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Thiacalix[4]arene derivatives bearing imidazole units: a ditopic hard/soft receptor for Na^+/Ag^+ and K^+/Ag^+ with allosteric effect and a reusable extractant for dichromate anions

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Abstract: Two novel receptors **L1** and **L2** possessing imidazole moieties based on thiacalix[4]arene in the 1,3-*alternate* conformation have been synthesized and characterized. The crystal structures of **L1** and **L2** have been determined. The binding behaviour towards Li^+ , Na^+ , K^+ and Ag^+ ions has been examined by ^1H NMR titration experiments in ($\text{CDCl}_3/\text{CD}_3\text{CN}$; 10:1, v/v) solution. The exclusive formation of mononuclear complexes of **L1** with metal cations is of particular interest revealing a negative allosteric effect in the thiacalix[4]arene family. Liquid-liquid extraction experiments indicate that synthesized **L2** can be utilized as an efficient reusable extractant for dichromate anion by controlling the pH of the aqueous solution.

Introduction

Allosteric regulation between subunits within a receptor system is one of nature's elegant strategies for precisely regulating and controlling the diverse functions in biological systems.¹ The use of allosteric regulation has also been utilized by chemists to control molecular function by external stimuli to transduce chemical signals, and to achieve chemical feedback regulation.² Inspired by this, much effort has been devoted in supramolecular chemistry to construct artificial systems to achieve analogous

functions such as molecular recognition and signal amplification.

Di- or poly-topic receptors have been constructed with two or more binding subunits within the same macrocyclic structure.³ It is well known that such systems are suitable candidates for the allosteric regulation of host-guest interactions with metal cations.^{1d,4} Thiacalix[4]arenes are macrocyclic molecules which can be relatively easily functionalized and have pre-organized binding sites. In particular, the 1,3-*alternate* conformation is capable of possessing binding subunits in the two opposite domains of the molecule, and is thus a potentially ideal structure for allosteric regulation.⁵ Consequently, we have been interested in being able to incorporate two subunits having different binding properties onto a thiacalix[4]arene and to control or maintain a 1,3-*alternate* conformation. This would therefore permit the construction of a di-topic receptor system which should possess allosteric features.

The development of systems for the fast estimation, removal and separation of silver (soft metal), together with the use of Ag^+ complexes in photographic materials and their potential use in cancer radioimmunotherapy has attracted the attention of supramolecular chemists towards designing effective Ag^+ -selective receptors.⁶ Recently, we undertook the synthesis and evaluation of thiacalix[4]arene and homotrioxacalix[3]arene ligands as Ag^+ ionophores and found that the introduction of imidazole groups at the lower rim of the calixarene skeleton resulted in a high affinity for Ag^+ .⁷ On the other hand, it has been reported that by introducing an ester group at its lower or upper rim, the thiacalix[4]arene derivative can selectively complex alkali metal cations (hard metals), such as Na^+ and K^+ .⁸ Thus, the introduction of imidazole groups onto the thiacalix[4]arene framework as one binding subunit and the introduction of ester groups on the opposite side as the other binding subunit, was envisioned. Such a system could be used as a ditopic receptor with two binding subunits pre-organised for both hard (Na^+ and K^+) and soft (Ag^+) cations, and with possible switching of complexation preferences.

Herein, the synthesis, X-ray structure, and complexation studies of a novel ditopic receptor **L1** which possesses two binding subunits (imidazole and ester moieties) based on a thiacalix[4]arene in the 1,3-*alternate* conformation is reported. In order to further investigate the allosteric effects, the mono-topic receptor **L2**, with a similar structure, was also produced. Additionally, due to the amphoteric nature of the imidazole group can function not only as an effective cation but also as an anion receptor under appropriate conditions. Also, as a continuation of our search for dichromate anion extractants based on thiacalixarene derivatives,^{7,13} the extraction efficiency of the systems

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Scheme 1. The synthetic routes to receptors **L1** and **L2**.

described herein towards dichromate anion was conducted by liquid-liquid extraction experiments.

Results and Discussion

Synthesis

The preferential formation of the 1,3-*alternate* conformer of thiocalix[4]arene occurs in the presence of a cesium cation whose size is compatible with that of the thiocalix[4]arene cavity and thus contributes significantly to the cation- π interaction.⁵ Receptor **L1** could therefore be obtained in 55% yield by the stereoselective *O*-alkylation of **1**¹⁰ with 2-chloromethyl-1-methyl-1*H*-imidazole⁹ in the presence of Cs_2CO_3 in dry acetone (Scheme 1). Similarly, receptor **L2** was obtained in 44% yield by the stereoselective *O*-alkylation of **2**¹¹ with 2-chloromethyl-1-methyl-1*H*-imidazole in the presence of Cs_2CO_3 in dry acetone (Scheme 1).

The ^1H NMR spectrum of **L1** exhibits two singlets for the *tert*-butyl protons at up-field positions, viz δ 1.10 and 1.26 ppm; two singlets for the aromatic protons at δ 7.24 ppm and 7.46 ppm (Figure S1), all of which is indicative of a C_2 -symmetric structure for the 1,3-*alternate* conformation. Obviously, receptor **L2** is also in the 1,3-*alternate* conformation revealing two singlets for the *tert*-butyl protons (δ 0.82 and 1.15 ppm) and two singlets for the aromatic protons (δ 7.12 and 7.27 ppm, Figure S4). Surprisingly, remarkable shielding effects are experienced

Scheme 2. The synthetic route of reference compound **L3**.

Table 1. Partial chemical shifts of **L1**, **L2** and reference compound **L3**.^a

Compound	Chemical shifts, δ (ppm)		
	-N-CH ₃	H ₄	H ₅
L1	2.78	6.65	6.96
L3	3.70	6.82	6.94
L2	2.57	6.68	6.99
$\Delta\delta_{\text{L1}}^b$	-0.92	-0.17	+0.02
$\Delta\delta_{\text{L2}}^b$	-1.13	-0.14	+0.05

^a $\Delta\delta$ value is the difference of the chemical shift between **L1**, **L2** and reference compound **L3** in CDCl_3 at 27 °C. ^b A plus sign (+) denotes a shift to lower magnetic field, whereas, a negative sign (−) denotes a shift to higher magnetic field.

by the N-CH₃ protons of **L1** and **L2** (Table 1), compared with the reference compound **L3**,⁷ which is prepared by *O*-alkylation of 4-*tert*-butyl-2,6-dimethylphenol **3**¹² with 2-chloromethyl-1-methyl-1*H*-imidazole in the presence of NaH (Scheme 2). It strongly suggests that the heteroaromatic protons of the imidazole groups for both of **L1** and **L2** are exposed to the ring current shielding effect area operating between two of the thiocalixarene benzene rings.^{7,13}

Furthermore, X-ray crystallographic analysis further confirmed the molecular structure of **L1** and **L2** as shown in Figure 1. Both **L1** (Fig. 1a) and **L2** (Fig. 1c) are in the 1,3-*alternate* conformation. As expected, the imidazole ring containing N(1) and C(45) of **L1** and **L2** are pointing into the thiocalix[4]arene cavity which is consistent with the significant up-field shift for the N-CH₃ group in the ^1H NMR spectra. A slightly distorted square is observed for receptor **L1** (Fig. 1b, S1...S2 = 5.636 Å, S2...S3 = 5.562 Å, S3...S4 = 5.546 Å and S4...S1 = 5.579 Å); however, an approximate square is observed for receptor **L2** (Fig. 1d, S1...S2 = 5.559 Å, S2...S3 = 5.552 Å, S3...S4 = 5.535 Å and S4...S1 = 5.558 Å). In other words, the cavity size of receptor **L1** is a little larger than receptor **L2** based on the sum of the S...S distances.

Figure 1. Single-crystal structure of **L1** showing (a) the side view (b) the top view; Single-crystal structure of **L2** showing (c) the side view (d) the top view. Hydrogen atoms, ethanol and water molecules as solvent of crystallization, and minor disorder components have been omitted for clarity.

Complexation studies

At the onset of the study, it was anticipated that multi-recognition of both hard metals (Na^+ , K^+) and soft metals (Ag^+) by the ditopic receptor **L1** could be detected. This of course, being due to the presence of the two ester moieties⁸ at one face of the thiacalix[4]arene cavity and the two imidazole moieties⁷ at the opposite face. The binding affinities of **L1** and **L2** toward metal cations were therefore evaluated by ^1H NMR titration experiments ($\text{CDCl}_3/\text{CD}_3\text{CN} = 10:1$, v/v).

^1H NMR titration studies

Both **L1** and **L2** possess imidazole moieties which would preferentially exhibit higher affinity towards Ag^+ ion. Hence, we conducted ^1H NMR titration experiments with $\text{CF}_3\text{SO}_3\text{Ag}$. Titration of a solution of **L1** with Ag^+ ions resulted in dramatically downfield shifts ($\Delta\delta = +0.86$ ppm) for the imidazole- $\text{N}-\text{CH}_3$ protons at δ 3.68 ppm after complexation with 1.0 equiv. Ag^+ (Figure 2). It was noteworthy that δ 3.68 ppm was almost the same chemical shift for the imidazole- $\text{N}-\text{CH}_3$ protons (δ 3.70 ppm, Table 1) of the reference compound **L3**. It strongly suggested that the imidazole- $\text{N}-\text{CH}_3$ group of **L1** escaped from the shielding area to the deshielding area upon Ag^+ capture by receptor **L1**. Subsequently, the adjacent imidazolyl-proton H_4 was also affected by the change in the position of the $\text{N}-\text{CH}_3$ group, and exhibited a downfield shift ($\Delta\delta = +0.46$ ppm) at δ 7.14 ppm. In contrast, another significantly up-field shift ($\Delta\delta = -0.15$ ppm) for the methylene protons of OCH_2Imid at δ 5.04 ppm was also observed. Thus chemical shift change may be attributed to the OCH_2Imid methylene protons being folded into the shielding area of the thiacalix[4]arene-cavity in order to form an efficient complex with Ag^+ . All of the evidence strongly suggested that Ag^+ was complexed by the nitrogen atoms of the imidazole moieties via $\text{N}\cdots\text{Ag}^+$ interactions.

Similar phenomena were observed for the titration experiment of **L2** with Ag^+ (Figure S7). The proton resonances of $\text{N}-\text{CH}_3$ and H_4 in the imidazole rings were gradually shifted to downfield upon addition of Ag^+ ions which could be attributed to the conformational change of receptor **L2** with a concomitant deshielding effect. The methylene protons of OCH_2Imid were slightly shifted up-field after being complexed with one equiv. Ag^+ , which may also be attributed to the OCH_2Imid methylene protons being folded into the shielding field of the thiacalix[4]arene-cavity. Both **L1** and **L2** exhibited slight chemical shift changes of the aromatic protons which are also attributed to the conformational changes upon complexation. On increasing the titration amount

Figure 2. Partial ^1H NMR spectra of **L1** (5.0 mM) and increasing concentrations of Ag^+ in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (10:1, v/v) at 298 K.

Figure 3. Partial ^1H NMR spectra of **L1** (5.0mM) and increasing concentrations of K^+ in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (10:1, v/v) at 298 K.

of Ag^+ to 2.0 equiv., no further significant changes were observed for **L1** and **L2**. According to the corresponding titration curve, the association constants were calculated to be 44 M^{-1} and 83 M^{-1} , respectively (Figure S16 and S19). All of the observed phenomenon suggested that receptor **L1** and **L2** possess higher affinity towards Ag^+ ion via $\text{N}\cdots\text{Ag}^+$ interactions.

The affinity towards alkali metal cations was also investigated, given that K^+ and Na^+ ions are known to interact with the ester moiety.⁸ ^1H NMR titration experiments with $\text{CF}_3\text{SO}_3\text{K}$, $\text{CF}_3\text{SO}_3\text{Na}$ and $\text{CF}_3\text{SO}_3\text{Li}$ were carried out. The addition of an equiv. of $\text{CF}_3\text{SO}_3\text{K}$ to **L1** caused immediate complexation as demonstrated by the downfield shifts of the ester ethyl group resonances (OCH_2CO , $\Delta\delta = +0.25$; COOCH_2 , $\Delta\delta = +0.12$ ppm, Figure 3) for the 1:1 complex of **L1** with an association constant of 253 M^{-1} (Figure S17). The slightly downfield shifts of the thiacalixarene benzene protons may be attributed to the decreased shielding effect operating in two of the thiacalixarene benzene rings upon complexation of the ester moieties with K^+ . The signals of the imidazole group's protons were broadened, showing slow ligand exchange on the NMR time scale. A similar phenomenon was observed in the presence of an equiv. of $\text{CF}_3\text{SO}_3\text{Na}$ (OCH_2CO , $\Delta\delta = +0.15$; COOCH_2 , $\Delta\delta = +0.07$ ppm, Figure S8) which formed a 1:1 complex of **L1** with an association constant of 92 M^{-1} (Figure S18). $\text{CF}_3\text{SO}_3\text{Li}$ did not cause detectable spectral changes for **L1** due to the small atom radius which could not form an efficient complex (Figure S9). According to the corresponding association constants for these processes, it is clear that the association constants for alkali metal cations directly follow the radius of the alkali metal cations: $\text{K}^+ > \text{Na}^+ >$

Figure 4. ^1H NMR shift of CH_2 (blue peak) in **L1** with Ag^+ , K^+ , Na^+ and **L2** with Ag^+ . [In the presence of 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 2.0 equiv. of cations in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (10:1, v/v), respectively.]

Figure 5. Chemical shift changes of **L1** and **L2** in the presence of different metal ions; (+) denotes the downfield shift and (–) denotes the up field shift.

Li^+ which reflects the size recognition ability of receptor **L1.**

Given the fact that receptor **L2** is unable to bind alkali metal cations due to one side having phenyl moieties present, which are inactive for recognition of alkali metal cations, as expected, no significant changes were observed during the ^1H NMR titration experiments with alkali metal cations. The change of the chemical shift of the CH_2 groups of receptor **L1** and **L2** plotted against the amount of cations (Ag^+ , K^+ and Na^+) is shown in Figure 4. The $\Delta\delta$ value increased in proportion to the amount of cations and became almost constant after the addition of 1.0 equiv. of cations, which indicated the 1:1 stoichiometry of the receptors–cations complex that was formed.

MALDI-TOF-MS data also supported the formation of a stable 1:1 host–guest complex. As shown in Figure S10 ~ S12, the mass spectrum of **L1** with cations exhibited peaks at 1187.123, 1119.301 and 1103.285 corresponding to masses of $[\text{L1} + \text{Ag}]^+$, $[\text{L1} + \text{K}]^+$ and $[\text{L1} + \text{Na}]^+$, respectively. And the mass spectrum of **L2** with cation exhibited peaks at 1195.107 corresponding to masses of $[\text{L2} + \text{Ag}]^+$ (Figure S13). In other words, the 1:1 stoichiometry complex between receptors and guest cations were unambiguously confirmed by Mass. Consequently, the proposed binding model and chemical shift changes ($\Delta\delta$) of **L1** and **L2** with metal ions are summarized in Figure 5.

Allosteric studies

The presence of an allosteric effect with **L1** was studied by ^1H NMR titration. Upon titration with one equiv. of Ag^+ to the 1:1 $\text{M}^+ \subset \text{L1}$ ($\text{M}^+ = \text{Li}^+$, Na^+ or K^+) complex solution, the corresponding peaks were dramatically shifted to the same chemical shift positions as were noted for the 1:1 $\text{Ag}^+ \subset \text{L1}$ complex. This therefore implied that Ag^+ was bound to the imidazole site and induced the decomplexation of hard metal cations (Li^+ , Na^+ or K^+) from the ester site (Figure 6). Furthermore, the 1:1 $\text{Ag}^+ \subset \text{L1}$ complex was also titrated with an equiv. of M^+ ions ($\text{M}^+ = \text{Li}^+$, Na^+

Figure 6. Partial ^1H NMR spectra of receptor **L1** (5.0 mM) in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (10:1, v/v) complex with an equiv. of various metal ions; M^+ denoted the alkali metal cations ($\text{M}^+ = \text{Li}^+, \text{Na}^+ \text{ or } \text{K}^+$).

or K^+). None of the spectral patterns of $\text{Li}^+ < [\text{Ag}^+ < \text{L1}]$, $\text{Na}^+ < [\text{Ag}^+ < \text{L1}]$ and $\text{K}^+ < [\text{Ag}^+ < \text{L1}]$ complexes showed any detectable signal changes. These results indicated that the complexation of Ag^+ completely suppressed the recognition of Li^+ , Na^+ or K^+ by the ester moiety. The concept of a negative allosteric effect by receptor **L1** is shown in Figure 7.

Figure 7. Proposed negative allosteric effect of ditopic receptor **L1**. M^+ denotes the alkali metal cations ($\text{M}^+ = \text{Li}^+, \text{Na}^+ \text{ or } \text{K}^+$).

Two-phase solvent extraction

Chromium and its compounds are widely used in our daily life, such as., tanning, plating, leather dyes, and in the photographic industry, all of which produce large quantities of toxic pollutants.²¹ However, high concentrations of hexavalent chromium (VI) ion is toxic to the human body, as it can diffuse as $\text{Cr}_2\text{O}_7^{2-}$ or HCr_2O_7^- through cell membranes and oxidize biological molecules.²² Thus, selective treatment of pollutional water containing Cr (VI) prior to discharge is essential. The dichromate ($\text{Cr}_2\text{O}_4^{2-}$ and HCr_2O_7^-) ions are anions with oxide functionalities at their periphery. These oxide moieties are potential sites for hydrogen bonding to the complexant or host molecule(s). Imidazole group, among such heterocyclic units, the imidazole ring behaves as an excellent hydrogen bond donor moiety in synthetic anion receptor systems, and the acidity of the NH proton of the imidazole can be tuned by changing the electronic properties of the imidazole substituents.¹⁴ Thus, the introduction of a imidazole moiety to thiacalix[4]arene would potentially lead to an effective extractant for dichromate anions.

To investigate further the applicability of the receptors **L1** and **L2** which possess imidazole groups, liquid-liquid extraction experiments were performed to examine the extraction ability of **L1** and **L2** toward dichromate anion from the aqueous phase into the organic phase (dichloromethane) over the range of pH

1.5–7.0. It has been clearly demonstrated that the lower the pH, the higher the extractability is found for both of **L1** and **L2** (Figure 8). This could be attributed to an ion-pair (hydrogen bonded) complex formed in the two-phase extraction system following proton transfer to the nitrogen atoms of the imidazole units in **L1** and **L2** and then complexation of $\text{Cr}_2\text{O}_7^{2-}/\text{HCr}_2\text{O}_7^-$.

Figure 8. E% values of dichromate anion with ionophores **L1** and **L2** (2.0×10^{-4} M, 2 h at 25 °C) at pH 1.5–7.0 ($\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$:10/10 (v/v); $\text{K}_2\text{Cr}_2\text{O}_7 = 1 \times 10^{-4}$ M).

Interestingly, according to the reference reports,⁷ the reference compound **L3** showed almost no significant selective binding of dichromate anions even at low pH. It strongly suggests that the thiacalix[4]arene platform plays an important role in confirming cooperative participation of the peripheral imidazole groups. Furthermore, the extraction results also indicated that extractant **L2** was more effective for the extraction of dichromate anions at low pH (pH 1.5) than extractant **L1**. This could be ascribed to the cavity size of extractant **L2** is smaller and more symmetrical than extractant **L1** (Figure 1, X-ray results). In other words, extractant **L2** maybe provided a more ideal mutual distance needed for hydrogen bonding between two imidazole groups to extract dichromate anions.

Additionally, the extractants **L1** and **L2** possess 'proton-switchable' binding sites, namely the imidazole moieties, which can be protonated at low pH.¹⁵ The protonated forms of **L1** and **L2** are more effective at complexing with dichromate anion through hydrogen bonds. In other words, the extraction of dichromate anion by extractants **L1** and **L2** only occurs when the aqueous phase is acidic, especially at lower pH, in order to form efficient hydrogen bonds. Thus, a reusable extractant concept is possible for extractants **L1** and **L2** by controlling the pH of the aqueous solution (Figure 9).

Figure 9. A proposed reusable extractant concept of **L2** with $\text{Cr}_2\text{O}_7^{2-}$.

Conclusions

Two new thiocalix[4]arene receptors **L1** and **L2** which each possess imidazole moieties in the 1,3-*alternate* conformation have been synthesized and characterized. The X-ray crystal structures of both **L1** and **L2** have been determined, confirming their 1,3-*alternate* conformations. The binding behaviour towards Na⁺, K⁺ and Ag⁺ ions have been examined by ¹H NMR titration experiments in (CDCl₃/CD₃CN; 10:1, v/v) solutions. The ditopic receptor **L1** showed affinity not only toward hard alkali metal cations but also toward soft metal Ag⁺ cations, owing to the presence of the two ester moieties at one face of the thiocalix[4]arene cavity and two imidazole moieties at the opposite face. However, the monotopic receptor **L2** only exhibited affinity toward Ag⁺ and was unable to bind alkali metal cations due to its lack of the ester groups. The exclusive formation of mononuclear complexes of **L1** with metal cations is of particular interest with respect to negative allosteric effects in the thiocalix[4]arene family. These findings further demonstrate that preorganization, suitable conformational changes and affinity have a pronounced effect on the complexation process between the two different arms placed at the two edges of the thiocalix[4]arene platform. Due to its amphoteric nature, the imidazole ring can function as an effective cation and/or anion receptor system. Furthermore, the extraction abilities of **L1** and **L2** toward dichromate anion were evaluated by a liquid-liquid extraction method. The extraction results indicate that the synthesized **L2** can be utilized as a reusable extractant by control of the pH of the aqueous solution.

Experimental Section

General procedures

Unless otherwise stated, all reagents used were purchased from commercial sources and were used without further purification. All solvents used were dried and distilled by the usual procedures prior to use. All melting points (Yanagimoto MP-S1) are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded on a Varian-400MR-vnmrs 400 with SiMe₄ as an internal reference: *J*-values are given in Hz. Mass spectra were obtained with 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. UV-vis spectra were recorded using a Shimadzu UV-3150UV-vis-NIR spectrophotometer.

Materials

2-Chloromethyl-1-methyl-1*H*-imidazole hydrochloride,⁹ 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(ethoxycarbonyl)methoxy]-26,28-dihydro-xy-2,8,14,20-tetrathiocalix[4]arene **1**¹⁰ and 25,27-dibenzoyloxy-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiocalix[4]arene-26,28-diol **2**¹¹ were prepared according to the reported procedures.

Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(ethoxycarbonyl)methoxy]-26,28-bis-[1-methyl-(imidazole)-methoxy]-2,8,14,20-tetrathiocalix[4]arene (**L1**):

A mixture of *diester 1* (200 mg, 0.224 mmol) and Cs₂CO₃ (728 mg, 2.24 mmol) in dry acetone (30 mL) was heated at reflux for 1 h under nitrogen. Then 2-chloromethyl-1-methyl-1*H*-imidazole hydrochloride (372 mg, 2.24 mmol) was added and the mixture was heated at reflux for another 20 h. After cooling the reaction mixture to room temperature, it was acidified with 1 M HCl (15 mL) and extracted with CH₂Cl₂ (20 mL × 3). The combined extracts were washed with water (30 mL × 2) and then brine (30 mL × 1), and dried with Mg₂SO₄. The organic solvent was removed under reduced pressure and the crude product was purified by

column chromatography with chloroform–ethyl acetate (1:1) as an eluent to give **L1** (133 mg, 55%) as colourless prisms, M.p. 239–241 °C. ¹H NMR (400 MHz, CDCl₃): δ = 1.10 (s, 18 H, *t*-Bu), 1.21 (t, 6 H, *J* = 7.1 Hz, CH₂CH₃), 1.26 (s, 18 H, *t*-Bu), 2.78 (s, 6 H, Imid-CH₃), 4.14 (q, 4 H, *J* = 7.1 Hz, COOCH₂), 4.52 (s, 4 H, OCH₂COO), 5.21 (s, 4 H, OCH₂Imme), 6.65 (s, 2 H, Imid-*H*₄), 6.96 (s, 2 H, Imid-*H*₅), 7.24 (s, 4H, Ar-*H*) and 7.46 (s, 4 H, Ar-*H*) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 31.0, 31.1, 33.0, 34.1, 34.2, 60.3, 65.1, 65.9, 121.8, 127.5, 127.6, 128.4, 129.3, 131.9, 143.5, 146.6, 146.8, 155.4, 156.8 and 167.7 ppm. FABMS: *m/z* [M+H]⁺ Calcd for C₅₈H₇₃N₄O₈S₄ 1081.4311; Found 1081.4319.

Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(benzyl)methoxy]-26,28-bis-[1-methyl-(imidazole)methoxy]-2,8,14,20-tetrathiocalix[4]arene (**L2**):

A mixture of *distal 2* (200 mg, 0.221 mmol), Cs₂CO₃ (720 mg, 2.21 mmol) in dry acetone (30 mL) was heated at reflux for 1 h under nitrogen. Then a solution of 2-chloromethyl-1-methyl-1*H*-imidazole hydrochloride (369 mg, 2.21 mmol) was added and the mixture was heated at reflux for another 20 h. After cooling the reaction mixture to room temperature, it was acidified with 1 M HCl (15 mL) and extracted with CH₂Cl₂ (20 mL × 3). The combined extracts were washed with water (30 mL × 2) and then brine (30 mL × 1), dried with (Mg₂SO₄). The organic solvent was removed under reduced pressure and the crude product was purified by column chromatography with chloroform as an eluent to give **L2** (105 mg, 44%) as colourless prisms, M.p. 252–253 °C. ¹H NMR (400 MHz, CDCl₃): δ = 0.82 (s, 18 H, *t*-Bu), 1.15 (s, 18 H, *t*-Bu), 2.57 (s, 6 H, Imid-CH₃), 5.05 (s, 4 H, OCH₂Ph), 5.18 (s, 4 H, OCH₂Imid), 6.68 (d, *J* = 0.7 Hz, 2 H, Imid-*H*₄), 6.91 (d, *J* = 7.3 Hz, 4 H, Ph-*H*) 6.99 (d, *J* = 0.9 Hz, 2 H, Imid-*H*₅), 7.06 (t, *J* = 7.5 Hz, 4 H, Ph-*H*), 7.12 (s, 4 H, Ar-*H*), 7.16 (t, *J* = 7.3 Hz, 2 H, Ph-*H*) and 7.27 (s, 4 H, Ar-*H*) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 30.7, 31.2, 32.8, 33.9, 34.3, 64.5, 70.7, 122.1, 126.9, 127.2, 127.4, 128.0, 128.6, 128.9, 129.3, 129.5, 137.3, 143.6, 146.8, 146.9, 156.2 and 156.6 ppm. FABMS: found 1089.35 [M+H]⁺. Anal. calcd. For C₆₄H₇₃N₄O₄S₄ ([M + H]⁺ *m/z* = 1089.45): C, 70.55; H, 6.66; N, 5.14 %, found: C, 70.44; H, 6.43; N, 5.10%.

Liquid-liquid extraction studies¹⁷

Two-phase solvent extraction was carried out between K₂Cr₂O₇ aqueous (10 mL, [dichromate anion] = 1.0 × 10^{−4} M) and host (10 mL, [host] = 2 × 10^{−4} M in CH₂Cl₂). A few drops of 0.01 M KOH/HCl solution were added in order to obtain the desired pH at equilibrium and maintain the ionic strength. The two phase mixture in a stoppered flask was immersed in a thermostated water bath at 25 °C which was shaken at 300 strokes per min for 4 h and then kept at the same temperature for 1 h, allowing the complete separation of the two phases. Each extraction experiment was repeated three times. The concentration of dichromate ion remaining in the aqueous phase was determined by UV spectroscopy. Blank experiments showed that no dichromate extraction occurred in the absence of thiocalix[4]arene derivatives **L1** and **L2**. The percent extraction (*E*%) has been calculated using the following expression:

$$E\% = (C_0 - C/C_0) \times 100$$

where *C*₀ and *C* are the initial and final concentrations of the metal dichromate before and after the extraction, respectively.

¹H-NMR complexation experiments

To a CDCl₃/CD₃CN (v/v 10:1, v/v) solution of **L1** and **L2** (5 × 10^{−3} M) in an NMR tube was gradually added 0.2 – 2.0 equivalent of the related metal perchlorates. The spectrum was recorded after the addition and the temperature of the NMR probe was kept constant at 27 °C.

The ¹H NMR data of the most representative complexes is given below:

Ag⁺ < **L1** (1:1), (400 MHz, CDCl₃/CD₃CN, 10:1): δ = 1.01 (s, 18 H, *t*-Bu), 1.24 (t, 6 H, *J* = 7.2 Hz, CH₂CH₃), 1.29 (s, 18 H, *t*-Bu), 3.68 (s, 6 H, Imid-CH₃), 4.18 (q, 4 H, *J* = 7.0 Hz, CO₂CH₂), 4.60 (s, 4 H, OCH₂CO₂), 5.04 (s,

4 H, OCH₂Imid), 6.90 (s, 2 H, Imid-H₅), 7.08 (s, 4 H, Ar-H), 7.14 (s, 2 H, Imid-H₄), 7.54 (s, 4 H, Ar-H).

K⁺ c L1 (1:1), (400 MHz, CDCl₃/CD₃CN, 10:1): δ = 1.27 (s, 36 H, t-Bu), 1.34 (m, 6 H, CH₂CH₃), 3.05 (s, 6 H, Imid-CH₃), 4.27 (m, 4 H, CO₂CH₂), 4.76 (s, 4 H, OCH₂CO₂), 5.22 (s, 4 H, OCH₂Imid), 6.87 (s, 2 H, Imid-H₄), 7.04 (s, 2 H, Imid-H₅), 7.34 (s, 4 H, Ar-H), 7.48 (s, 4 H, Ar-H).

Na⁺ c L1 (1:1), (400 MHz, CDCl₃/CD₃CN, 10:1): δ = 1.09 (s, 18 H, t-Bu), 1.26 (s, 18 H, t-Bu), 1.30 (m, 6 H, CH₂CH₃), 2.94 (s, 6 H, Imid-CH₃), 4.22 (m, 4 H, CO₂CH₂), 4.66 (s, 4 H, OCH₂CO₂), 5.23 (s, 4 H, OCH₂Imid), 6.80 (s, 2 H, Imid-H₄), 6.94 (s, 2 H, Imid-H₅), 7.27 (s, 4 H, Ar-H), 7.48 (s, 4 H, Ar-H).

Ag⁺ c L2 (1:1), (400 MHz, CDCl₃/CD₃CN, 10:1): δ = 0.85 (s, 18 H, t-Bu), 1.03 (s, 18 H, t-Bu), 3.66 (s, 3 H, Imid-CH₃), 5.06 (s, 4 H, OCH₂Ph), 5.09 (s, 4 H, OCH₂Imid), 6.89 (s, 2 H, Imid-H₅), 6.95 (d, J = 7.4 Hz, 4 H, Ph-H), 6.96 (s, 2 H, Imid-H₄), 7.12 (m, 4 H, Ph-H), 7.14 (s, 4 H, Ar-H) and 7.19 (s, 4 H, Ar-H), 7.22 (m, 2 H, Ph-H).

X-ray Crystallography

Diffraction data were collected on a Bruker APEX 2 CCD diffractometer equipped with graphite-monochromated Mo-Kα radiation for L1·3EtOH·H₂O and with synchrotron radiation for L2·2.58EtOH.¹⁸ Data were corrected for Lorentz and polarisation effects and for absorption.¹⁸ The structures were solved by charge flipping or direct methods algorithms and refined by full-matrix least-squares methods, on F².¹⁹ In L1·3EtOH·H₂O Atom C(49) was modelled as 2-fold disordered with major component 55.1(13)%. One of the ethanol molecules was modelled as a region of diffuse electron density using the Platon Squeeze procedure.²⁰

Table 3 Summary of crystal data for the receptors L1, and L2

Complex	L1	L2
Empirical formula	C ₅₈ H ₇₂ N ₄ O ₈ S ₄ ·3EtOH·H ₂ O	C ₆₄ H ₇₂ N ₄ O ₄ S ₄ ·2.58EtOH
Formula weight	1237.65	1208.05
Crystal system	Triclinic	Triclinic
Space group	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$
<i>a</i> [Å]	13.9134(18)	14.6911(6)
<i>b</i> [Å]	15.4414(19)	14.8673(6)
<i>c</i> [Å]	17.086(2)	15.0303(7)
α [°]	103.616(2)	85.407(3)
β [°]	104.584(2)	86.152(3)
γ [°]	96.412(2)	79.641(3)
Volume[Å ³]	3395.2(7)	3214.3(2)
<i>Z</i>	2	2
Crystal size[mm ³]	0.88 × 0.42 × 0.20	0.11 × 0.09 × 0.01
λ [Å]	0.71073	0.7749
D _{calc} [Mg/m ³]	1.211	1.248
μ [mm ⁻¹]	0.20	0.25
temperature [K]	150(2)	100(2)
Measured reflns	37601	22331
unique reflns	12465	8081
obsd reflns	8007	5494
parameters	815	942
<i>R</i> (int)	0.062	0.060
<i>R</i> [$\Sigma 2\sigma(I)$] ^a	0.069	0.087
<i>wR</i> ₂ [all data] ^b	0.193	0.256
GOF on <i>F</i> ²	1.03	1.05

^a Conventional *R* on *F*_{hkl}: $\Sigma ||F_o| - |F_c|| / \Sigma |F_o|$. ^b Weighted *R* on $|F_hkl|^2$: $\Sigma [w(F_o^2 - F_c^2)] / \Sigma [w(F_o^2)^{1/2}]$

The water molecule was also 2-fold disordered and the minor component was modelled with Squeeze. In L2·2.58EtOH The non-integer amount of EtOH is a consequence of the nature of the imidazole disorder. The benzyl group containing C(58) > C(64) was modelled as disordered over two sets of positions with major site occupation factor of 54.9(12)%. The 1-methylimidazole group attached to C(53), and C(53) itself, were modelled as disordered over two sets of positions with major site occupation factor of 57.3(5)%. Both positions are pointing outside the calixarene cavity. The ethanol molecule containing O(5) was modelled as disordered over three sets of positions. Those containing O(5) and O(5Y) are present when the major disorder component of imidazole group containing C(53) is present and has the same occupation factor. That containing O(5X) is present when the minor imidazole disorder component containing C(53X) is present and has the same occupation factor of 42.7(5)%.

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1445271 & 1445272. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Thiacalix[4]arene derivatives bearing imidazole units: a ditopic hard/soft receptor for Na^+/Ag^+ and K^+/Ag^+ with allosteric effect and a reusable extractant for dichromate anions

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