried over calcium hydride and then double-distilled fractionally to give anhydrous solvent (<3 × 10^{-7} S cm^{-1}). The following salts were obtained from the suppliers indicated: $LiClO_4$ (Aldrich, 95%), $NaClO_4$ (Sigma, 99%), $KClO_4$ (Fluka, Chemica, >99.5%), $RbClO_4$ (Aldrich), $CsNO_3$ (Aldrich, 99%), $AgNO_3$ (GCC, 99%), $HgBr_2$ (BDH, 98%), $Cu(ClO_4)_2{\cdot}6H_2O$ (Aldrich), $Zn(ClO_4)_2{\cdot}6H_2O$ (Aldrich), $Cd(ClO_4)_2$ (Aldrich), $MnCl_2{\cdot}4H_2O$ (Aldrich), $Cr(NO_3)_3{\cdot}9H_2O$ (Aldrich), $Pb(ClO_4)_2{\cdot}3H_2O$ (Aldrich), $Co(ClO_4)_2{\cdot}6H_2O$ (Alfa), $Ni(NO_3)_2{\cdot}6H_2O$ (BDH, 99%), $Mg(ClO_4)_2$ (Aldrich). Chromatographic separations were performed on silica gel columns (60–120 mesh, CDH). Thin layer chromatography (TLC) was carried out using silica gel GF_{254} (Fluka). Unless otherwise noted, all reactions were carried out under dry nitrogen.

Synthesis: pathway A

***o*-(Ethoxycarbonylmethoxy)benzaldehyde (3) and ethyl 1-benzofuran-2-carboxylate (4).** In a 100 ml two-necked flask equipped with a magnetic stirrer bar and a reflux condenser, salicylaldehyde (2.50 g, 0.021 mol), ethyl bromoacetate (3.75 g, 0.021 mol) and anhydrous K_2CO_3 (3.06 g, 0.021 mol) were mixed in anhydrous CH_3CN (75 ml). The mixture was refluxed for 3–4 h and then allowed to cool to room temperature. The solid was separated by filtration and washed with acetonitrile. The combined organic solution was then evaporated to dryness to obtain a yellow oily residue. The crude product was purified by column chromatography using ethyl acetate–hexane (2 : 8) to give in order of increasing R_f values: **4** as a yellow oil (1.41 g, 37%), ^{1}H NMR δ_H 1.45 (t, J = 8 Hz, 3H, $OCH_2\mathit{CH_3}$), 4.46 (q, J = 8 Hz, 2H, $O\mathit{CH_2}CH_3$), 7.27–7.72 (m, 5H, aromatic); ^{13}C NMR δ_C 14.1, 61.4, 112.4, 113.8, 122.8, 123.7, 127.0, 128.6, 145.8, 155.5, 159.1; +APCI HRMS calcd for $C_{11}H_{11}O_3$ $(M + 1)^+$ 191.071, found 191.15. Compound **3** was obtained as pale yellow solid (1.81 g, 61%), mp 39–40 °C; ^{1}H NMR δ_H 1.31 (t, J = 8 Hz, 3H, $OCH_2\mathit{CH_3}$), 4.33 (q, J = 8 Hz, 2H, $O\mathit{CH_2}CH_3$), 4.81 (s, 2H, $O\mathit{CH_2}CO$), 6.91 (d, J = 4 Hz, 1H), 7.12 (t, J = 4 Hz, 1H), 7.56 (t, J = 4 Hz, 1H), 7.91 (d, J = 4 Hz, 1H), 10.61 (s, 1H, CHO); ^{13}C NMR δ_C 14.0, 61.2, 65.3, 112.5, 121.2, 125.0, 128.0, 135.5, 159.8, 168.0, 189.5; +APCI HRMS calcd for $C_{11}H_{13}O_4$ $(M + 1)^+$ 209.081, found 209.15. Longer reaction times (36 h) produced **4** in 78% yield. When acetonitrile was replaced with anhydrous acetone only **3** was produced (88%) yield in addition to a trace amount of salicylaldehyde. Purification was conducted by dissolving the crude product in diethyl ether and washing with aqueous 5% NaOH followed by water until the aqueous washes were neutral to pH paper.

***o*-(Ethoxycarbonylmethoxy)benzyl alcohol (5).** To a solution of **3** (0.30 g, 1.44 mmol) in MeOH (10 ml) was added $NaBH_4$ (30 mg, 72 mmol) at −5–0 °C. The reaction was stirred for 15 min and then quenched by adding 2 ml of cold water, followed by aqueous 5% HCl until the solution become acidic to pH paper. The mixture was extracted with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to give **5** as a colorless oil in 95% yield; ^{1}H NMR δ_H 1.3 (t, J = 6 Hz, 3H, $OCH_2\mathit{CH_3}$), 3.43 (t, 1H, OH), 4.25 (q, J = 6 Hz, 2H, $O\mathit{CH_2}CH_3$), 4.71 (2s, 4H, $\mathit{CH_2}$OH and $O\mathit{CH_2}CO$), 6.79 (d, J = 4 Hz, 1H), 6.95 (t, J = 6 Hz, 1H), 7.18–7.30 (m, 2H); ^{13}C NMR δ_C 14.1, 61.5, 62.0, 65.5, 112.0, 122.0, 129.1, 129.6, 130.2, 155.5, 169.1; + APCI MS (m/z): 193.15 (M^+ − OH).

***o*-(Ethoxycarbonylmethoxy)benzyl chloride (7).** To a solution of **5** (3.05 g, 15 mmol) in dry CH_2Cl_2 (150 ml) at 0 °C was added freshly distilled $SOCl_2$ (2.1 ml, 29 mmol). The reaction mixture was stirred at 0 °C for 15 min and then was quenched by adding 20 ml of cold water. The organic layer was washed with water until the aqueous layer was neutral to pH paper. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to give **7** as a pale yellow oil in 92% yield; ^{1}H NMR δ_H 1.3 (t, J = 6 Hz, 3H, $OCH_2\mathit{CH_3}$), 4.23 (q, J = 6 Hz, 2H, $O\mathit{CH_2}CH_3$), 4.71 (s, 2H, $\mathit{CH_2}$Cl), 4.76 (s, 2H, $O\mathit{CH_2}CO$), 6.29 (d, J = 4 Hz, 1H), 6.97 (t, J = 4 Hz, 1H), 7.28 (t, J = 4 Hz, 1H), 7.38 (d, J = 4 Hz, 1H);

^{13}C NMR δ_C 14.5, 41.7, 61.5, 66.0, 112.1, 122.0, 126.8, 130.2, 131.0, 156.0, 169.0, +APCI MS (*m*/*z*): 193.15 ($M^+ - {}^{35}Cl$).

Base-mediated coupling of 7 with ethanedithiol to give 8. To a suspension of ethanedithiol (0.88 g, 9.36 mmol) in 95% ethanol (100 ml) at room temperature was added KOH (1.10 g, 20 mmol). The reaction was left to stir for 1 h. A solution of **7** (4.14 g, 18.72 mmol) in benzene (50 ml) was added dropwise. The reaction was stirred for an additional 1 h and then the mixture was filtered. The filtrate was added to $CHCl_3$ (100 ml) and then washed with water. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to give **8** as a colorless solid in quantitative yield. The sample was pure enough for use in the subsequent reaction. An analytical sample was purified by TLC using ethyl acetate–hexane (3 : 7), mp 74–75 °C; ^{1}H NMR δ_H 1.3 (t, J = 4 Hz, 6H, OCH_2CH_3), 2.72 (s, 4H, SCH_2CH_2S), 3.85 (s, 4H, $ArCH_2S$), 4.15 (q, J = 4 Hz, 4H, OCH_2CH_3), 4.68 (s, 4H, OCH_2CO), 6.72 (d, J = 4 Hz, 2H), 6.92 (t, J = 4 Hz, 2H), 7.15–7.28 (m, 4H); ^{13}C NMR δ_C 9.4, 30.1, 31.8, 38.6, 61.5, 66.0, 112.0, 122.0, 127.8, 128.0, 131.0,169.0; +APCI HRMS calcd for $C_{24}H_{31}S_2O_6$ $(M + 1)^+$ 479.156, found 479.20.

Base-mediated coupling of 7 with 2-mercaptoethyl sulfide to give 9. Mercaptoethyl sulfide (1.22 g, 7.92 mmol) in 95% ethanol (100 ml), KOH (0.93 g, 16.6 mmol) and **7** (3.33 g, 15.8 mmol) in benzene (40 ml) were subjected to the same reaction conditions as **8** to afford **9** as a colorless oil in quantitative yield. The sample was pure enough for use in the subsequent reaction. An analytical sample was purified by TLC using ethyl acetate–hexane (3 : 7); ^{1}H NMR δ_H 1.31 (t, J = 4 Hz, 6H, OCH_2CH_3), 2.65 (m, 8H, SCH_2CH_2S), 3.85 (s, 4H, $ArCH_2S$), 4.31 (q, J = 4 Hz, 4H, OCH_2CH_3), 4.70 (s, 4 H, OCH_2CO), 6.73 (d, J = 4 Hz, 2H), 6.86 (t, J = 4 Hz, 2H), 7.14–7.30 (m, 4H); ^{13}C NMR δ_C 14.5, 30.0, 31.6, 32.2, 61.5, 66.0, 112.0, 121.9, 128.0, 128.5, 131.0, 155.7 169.0; +APCI HRMS calcd for $C_{26}H_{34}S_3O_6$ $(M + 1)^+$ 539.160, found 539.50.

LAH reduction of 8. To a suspension of LAH (0.3 g, 7.8 mmol) in anhydrous THF (50 ml) was added a solution of **8** (0.93 g, 1.95 mmol) in anhydrous THF (25 ml) at room temperature. The reaction mixture was stirred for 5 min and then was quenched by adding the mixture into wet diethyl ether (100 ml) at 0 °C. The mixture was then acidified with aqueous 5% HCl. The organic layer was separated and the aqueous layer was extracted with diethyl ether (50 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated to give **10** as a colourless oil in near 98% yield; ^{1}H NMR δ_H 2.65 (s, 4H, SCH_2CH_2S), 3.32 (br, 2H, OH), 3.78 (s, 4H, $ArCH_2S$), 3.92 (br, 4H, OCH_2CH_2O), 4.18 (s, 4H, OCH_2CH_2O), 6.81–6.92 (m, 4H), 7.12–7.28 (m, 4H); ^{13}C NMR δ_C 31.0, 31.2, 61.2, 69.9, 112.1, 121.0, 126.8, 129.0, 130.8, 156.5; +APCI HRMS calcd for $C_{20}H_{26}S_2O_6$ $(M + 1)^+$ 395.135, found 395.20.

LAH reduction of 9. Compound **9** (2.01 g, 3.71 mmol) was subjected to the same conditions as **8** to afford **11** as a colorless oil in 97% yield; ^{1}H NMR δ_H 2.61 (s, 8H, SCH_2CH_2S), 3.13 (br, 2H, OH), 3.80 (s, 4H, $ArCH_2S$), 3.92 (br, 4H,OCH_2CH_2O), 4.18 (s, 4H, OCH_2CH_2O), 6.85–6.95 (m, 4H), 7.17–7.29 (m, 4H); ^{13}C NMR δ_C 31.8, 31.9, 32.0, 61.5, 69.9, 112.1, 121.0, 126.8, 126.1, 129.0, 131.0, 156.1; +APCI HRMS calcd for $C_{22}H_{31}S_3O_4$ $(M + 1)^+$ 455.138, found 455.30.

Bis(tolylsulfonyloxy) compound 12. To a mixture of freshly purified toluene-*p*-sulfonyl chloride (0.84 g, 4.45 mmol) and diol **10** (0.70 g, 1.78 mmol) in anhydrous diethyl ether (60 ml) was added freshly machine-powdered KOH (1.25 g, 22.25 mmol) with vigorous stirring and cooling at −5–0 °C. Stirring with cooling at 0 °C was continued for 3 h. The mixture was then poured into ice–water (30 g). After vigorous stirring, a colorless solid was filtered off and washed several times with water until the aqueous washes became neutral to pH paper. After drying in air **12** was obtained in 52% yield, mp 108–109 °C; ^{1}H NMR δ_H 2.42 (s, 6H, CH_3), 2.50 (s, 4H, SCH_2CH_2S), 3.61 (s, 4H, $ArCH_2S$), 4.18 (t, J = 4 Hz, 4H, OCH_2CH_2O), 4.38 (t, J = 4 Hz, 4H, OCH_2CH_2O), 6.72 (d, J = 4 Hz, 2H), 6.91 (t, J = 4 Hz, 2H), 7.18 (t, J = 4 Hz, 2H), 7.12–7.20 (m, 4H), 7,33 (d, J = 8 Hz, 4H), 7.83 (d, J = 8 Hz, 4H); ^{13}C NMR δ_C 22.0, 30.2, 31.6, 65.8, 68.4, 112.0, 121.5, 127.7, 128.1, 128.6, 130.0, 130.5, 145.0, 156.5; +APCI HRMS calcd for $C_{34}H_{39}S_4O_8$ $(M + 1)^+$ 703.153, found 703.40.

Bis(tolylsulfonyloxy) compound 13. Compound **11** (1.02 g, 2.20 mmol) was subjected to the same conditions as **10** to afford **13** as a viscous product in 80% yield after column chromatographic purification using ethyl acetate–hexane (7 : 3); ^{1}H NMR δ_H 2.45 (s, 6H, CH_3), 2.57 (s, 8H, SCH_2CH_2S), 3.64 (s, 4H, $ArCH_2S$), 4.20 (m, 4H,OCH_2CH_2O), 4.38 (m, 4H, OCH_2CH_2O), 6.76 (d, J = 4 Hz, 2H), 6.93 (d, J = 4 Hz, 2H), 7.14–7.23 (m, 4H), 7.32 (d, J = 8 Hz, 4H), 7.84 (d, J = 8 Hz, 4H); ^{13}C NMR δ_C 21.8, 29.9, 30.0, 32.0, 32.1, 66.0, 68.2, 112.0, 121.5, 127.5, 128.0, 128.6, 130.0, 130.6, 144.9, 155.2; +APCI HRMS calcd for $C_{36}H_{43}S_5O_8$ $(M + 1)^+$ 763.150, found 763.50.

25,27-*O*-[Ethylenedithiodimethylenedi-*o*-phenylenedioxydiethylene]-*p*-*tert*-butylcalix[4]arene 1. In a 500 ml two-necked flask equipped with a magnetic stirrer bar and a reflux condenser, *p*-*tert*-butylcalix[4]arene (3.2 g, 4.93 mmol) and anhydrous K_2CO_3 (7.04 g, 51.0 mmol) were mixed in anhydrous CH_3CN (150 ml). The mixture was stirred at room temperature for 3 h and then heated to reflux. To the refluxing solution, a solution of **12** (3.5 g, 4.93 mmol) in anhydrous CH_3CN (150 ml) was added dropwise over a period of 10 h. The reaction mixture was refluxed with stirring for 7 d after which time the CH_3CN was evaporated and the residue was dissolved in $CHCl_3$ (100 ml). Aqueous 5% HCl was added until the aqueous become slightly acidic. The organic layer was dried over anhydrous $MgSO_4$ and then evaporated. The crude product was chromatographed on silica gel using ethyl acetate–hexane (1 : 9) as eluent to give **1** as a colorless solid (1.51 g, 30%). The product was further purified by washing with diethyl ether, mp 269–271 °C; ^{1}H NMR δ_H 0.98 (s, 18H, *t*-But), 1.30 (s, 18H, *t*-But), 2.70 (s, 4H, SCH_2CH_2S), 3.31 (d, J = 12 Hz, 4H, $ArCH_2Ar$), 3.99 (s, 4H, $ArCH_2S$), 4.35–4.53 (m, 12H, OCH_2CH_2O and $ArCH_2Ar$), 6.81 (s, 4H), 6.83–7.0 (m, 4H), 7.04 (s, 4H), 7.28 (s, 2H, OH), 7.18–7.32 (m, 4H);^{13}C NMR δ_C 29.6, 31.1, 31.8, 32.0, 34.1, 66.5, 74.7, 111.5, 121.6, 125.3, 125.8, 128.0, 128.2, 128.5, 131.2, 132.6, 141.2, 147.1, 150.0, 150.6, 151.0, 156.5; +APCI HRMS calcd for $C_{64}H_{79}S_2O_6$ $(M + 1)^+$ 1007.531, found 1007.9. Anal. calcd for $C_{64}H_{78}S_2O_6.(CH_3CN)_4$: C, 73.81; H, 7.74; S, 5.47, found: C, 72.51; H, 7.37; S, 5.46%.

25,27-*O*-[Thiodiethylenedithiodimethylenedi-*o*-phenylenedioxydiethylene]-*p*-*tert*-butylcalix[4]arene 2. Compound **13** (3.0 g, 3.94 mmol) was subjected to the same reaction conditions as **12** to afford **2** as a colourless solid (1.6 g, 39%). The product was further purified by washing with diethyl ether, mp 248–250 °C; ^{1}H NMR δ_H 0.80 (s, 18H, *t*-But), 1.30 (s, 18H, *t*-But), 2.51 (s, 8H, SCH_2CH_2S), 3.31 (d, J = 14 Hz, 4H, $ArCH_2Ar$), 3.90 (s, 4H, $ArCH_2S$), 4.30–4.45 (m, 12H, OCH_2CH_2O and $ArCH_2Ar$), 6.75 (s, 4H), 6.88 (s, 2H, OH), 6.86–6.98 (m, 4H), 7.06 (s, 4H), 7.15–7.35 (m, 4H); ^{13}C NMR δ_C 29.5, 31.1, 31.5, 31.8, 31.9, 32.0, 34.0, 66.9, 74.8, 111.5, 121.2, 125.1, 125.6, 127.6, 128.0, 128.1, 131.0, 132.4, 141.5, 146.9, 149.8, 150.5, 156.5; +APCI HRMS calcd for $C_{66}H_{83}S_3O_6$ $(M + 1)^+$ 1067.535, found 1067.90. Anal. calcd for $C_{66}H_{82}S_3O_6$: C, 74.12; H, 7.74; S, 8.99, found: C, 74.24; H, 7.82; S, 9.11%.

Pathway B

***o*-(2-Bromoethoxy)benzaldehyde (14).** In a 250 ml two-necked flask equipped with a magnetic stirrer bar and a reflux con-

denser, salicylaldehyde (3.90 g, 32 mmol), 1,2-dibromoethane (60.1 g, 320 mmol) and anhydrous K_2CO_3 (8.83 g, 64.0 mmol) were mixed with anhydrous CH_3CN (200 ml). The mixture was refluxed for 30 h and then cooled to room temperature, filtered and the solid was washed with CH_3CN. The filtrate was evaporated to dryness. The crude product was purified by column chromatography on silica gel using $CHCl_3$–hexane (8 : 2) to give **14** as a pale yellow solid (4.81 g, 66%), mp 51–52 °C; ^{1}H NMR δ_H 3.61 (t, 2H, OCH_2CH_2Br), 4.34 (t, 2H, OCH_2CH_2Br), 6.88 (d, 1H), 6.98 (t, 1H), 7.45 (t, 1H), 7.81 (d, 1H); ^{13}C NMR δ_C 29.1, 68.0, 103.0, 121.8, 125.2, 128.7, 136.0, 160.5, 189.8; +APCI HRMS calcd for $C_9H_{10}BrO_2$ $(M + 1)^+$ 228.9864, found 228.95.

25,27-*O*-Bis(2-formylphenoxyethyl)-*p*-*tert*-butylcalix[4]arene (15). In a 100 ml two-necked flask equipped with a magnetic stirrer bar and a reflux condenser, *p*-*tert*-butylcalix[4]arene (0.40 g, 0.62 mmol), and anhydrous K_2CO_3 (0.09 g, 0.62 mmol) were mixed with anhydrous CH_3CN (20 ml) and refluxed for 1 h. At the reflux temperature, a solution of **14** (0.282 g, 1.24 mmol) in CH_3CN (5 ml) was added dropwise. The mixture was further refluxed for 4 days and then cooled, filtered and the solid was washed with CH_3CN. The combined filtrate was evaporated to dryness. The residue was dissolved with $CHCl_3$ and washed with aqueous 5% HCl. After drying and evaporation of the organic solvent the crude product was washed with diethyl ether to afford a **15** as a colourless solid, (0.45 g, 75%), mp 93–95 °C; IR (KBr, ν/cm^{-1}) 1684 (CHO), 3459 (OH); ^{1}H NMR δ_H 1.03 (s, 18H, *t*-But), 1.28 (s, 18H, *t*-But), 3.31 (d, J = 12 Hz, 4H, $ArCH_2Ar$), 4.33 (d, J = 12 Hz, 4H, $ArCH_2Ar$), 4.42 (m, 8H, OCH_2CH_2O), 6.88 (s, 4H), 7.0 (s, 4H), 6.96–7.04 (m, 4H), 7.42–7.52 (m, 4H, aromatic and OH), 7.82 (d, J = 8 Hz, 2H), 10.48 (s, 2H, CHO); ^{13}C NMR δ_C 29.8, 31.0, 31.5, 31.6, 34.0, 67.7, 73.8, 112.6, 121.1, 125.2, 126.0, 128.0, 128.2, 133.0, 136.0, 141.9, 147.5, 150.0, 150.6, 161.0, 190.2; +APCI HRMS calcd for $C_{62}H_{73}O_8$ $(M + 1)^+$ 945.531, found 945.90.

25,27-*O*-Bis[2-(hydroxymethyl)phenoxyethyl]-*p*-*tert*-butylcalix[4]arene (16). To a solution of **15** (0.301 g, 0.317 mmol) in THF (10 ml) at room temperature was added $NaBH_4$ (50 mg, 1.27 mmol). After 10 min the reaction was quenched by adding 5 ml of cold water followed by 5 ml of aqueous 5% HCl. The mixture was extracted with $CHCl_3$ (20 ml). The organic layer was dried over anhydrous $MgSO_4$ and then evaporated to afford **16** as a colourless solid in 100% yield, mp 205–207 °C; ^{1}H NMR δ_H 1.16 (s, 18H, *t*-But), 1.24 (s, 18H, *t*-But), 3.39 (d, J = 10 Hz, 4H, $ArCH_2Ar$), 4.28–4.38 (m, 12H, OCH_2CH_2O and $ArCH_2Ar$), 4.63–4.82 (m, 6H, CH_2OH), 6.65 (d, J = 6 Hz, 2H), 6.88–7.35 (m, 14H), 8.94 (s, 2H, OH); ^{13}C NMR δ_C 31.0, 31.1, 31.7, 32.2, 61.2, 66.9, 74.8, 111.1, 121.0, 125.7, 126.1, 128.2, 129.6, 130.0, 130.8, 133.6, 142.7, 148.0, 149.6; +APCI HRMS calcd for $C_{62}H_{77}O_8$ $(M + 1)^+$ 949.562, found 949.90.

25,27-*O*-Bis[2-(chloromethyl)phenoxyethyl]-*p*-*tert*-butylcalix[4]arene (17). To a solution of **16** (0.55 g, 0.58 mmol) in anhydrous benzene (50 ml) was added freshly distilled $SOCl_2$ (0.16 ml, 2.32 mmol) at room temperature. The reaction was stirred for 15 min and then cold water was added. The organic layer was separated and washed with water, dried and evaporated. The crude product was purified by column chromatography using ethyl acetate–hexane (2 : 8) to afford **17** as a colorless solid (0.33 g, 58%), mp 197–198 °C; ^{1}H NMR δ_H 1.05 (s, 18H, *t*-But), 1.30 (s, 18H, *t*-But), 3.32 (d, J = 16 Hz, 4H, $ArCH_2Ar$), 4.32–4.41 (m, 12H, OCH_2CH_2O and $ArCH_2Ar$), 4.73 (s, 4H, CH_2Cl), 6.88–7.10 (m, 12H), 7.23–7.38 (m, 4H), 7.65 (s, 2H, OH); ^{13}C NMR δ_C 29.5, 31.0, 31.6, 31.7, 34.0, 42.0, 67.5, 74.4, 111.8, 121.0, 125.1, 125.6, 126.3, 128.0, 120.9, 130.8, 133.0, 141.8, 147.5, 149.9, 150.5; +APCI HRMS calcd for $C_{62}H_{74}Cl_2O_6$ $(M + 1)^+$ 984.486, found 985.80.

Base-mediated coupling of 17 with 2-mercaptoethyl sulfide to give 2. To a solution of KOH (0.12 g) in 95% ethanol (60 ml) was added a solution of **17** (0.54 g, 0.548 mmol) and 2-mercaptoethyl sulfide (0.084 g, 0.548 mmol) in benzene (30 ml) dropwise over 3 h. The reaction was stirred for an additional 3 h and then the organic solvents were evaporated. The residue was dissolved in CH_2Cl_2 (20 ml) and washed with aqueous 5% HCl. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The crude product was washed with diethyl ether to afford a colorless solid (0.43 g, 74%) whose mp and spectroscopic properties were identical to those of **2** as obtained by pathway A.

Conductance measurements

Solutions having metal ion concentrations of approximately 1.0–1.10 × 10^{-4} M were prepared by dissolving a known amount of each salt in anhydrous acetonitrile. These solutions were also used as solvents for preparing the calix[4]thiacrowns with concentrations of approximately 1.5–1.6 × 10^{-3} M in order to keep the electrolyte concentration constant during the titration. Conductance measurements were carried out with a microprocessor conductivity meter (WTW/LF537). A calibrated cell (WTW/Tetracon 96) having cell constant of 0.609 cm^{-1} was used. The cell was calibrated using analytical grade KCl (Merck) in triply-distilled deionized water. The temperature of the solution was controlled to ±0.1 °C using a thermostatted circulator water bath (HAAKE D1) equipped with a refrigeration unit. In order to determine the complex formation constant with the different metal cations used, 50 ml of the desired salt solution were placed in a specially-designed water-jacketed cell (150 ml, Pyrex®) which was equipped with a magnetic stirrer and was connected to the thermostatted circulator water bath at 25 °C. The conductances of the solutions were measured at 25 °C. Known amounts (0.5 ml of solutions of calix[4]thiacrown **1** or **2**) were added in a stepwise manner using a calibrated micro-pipette. The conductivity of the mixture was then measured after stirring and temperature equilibration. This procedure was repeated in the same manner for each addition. Addition of the ligand was continued until the desired ligand-to-cation mole ratio was achieved. Mathematical calculation of the stability constant K value from the conductivity data was achieved by means of the simplex program listed elsewhere.[19] The conductometric measurements showed that the anhydrous acetonitrile solutions of the ligands **1** or **2** behave as non-electrolytes (0.0 S cm^{-1}).

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