The first study about the relationship between the extractability of thiacalix[4]arene derivatives and the position of the coordination binding sites

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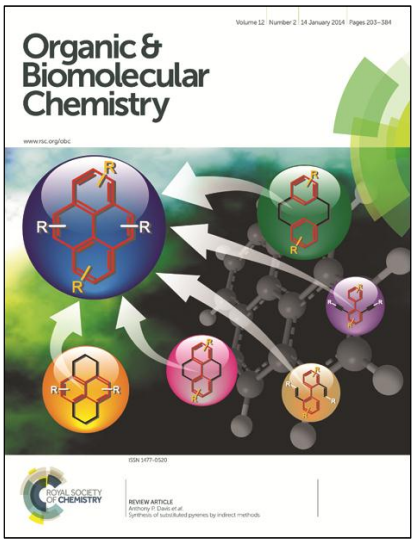

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The first study about the relationship between the extractability of thiacalix[4]arene derivatives and the position of the coordination binding sites †

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Three organic ionophores (**2** – **4**) based on the *p-tert*-butylthiacalix[4]arene backbone, blocked in the 1,3-*alternate* conformation, bearing two pyridyl coordinating moieties (*ortho* for **2**, *meta* for **3** and *para* for **4**), have been synthesized and characterized in the solid state. The solvent extracted experiments of the metal ions showed that the ability of these derivatives to complex with Ag^+ appeared to be largely dependent on the position of the nitrogen atoms of the pyridyl ring. Two different complexation modes have been confirmed by ^{1}H NMR titration, ionophore **2** armed with two pyridyl, complexed with Ag^+ cation through N···Ag^+···S interactions; however, ionophore **3** and ionophore **4**, complexed with Ag^+ through metal-nitrogen (N···Ag^+) interactions. The DFT computational studies were consistent with the experimental findings. These findings will provide us an important rule to design an appropriate thiacaixarene ionophore in the future. Another studied on the possibility for application of ionophores **2** – **4** to the treatment of waste water containing Cr (VI) and Cr (III), showed that ionophore **3** was meaningful for applying solvent extraction method in selective treatment of waste water containing Cr (VI) and Cr (III) prior to discharge.

Introduction

Thiacalix[4]arene is widely used as a macrocyclic platform for designing and building synthetic receptors toward metal cations.[1] The complexation properties of these molecules appear to be highly dependent upon the nature and number of donor atoms and also upon the conformation of the calix[*n*]arene moiety.[2] It is found that thiacalix[4]arene has a very high ability to bind transition metal ions,[3] which has been quite unexpected considering the poor binding ability of calix[4]arene. The 1,3-*alternate* stereoisomer, which shows an allosteric effect in metal cation binding, or offers divergently oriented binding sites, is of special interest.[1,4] For the synthesis of macrocycles with controlled (switchable) binding sites of metal cations,[5] there is a need for the development of novel approaches to the design of tetrasubstituted thiacalix[4]arenes with various groups with specific conformations. Recently, our lab has reported the regioselective synthesis of distal-bis[(2-pyridylmethyl)oxy]tetra-thiacalix[4]arene in the 1,3-*alternate* conformation by a protection-deprotection method using benzyl groups as protecting groups.[6] Pyridine derivatives of thiacalix[4]arene can exist as positional isomers which differ by the positions of the nitrogen (N) atom on the pyridyl unit which can be *ortho*, *meta* and *para* to the phenolic oxygen attachment position. The N-hetero atoms can serve as additional coordination sites due to their electron lone pairs and can also undergo facile further modifcation. Given that the position of the nitrogen atoms of the pyridyl ring can differ in thiacalix[4]arene derivatives, it is interesting to assess what kind of ability these derivatives will provide to interact with metal cations (hard or soft).

Chromium (III) has been reported to be biologically essential to mammals as it maintains effective glucose, lipid, and protein metabolisms. However, chromium (VI) can be toxic, as it can diffuse as $Cr_2O_7^{2-}$ or $HCr_2O_7^-$ through cell membranes and oxidize biological molecules.[7] Therefore, selective treatment of waste water containing Cr (VI) and Cr (III) prior to discharge is essential. Solvent extraction is one of the most commonly used treatment methods and employs a selective complexant especially for ions in aqueous solution. Thus, the development of efficient extractants for anions has received considerable attention in recent years.[8] The dichromate ($Cr_2O_4^{2-}$ 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). Thiacalix[4]arene derivatives with nitrogen functionalities such as pyridine, amino, or imino groups on their lower rim have been shown to be capable of interacting with anions by hydrogen bonds as efficient extractants for oxoanions.[9] Thus, the introduction of a pyridyl moiety to thiacalix[4]arene would potentially lead to an effective extractant for dichromate anions.

In this study, a series of 1,3-*alternate* thiacalix[4]arenes bearing pyridyl moieties (*ortho*, *meta* and *para*) at the lower rim which should have the appropriate encapsulating ionophilic cavity were

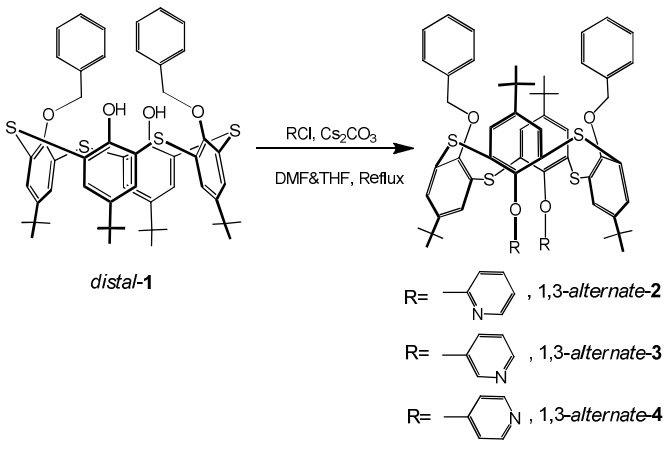
targeted for synthesis. The relationship between the position of the nitrogen atoms of the pyridyl ring and the ability of these derivatives to interact with various ionic species were evaluated.

Results and discussions

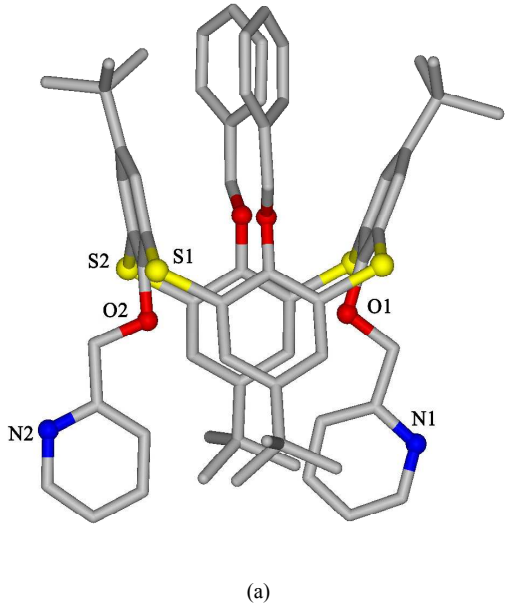
The synthesis of the new thiacalix[4]arene derivatives is given in Scheme 1. For the synthesis of thiacalix[4]arene derivatives based on different functional units (1,3-*alternate*-**2**, 1,3-*alternate*-**3** and 1,3-*alternate*-**4**), the parent compound (*distal*-**1**) was prepared according to published literature procedures.[6] The reaction of bisbenzylated compound *distal*-**1** with 3-(chloromethyl)pyridine in THF-DMF in the presence of Cs_2CO_3 as base yielded 1,3-*alternate*-**3** in 59% yield. 1,3-*alternate*-**2** and 1,3-*alternate*-**4** were prepared as following a published procedure.[6,10] All of the structures were confirmed by their ^{1}H- and ^{13}C-NMR and IR spectra, MS, elemental analyses and by X-ray crystallography.

The ^{1}H NMR spectrum of 1,3-*alternate*-**3** shows two singlets for *tert*-butyl protons, in which both *tert*-butyl protons were observed at higher field, at δ 0.85 and 0.86 ppm due to the ring current effect arising from the two benzyl benzene rings and the two pyridine rings introduced; two singlets for the methylene protons at δ 5.06 ppm (O*CH*$_2$Benzyl) and 5.19 ppm (O*CH*$_2$Pyridyl), respectively, indicating a C_2-symmmetric structure for the 1,3-*alternate*-**3** (Figure S1).

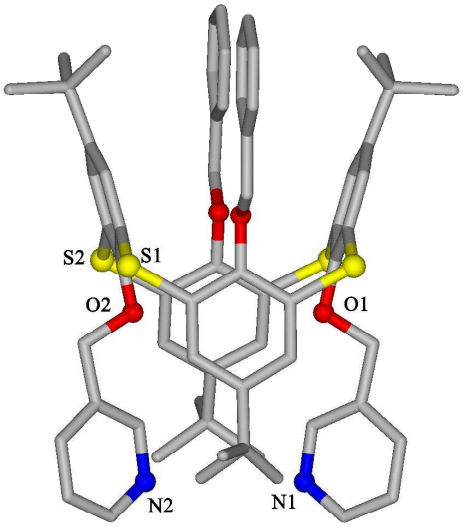
X-ray quality colourless crystals of 1,3-*alternate*-**2**, and 1,3-*alternate*-**3** were obtained by recrystallizations from mixed MeOH and $CHCl_3$ solutions. The single crystal X-ray diffraction Ortep (Pluto) representations of **2** and **3** are shown in Figure 1. It is clear that these compounds adopt 1,3-*alternate* conformations. Interestingly, both of the pyridine nitrogen atoms in **2** are orientated outwards, the distance between them being 9.079 Å. However, the pyridine nitrogen atoms in **3** are orientated inwards, the distance between them being only 3.883 Å. This may be attributed to the distances between the pyridine nitrogen atoms and the oxygen atoms (N1···O1 and N2···O2). In the case of compound **2**, the distances between N1···O1 and N2···O2 are shorter; but for **3** the corresponding N1···O1 and N2···O2 distances are longer enough.



Scheme 1 *O*-Alkylation of *distal*-**1** with (chloromethyl)pyridine in the presence of Cs_2CO_3.



(a)



(b)

Fig. 1 X-ray structures of (*a*) **2**[6] and (*b*) **3**. Hydrogen atoms have been omitted for clarity.

The shorter distances and hence, the stronger electron repulsion could therefore be the factors which control the different orientations of the nitrogen atoms toward each other.

Recently, the synthesis of calix[4]arenes bearing pendant pyridine groups at the lower rim as potential ligands for transition metal cations have been reported.[11] A similar investigation has also been conducted using hexahomotrioxacalix[3]arene and homocalix-[3]arene-based derivatives.[12] It is well-known that the metal selectivity and extractability of these types of receptors are dependent on the ring size and the nature of the *O*-alkyl substituents. However, it is still unknown whether the metal extractability can be affected by the position of the coordination binding sites of the substituents themselves. Therefore, it is of importance to assess the

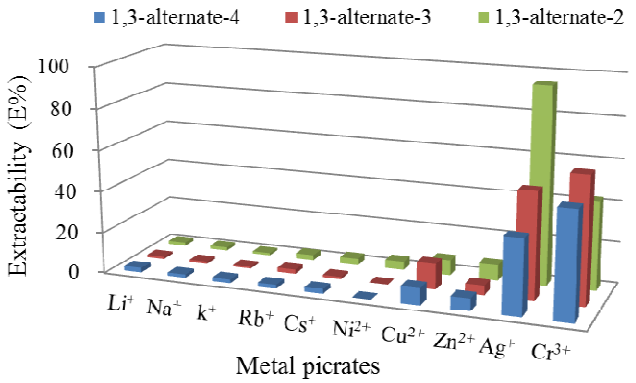


Fig. 2 Extraction percentages of metal picrates with ionophores **2** – **4** ([Host] = 4.0×10^{-5} M in CH_2Cl_2, [Guest] = 4.0×10^{-5} M in water at 25 °C).

relationship between the position of the nitrogen atoms of the pyridyl ring and the ability of these derivatives (**2** – **4**) to interact with ions. Experiments for solvent extraction of aqueous phase metal ions to the organic phase were therefore undertaken with **2** – **4**. The results showed that the extraction of transition metals by all three receptors **2** – **4** was higher than for the extraction of alkali metals, especially for Cr^{3+} and Ag^+ (Fig. 2). The E% values of Cr^{3+} *i.e.* 43%, 61% and 52% for **2** – **4**, respectively, showed that a higher Cr^{3+} affinity exists for these molecules. However, what is surprising is that the extractability for Ag^+, the E% values of 95%, 52% and 36% for **2** – **4**, respectively, showed that the extractability of Ag^+ by **2** to **4**, decreased gradually. These compounds are positional isomers differing only by the position of the nitrogen atom on the pyridyl ring. The position of the N atoms on the pyridyl rings (*ortho* for **2**, *meta* for **3** and *para* for **4**), which determines the distances between the nitrogen and the diaryl thiaether linkages were also reduced gradually. Recently, Ferlay has reported a 1,3-*alternate* conformation thiacalix[4]arene armed with four pyridyl (*ortho*), complexed with Ag+ cation through N···Ag^+···S interactions.[13] Thus, the extractability (E%) of **2** – **4** which followed the order of **2** > **3** >**4**, may be attributed to the shorter distance, the stronger N···Ag^+···S interactions, the higher extractability (E%). This hypothesis is supported by the stability constants, which follow the same order of **2** > **3** >**4**. The binding constants (K_a) value for the complexation with Ag^+ ion was determined to be $2.05 \times 10^4 \pm 875$ M^{-1} (**2**) , $3.86 \times 10^3 \pm 572$ M^{-1} (**3**), $2.25 \times 10^3 \pm 365$ M^{-1} (**4**) based on the Benesi–Hildebrand equation[23], respectively (Figure S13–18).

Due to the existence of the two potential metal-binding sites, namely, the pyridine moieties and two benzyl moieties, there are several possibilities for the metal complexation for compounds **2** – **4**. Both 1:1 and 1:2 metal complexation might be possible, attributable to electrostatic interactions as well as cation-π interactions. Job plots of **3** and **4** were carried out in the H_2O/CH_2Cl_2 phases. The E% values reach maxima at 0.5 mole fraction when **3** or **4** with Ag^+ are changed systematically. (Figure S12) Similar 1:1 coordination of **2** with Ag^+ was shown by Job plots in our previous study. (Figure S12) [6] Thus, it can be concluded that Ag^+ forms 1:1 complexes with **2** – **4**. These results suggest the major contribution of receptors **2** – **4** to Ag^+ binding are from the nitrogens of the pyridine rings, and not from the alternative cation-π-interactions.

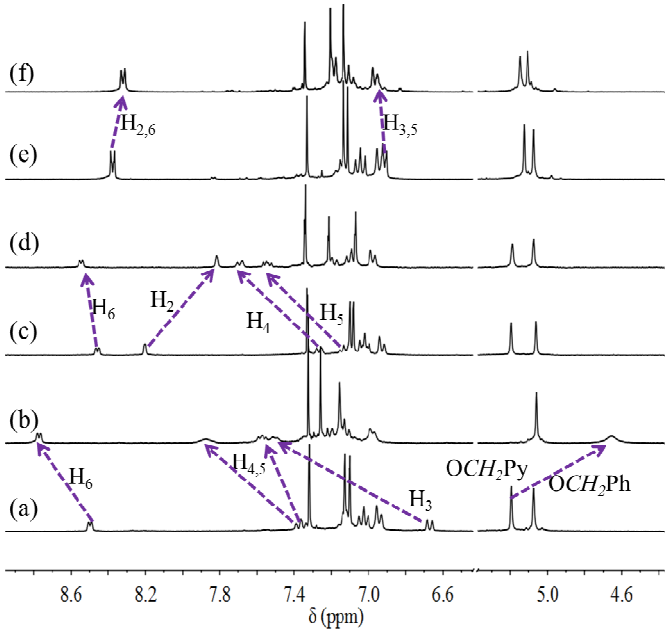


Fig. 3 ^{1}H NMR spectral changes of ionophores **2** – **4** (5×10^{-3} M) on addition of $AgClO_4$ (300 MHz, $CDCl_3$:CD_3CN = 10 : 1, [ionophores **2** – **4**] = 5×10^{-3} M). (a) Free **2**; (b) **2** in the presence of 1.0 equiv. of $AgClO_4$; (c) Free **3**; (d) **3** in the presence of 1.0 equiv. of $AgClO_4$; (e) Free **4**; (f) **4** in the presence of 1.0 equiv. of $AgClO_4$.

Furthermore, in order to look further into the binding properties of receptors **2** – **4** with Ag^+, ^{1}H NMR titration experiments were carried out in CD_3Cl : CD_3CN = 10 : 1 solution. The chemical shift changes for compound **2** – **4** on complexation with Ag^+ are illustrated in Figure 3 and are summarized in Figure 4.

Significant changes were observed for the pyridine ring protons after the complexation of each of **2** – **4** with 1.0 equiv. Ag^+. In the case of **2,** the protons in the pyridine rings were shifted to lower field with Δδ = +0.27, +0.21, +0.52 and +0.83 ppm for H_6, H_5, H_4, and H_3 protons, respectively. In contrast, the OCH_2Py methylene protons were shifted dramatically to-up field, with Δδ = -0.53. This may be due to both pyridine nitrogens of **2** close to the diaryl thiaether linkages (N2···S1= N2···S2 = 5.333 Å, Fig. 1a). Thus, when **2** complexes with Ag^+, the Ag^+ is easily captured through N···Ag^+···S interactions.[13] As a result, since the pyridine moieties orientated inwards, the ring current shielding effect[14] operating in the two thiacalixarene benzene rings is destroyed, forcing the steric conformation change. This affects the protons H_6, H_5, H_4 and H_3 of the pyridine rings which shift to lower field, due to the deshielding effect. Also, the OCH_2Py methylene protons become folded into the thiacalix[4]arene-cavity and are thus shifted strongly upfield (-0.53 ppm), due to the steric conformation changes.

However, a different phenomenon was observed in the complexation of **3** with Ag^+. From the X-ray results, both pyridine nitrogen atoms in **3** were orientated inwards and far from the diaryl thiaether linkages (N2···S1 = 6.360 Å and N2···S2 = 5.847 Å, Fig. 1b), which is exactly opposite to what is seen with **2**. The ^{1}H NMR spectrum of the Ag^+ of **3** reveals that the protons in the pyridine rings were shifted to lower field with Δδ = +0.09, +0.42 and +0.43 ppm for H_6, H_5 and H_4, protons, respectively. In contrast, a remarkable shielding effect experienced by proton H_2 (−0.38 ppm)

was observed. This maybe attribute that when **3** complexes with Ag^+, the Ag^+ is trapped in the cavity formed by the nitrogen atoms in pyridine, induce the proton H_2 become folded into the π-cavity formed by the two thiacalixarene benzene rings and are thus shifted strongly upfield (-0.38 ppm). Thus, **3** complexes Ag^+ through the metal-nitrogen interactions and thus, due to the interaction of the nirogens and the Ag^+, the H_6, H_5 and H_4 protons of the pyridine rings shift to lower fields.[15]

Similar phenomena were observed for the complexation of **4** with Ag^+; protons H_3 and H_5 in the pyridine rings of **4** shifted to lower field after complexation (+0.05 ppm), which are deshielded due to the N···Ag^+ interactions. Pyridine ring protons H_2 and H_6 in **4** shifted upfield after complexation (-0.06 ppm), which may be attributed to the weaker repulsion between the nitrogen atoms in the pyridine rings.[15]

The chemical shift changes of the thiacalixarene benzene protons and benzyl protons may also be attributed to the conformational changes of **2 – 4** upon complexation. The chemical shift changes (Δδ) of **2 – 4** upon complexation are in the order **2 > 3 > 4**, which corresponds with the extractability of Ag^+ which found to be in the same order.

To better understand the binding properties of receptors **2 – 4** with Ag^+, a computation study were carried out. The molecular geometry of the individual structures in the gas-phase were fully optimized using Gaussian09,[22] with the B3LYP level of DFT and the lanl2dz basis set. Significant conformational changes were observed for the pyridine ring protons of **2 – 4** after the complexation with Ag^+. The conformation changes for **2** on complexation with Ag^+ ion can be seen in Fig. 5 (See the Supporting Information for details of the computational study, Figure S19–24). Fig. 5 shows the structure (*right*) of the **2**⊃Ag^+ complex. The optimized molecular geometry suggests that the Ag^+ binds, in accord with the ^{1}H NMR complex study, via a N···Ag^+···S short contact distance bond, which results in the conformation change. The N···N distance between the pyridine ring nitrogens decreases from 8.001 to 3.761 (Å) since the nitrogen atoms move inwards after complexing with the Ag^+. All four bridge sulphur atoms are roughly the same distance from the Ag^+ and presumably take an equal part in the coordination bonding.

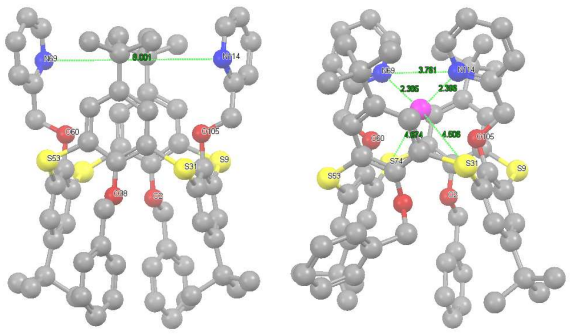


Fig. 5. Geometry-optimized (ball and stick) structures of: *Left*: **2** and *Right*: **2**⊃Ag^+complex. Color code for Ag^+ = magenta, pyridine nitrogen = blue, sulphur = yellow and oxygen atom = red. Hydrogen atoms have been omitted for clarity.

However, a different phenomenon was observed in the complexation of **3 – 4** with Ag^+. The N···N distance between the pyridine ring nitrogens decreases from 9.305 to 4.234 (Å) for **3** and 10.138 to 3.798 (Å) for **4** after complexing with the Ag^+. (Figure S19 – S24, Table S1) The optimized molecular geometry suggests that complexation of **3 – 4** with Ag^+ occurs via a N···Ag^+ interactions. The calculated complexation energies (ΔE kJ/mole) of the Ag^+ complexes of **2 – 4** are -488.096, -464.022 and -372.966 kJ/mole respectively (Table S2), which is in agreement with the trend observed for the experimentally observed complexation data.

A preliminary evaluation of the anion binding efficiencies of **2 – 4** as potential extractants for the dichromate anion has been carried out by solvent extraction of aqueous solution of $K_2Cr_2O_7$ into dichloromethane at different pH values according to reported procedure.[15,16] The extraction results summarized in Fig. 6, indicate that **3** showed a higher effective for the extraction of dichromate anions at low pH (pH 1.5) than either **2** and **4**. This is also consistent with the solvent extraction results seen with Cr^{3+} (Fig. 2). This could be attributed to the closer (3.883 Å) distance (Fig. 1) between the pyridine nitrogen atoms in **3**, which was easily formed an efficient ion-pair (hydrogen bonded) complex in the two-phase extraction

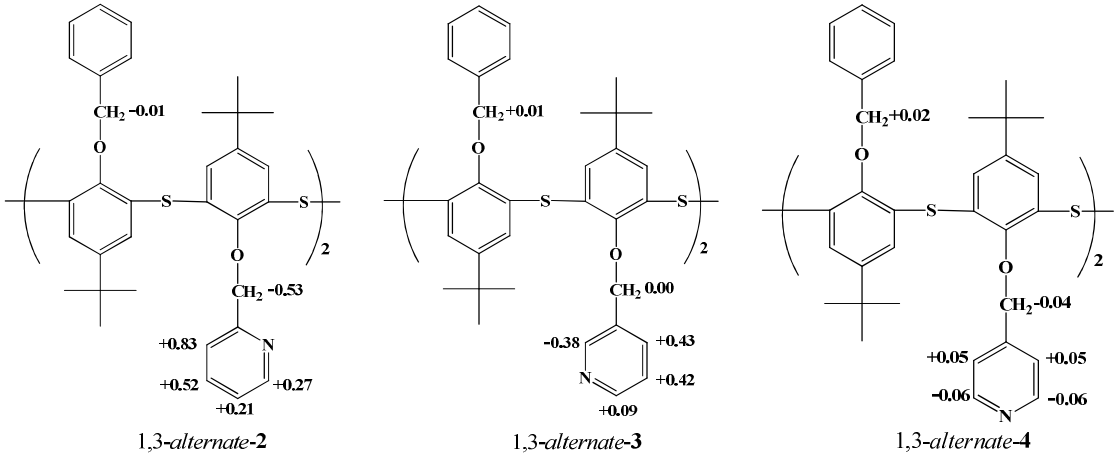


Fig. 4. Chemical shift changes of **2**, **3** and **4** induced in the presence of $AgClO_4$. + denotes the downfield and – denotes the upfield shift.

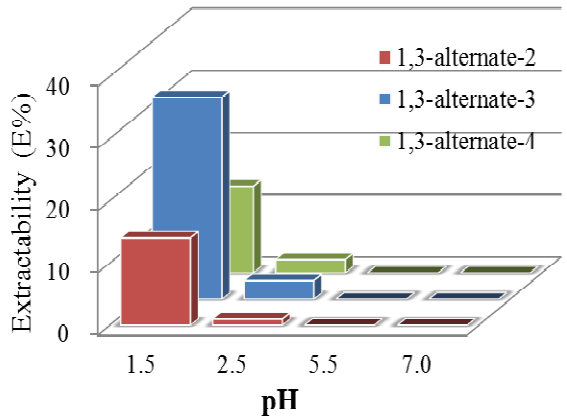


Fig. 6. E% values of dichromate anion with ionophores **2 – 4 (**2.0 × 10^{-4} M, 2 h at 25 °C) at pH 1.5–7.0 (H_2O/CH_2Cl_2:10/10 (v/v); $K_2Cr_2O_7$ = 1 × 10^{-4} M).

system following proton transfer to the nitrogen atoms. As the pH of the solution increased from 1.5 to 2.5 to 5.5 to 7.0, the E% for all three receptor ionophores decreased. This may directly be attributed to decreased proton concentrations in the solution.[17] In other words, **3** showed a high extractability with dichromate anions only at lower pH, but another high extractability of Cr^{3+} at higher pH. Since, Cr(VI) is highly toxic, carcinogenic and harmful to human beings because it can diffuse as $Cr_2O_7^{2-}$ or $HCr_2O_7^-$ through cell membranes and oxidize biological molecules,[7] whereas Cr(III) is an essential ion for mammals as it maintains effective glucose, lipid, and protein metabolisms[18] Thus, **3** could be a meaningful extractant when applying a solvent extraction method for the selective treatment of waste water containing Cr (VI) and Cr (III) prior to discharge.

Conclusion

Three 1,3-*alternate* thiacalix[4]arenes bearing pyridyl moieties (*ortho* for **2**, *meta* for **3** and para **4**) at the lower rim were regioselectively synthesized. The solvent extraction experiments of the metal ions showed that the ability of these derivatives to complex with Ag^+ (95%, 52% and 36% for **2, 3** and **4**, respectively) appeared to be largely dependent on the position of the pyridine nitrogen atoms. The mode of binding of the C_{2V}-symmetrical dipyridyl-substituted thiacalix[4]arenes, **2 – 4** with Ag^+ was elucidated clearly using a ^{1}H NMR titration method. Two different complexation modes were observed: **2** armed with two *ortho* pyridyl groups, complexed with Ag^+ via N···Ag^+···S interactions whereas **3** and **4**, complexed with Ag^+ through N···Ag^+ interactions. The DFT computational studies were consistent with the experimental findings. These findings will provide us an important rule to design a appropriate thiacaixarene ionophore in the future.

Another studies aimed at the potential for application of these extractants to the treatment of waste water containing Cr (VI) and Cr (III) were initiated. The combination of the two-phase solvent extraction data of Cr^{3+} and the results of the dichromate anion extraction by **3**, suggest that **3** could be meaningful for applying a solvent extraction method for the selective treatment of waste water containing Cr (VI) and Cr (III) ions prior to discharge.

Experimental Section

General

All melting points were determined using a Yanagimoto MP-S1. ^{1}H-NMR spectra were determined at 300 MHz with a Nippon Denshi JEOL FT-300 NMR spectrometer with $SiMe_4$ as an internal reference; *J*-values are given in Hz. IR spectra were measured as KBr pellets or as liquid films on NaCl plates in a Nippon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by a Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 mass spectrometer at an ionization energy of 70 eV using a direct inlet system through GLC. Elemental analyses were performed by a Yanaco MT-5.

Materials

25,27-Dibenzyloxy-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetra thiacalix[4]arene-26,28-diol (*distal*-1) was prepared from 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25, 26,27,28-tetraol in one step according to a reported procedure.[6]

O-Alkylation of 1 *distal*-1 with 3-(chloromethyl)pyridine in the presence of Cs_2CO_3.

A mixture of *distal*-**1** (400 mg, 0.44 mmol) and Cs_2CO_3 (1.60 g, 4.92 mmol) in dry tetrahydrofuran (THF) (8 mL) was heated at reflux for 1 h under N_2. A solution of 3-(chloromethyl)pyridine (4.92 mmol) [prepared by neutralization of 3-(chloromethyl)pyridine hydrochloride (807 mg, 4.92 mmol) in DMF (8 mL) with a solution of triethylamine (0.68 mL, 4.92 mmol) in THF (8 mL) at room temperature.] was then added and the mixture heated at reflux for an additional 24 h. After cooling the reaction mixture to room temperature, it was acidified with 1 M HCl (10 mL) and extracted with CH_2Cl_2 (100 mL × 2). The combined extracts were washed with water (50 mL × 2), and dried ($MgSO_4$) and condensed under reduced pressure to give a yellow oil. The residue was washed with methanol to give a mixture of tetra-*O*-alkylated products as a colorless precipitate. The precipitate was washed with ether (5 mL) to give a colourless solid. Recrystallization from MeOH:$CHCl_3$ (1:3) gave **3** as a colorless prisms (280 mg, 59%).

25,27-Dibenzyloxy-26,28-bis[(3-pyridylmethyl)oxy]-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene (3): Colourless prisms [MeOH:$CHCl_3$ (1:3)], m.p. 285.4–286.6 °C. IR ν_{max} (KBr)/cm^{-1}: 3058, 3030, 2958, 2902, 2868, 1575, 1546 and 1496. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.85 (s, 18H, tBu), 0.86 (s, 18H, tBu), 5.06 (s, 4H, Ar–OCH_2Ph), 5.19 (s, 4H, Ar–OCH_2Py), 6.92 (d, *J* = 7.2 Hz, 4H, Ph–*H*), 7.02 (t, *J* = 7.6 Hz, 6H, Ph–*H*), 7.07 (s, 4H, Ar–*H*), 7.10 (s, 4H, Ar–*H*), 7.12 (t, *J* = 7.6 Hz, 2H, Py–H_5), 7.24 (d, *J* = 8.0 Hz, 2H, Py–H_4), 8.22 (s, 2H, Py–H_2) and 8.46 (d, *J* = 4.8 Hz, 2H, Py–H_6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.77, 30.78, 33.89, 33.90, 67.74, 70.64, 122.99, 126.83, 127.18, 127.98, 128.38, 128.42, 128.48, 128.60, 133.20, 134.81, 137.47, 146.31, 146.58, 148.33, 148.92, 155.59 and 156.61 ppm. FABMS: *m/z*: 1083.30 (M^+). Anal. calcd. for $C_{66}H_{70}N_2O_4S_4$ (1083.53): C 73.16, H 6.51, N 2.59%. Found: C 71.85, H 6.56, N 2.38%.

Preparation of 25,27-Dibenzyloxy-26,28-bis[(2-pyridylmethyl)oxy]-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (**2**) was carried out as following our previous report.[6]

25,27-Dibenzyloxy-26,28-bis[(2-pyridylmethyl)oxy]-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (2): Colourless prisms [MeOH:$CHCl_3$ (1:3)], m.p. 274.8–275.5 °C. IR ν_{max} (KBr)/cm^{-1}: 3058, 3029,3008, 2955, 2901, 2866, 1571,1588, 1546, 1496. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.83 (s, 18 H, tBu), 0.85 (s, 18 H, tBu), 5.07 (s, 4 H, Ar–OCH_2Ph), 5.20 (s, 4 H, Ar–OCH_2Py), 6.66 (d, *J* = 7.2 Hz, 2 H, Py–H_3), 6.94 (d, *J* = 7.0Hz, 4 H, Ph–*H*), 7.02 (t, *J* = 7.5 Hz, 6 H, Ph–*H*), 7.09 (4 H, s, Ar–*H*), 7.12 (4 H, s, Ar–*H*), 7.35(t, *J* = 6.9 Hz, 4 H, Py–$H_{4,5}$) and 8.49 (d, *J* = 4.8 Hz, 2 H, Py–H_6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.73, 30.82, 30.88, 33.88, 70.65, 71.46, 121.99, 126.80, 127.19, 127.99, 128.23, 128.60, 128.71, 137.52, 146.15, 146.35, 148.33, 156.01, 156.67 and 157.70 ppm.

Preparation of 25, 27-Dibenzyloxy-26,28-bis[(4-pyridylmethyl)oxy]-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (**4**) was carried out as following our previous report.[10]

25,27-Dibenzyloxy-26,28-bis[(4-pyridylmethyl)oxy]-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (4): Colourless prisms [MeOH:$CHCl_3$ (1:3)], m.p. 283–285 °C. IR ν_{max} (KBr)/cm^{-1}: 3055, 3029, 2952, 2921, 2853, 1604, 1572, 1562. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.84 (s, 18 H, tBu), 0.86 (s, 18 H, tBu), 5.07 (s, 4 H, Ar–OCH_2Ph), 5.12 (s, 4 H, Ar–OCH_2Py), 6.90 (d, *J* = 5.5 Hz, 4 H, Py–$H_{3,5}$), 6.94 (d, *J* = 7.4 Hz, 4 H, Ph–*H*), 7.04 (t, *J* = 7.6 Hz, 4 H, Ph–*H*), 7.10 (s, 4 H, Ar–*H*), 7.12 (s, 4 H, Ar–*H*), 7.13 ~ 7.18(m, 2 H, Ph–*H*) and 8.40 (d, *J* = 5.8 Hz, 4 H, Py–$H_{2,6}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.70, 30.73, 33.86, 33.89, 69.10, 70.80, 121.80, 126.90, 127.14, 128.03, 128.26, 128.75, 129.11, 137.35, 146.39, 146.50, 146.71, 149.38, 155.97 and 156.72 ppm. FABMS: *m/z*: 1083.45 (M^+).

Extraction experiments and stoichiometry of metal complexation.

Metal picrates (4.0×10^{-5} M) were prepared *in situ* by dissolving the metal hydroxide (0.02 mol) in 4.0×10^{-5} M picric acid (1000 mL); triply distilled water was used for all aqueous solutions. Two-phase solvent extraction was carried out between aqueous picrates (10 mL, [metal picrate] = 4.0×10^{-5} M) and host (10 mL, [host] = 4×10^{-5} M in CH_2Cl_2). 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. This was repeated 3 times. The absorbance of each solution was determined by UV spectroscopy (λ = 356 nm). The method of continuous variation was employed to determine the stoichiometry in the complexes involving the host receptors **2**, **3** or **4**. The molar ratios of both the host and metal picrate were varied from 0 to 1, while the total concentration was kept at several constant levels. Job plots were generated by plotting the extracted [M^+] versus the mole fraction of metal. We confirmed that this period was sufficient to attain the distribution equilibrium. The extractability was determined spectrophotochemically from the decrease in the absorbance of the picrate ion in the aqueous phase, as described by Pedersen.[19]

^{1}H-NMR complexation experiments

To a $CDCl_3$–CH_3CN (10:1, v/v) solution (5×10^{-3} M) of **2, 3** or **4** in an NMR tube was added a CD_3CN solution (5×10^{-3} M) of $AgClO_4$. The spectra were recorded after the additions. The temperature of the NMR probe was kept constant at 27 °C. The ^{1}H NMR data of the most-representative complexes are given below:

2: ^{1}H NMR (300 MHz, $CHCl_3$–CH_3CN, 10:1, v/v): δ = 0.83 (s, 18H, tBu), 0.85 (s, 18H, tBu), 5.07 (s, 4 H, CH_2–Ph), 5.19 (s, 4H, CH_2–Py), 6.67 (d, *J* = 7.8 Hz, 2H, Py–H_3), 6.94 (d, *J* = 7.6 Hz, 4H, Ph–*H*), 7.03 (t, *J* = 6.6 Hz, 6H, Ph–*H*), 7.10 (s, 4H, Ar–*H*), 7.13 (s, 4H, Ar–*H*), 7.36 (t, *J* = 7.8 Hz, 4H, Py–$H_{4,5}$) and 8.49 (d, *J* = 4.7 Hz, 2H, Py–H_6) ppm.

2 ⊃Ag^+: ^{1}H NMR (300 MHz, $CHCl_3$–CH_3CN, 10:1, v/v): δ = 0.85 (s, 18H, tBu), 0.98 (s,18H, tBu), 4.65 (s, 4H, CH_2–Py), 5.06 (s, 4H, CH_2–Ph), 6.98 (d, *J* =7.5 Hz, 4H, Ph–*H*), 7.10–7.14 (m, 4H, Ph–*H*), 7.16 (s, 4H, Ar–*H*), 7.21 (t, *J* = 6.6 Hz, 2H, Ph–*H*), 7.26 (s, 4H, Ar–*H*), 7.50 (d, *J* = 7.8 Hz, 2H, Py–H_3), 7.57 (t, *J* = 5.7 Hz, 2H, Py–H_4), 7.82–7.92 (m, 2H, Py–H_5) and 8.77 (d, *J* = 4.9 Hz, 2H, Py–H_6) ppm.

3: ^{1}H NMR (300 MHz, $CHCl_3$–CH_3CN, 10:1, v/v): δ = 0.85 (s, 18H, tBu), 0.86 (s, 18H, tBu), 5.06 (s, 4H, CH_2–Ph), 5.19 (s, 4H, CH_2–Py), 6.93 (d, *J* = 7.2 Hz, 4H, Ph–*H*), 7.00–7.05 (m, 6H, Ph–*H*), 7.08 (s, 4H, Ar–*H*), 7.10 (s, 4H, Ar–*H*), 7.13 (m, 2H, Py–H_5), 7.27 (d, *J* = 7.8 Hz, 2H, Py–H_4), 8.20 (s, 2H, Py–H_2)*and* 8.46 (d, *J* = 3.9 Hz, 2H, Py–H_6) ppm.

3 ⊃Ag^+: ^{1}H NMR (300 MHz, $CHCl_3$–CH_3CN, 10:1, v/v): δ = 0.84 (s, 18H, tBu), 0.91 (s, 18H, tBu), 5.07 (s, 4H, CH_2–Ph), 5.19 (s, 4H, CH_2–Py), 6.98 (d, *J* = 7.5 Hz, 4H, Ph–*H*), 7.07 (s, 4H, Ar–*H*), 7.08–7.12 (m, 4H, Ph–*H*), 7.17–7.20 (m, 2H, Ph–*H*), 7.21 (s, 4H, Ar–*H*), 7.52–7.57 (m, 2H, Py–H_5), 7.69 (d, *J* = 7.9 Hz, 2H, Py–H_4), 7.82 (s, 2H, Py–H_2) and 8.55 (d, *J* = 5.1 Hz, 2H, Py–H_6) ppm.

4: ^{1}H NMR (300 MHz, $CHCl_3$–CH_3CN, 10:1, v/v): δ = 0.84 (s, 18H, tBu), 0.85 (s, 18H, tBu), 5.07 (s, 4H, CH_2–Ph), 5.13 (s, 4H, CH_2–Py), 6.91 (d, *J* = 5.5 Hz, 4H, Py–$H_{3,5}$), 6.94 (d, *J* = 7.4 Hz, 4H, Ph–*H*), 7.02–7.07 (m, 4H, Ph–*H*), 7.11 (s, 4H, Ar–*H*), 7.13 (s, 4H, Ar–*H*), 7.14–7.18 (m, 2H, Ph–*H*) and 8.38 (d, *J* = 5.9 Hz, 4H, Py–$H_{2,6}$) ppm.

4 ⊃Ag^+: ^{1}H NMR (300 MHz, $CHCl_3$–CH_3CN, 10:1, v/v): δ = 0.86 (s, 18H, tBu), 0.91 (s, 18H, tBu), 5.11 (s, 4H, CH_2–Ph), 5.15 (s, 4H, CH_2–Py), 6.94–6.99 (m, 4H, Py–$H_{3,5}$) 7.09 (d, *J* = 7.3 Hz, 2H, Ph–*H*), 7.13 (s, 4H, Ar–*H*), 7.16–7.21(m, 6H, Ph–*H*), 7.21 (s, 4H, Ar–*H*)and 8.32 (d, *J* = 6.0 Hz, 4H, Py–$H_{2,6}$) ppm.

Crystallographic analyses of 3

Diffraction data were collected on a Bruker APEX 2 CCD diffractometer equipped with graphite-monochromated Mo-Kα

radiation at 150(2)K.[20] Data were corrected for Lorentz and polarisation effects and for absorption.[20] The structures were solved by direct methods and refined by full-matrix least-squares methods, on F^2.[21] H atoms were refined using a riding model except for those on hetero atoms in **3** which were freely refined.

Crystal data for 3. $C_{66}H_{70}N_2O_4S_4$, M = 1083.48. Orthorhombic, space group $Pmn2_1$, a = 15.1668 (6), b = 14.7772 (7), c = 12.7612 (6) Å, V = 2860.1 (2) Å^3. Z = 2, Dc = 1.258 g.cm^{-3}, F(000) = 1152, T = 100 K, μ(Mo-Kα) = 0.17 mm^{-1}, λ(Mo-Kα) = 0.6525 Å, colourless crystal of size 0.20 × 0.20 × 0.06 mm^3. The total number of reflections measured, to θ_{max} = 30.3°, was 345676 of which 11331 were unique (R_{int} = 0.087); 10920 were 'observed' with $I > 2\sigma(I)$. For the 'observed' data only, R_1 = 0.037; wR_2 = 0.101 for all 11331 reflections and 400 parameters. Residual electron density within +/– 0.48 eÅ^{-3}.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 245644 for **2**[6] and 1021161 for **3**, respectively. 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].

Supporting information: ^{1}H, ^{13}C NMR, MS and IR spectra of **3,** computational study of **2** – **4** with Ag^+.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Details of single-crystal X-ray crystallographic data. For ESI and crystallographic data in CIF see DOI: 10.1039/b000000x/

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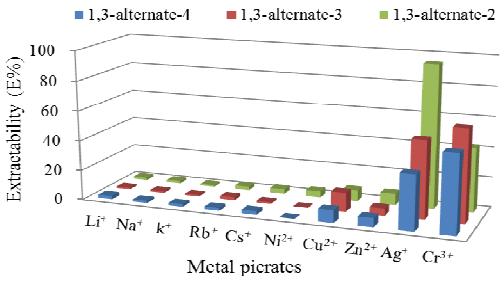
The extractability of thiacalix[4]arene derivatives **2** – **4** are largely dependent on the position of the binding sites.



SUPPORTING INFORMATION

Manuscript title: **A study of the position of nitrogen atoms in pyridyl ring to affect the ability of thiacalix[4]arene derivatives to interact with ions†**

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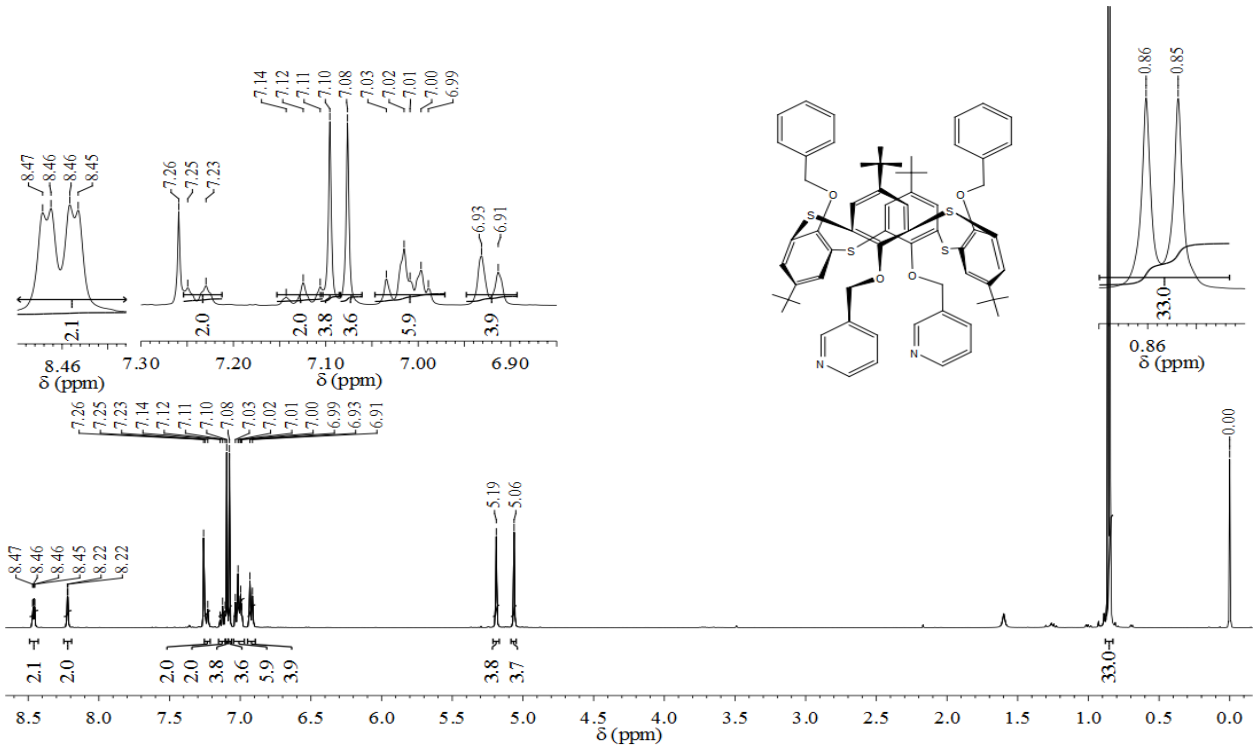

Figure S1. ^{1}H–NMR spectrum of compound **3** (400 MHz, $CDCl_3$, 293 K).

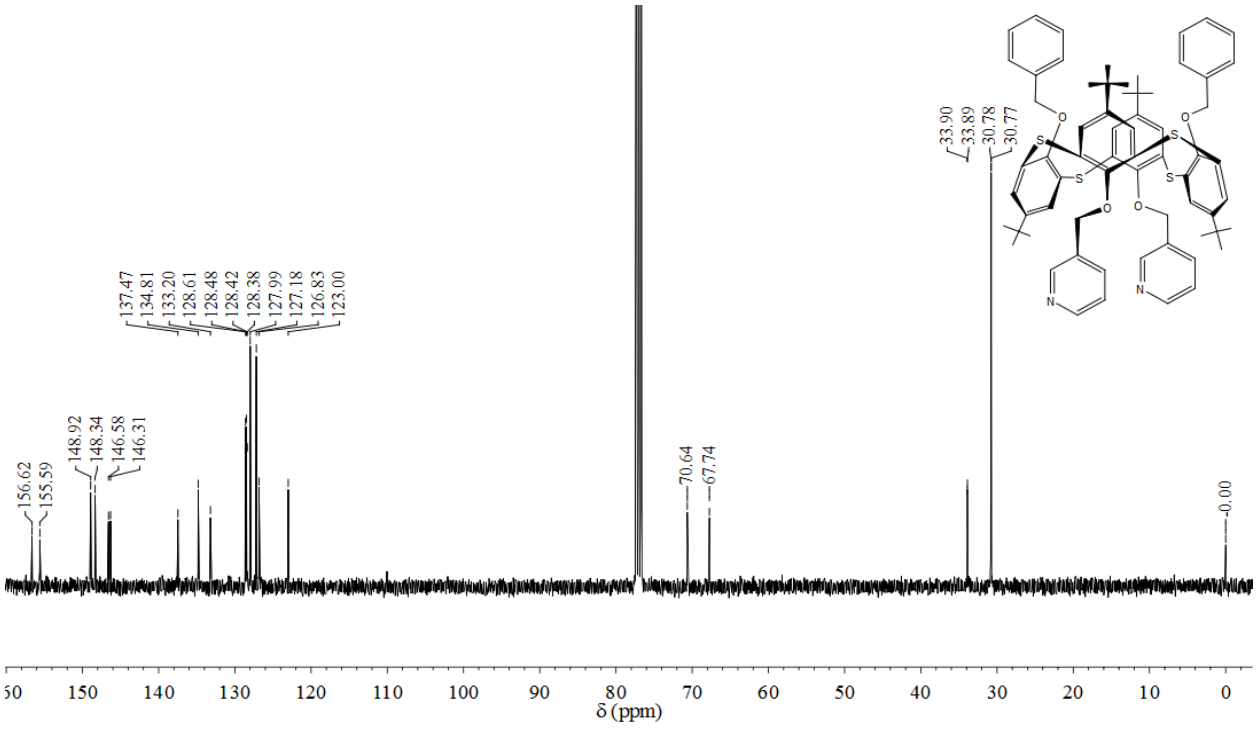

Figure S2. ^{13}C–NMR spectrum of compound **3** (100 MHz, $CDCl_3$, 293 K).

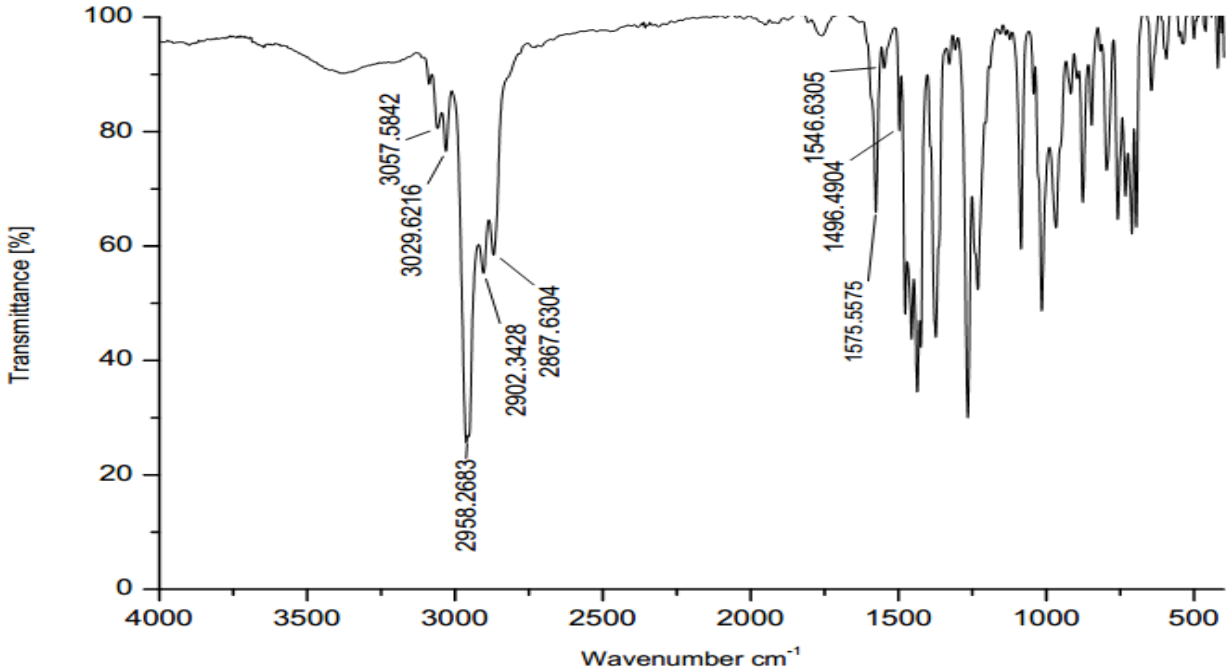

Figure S3. IR spectrum of compound **3**.

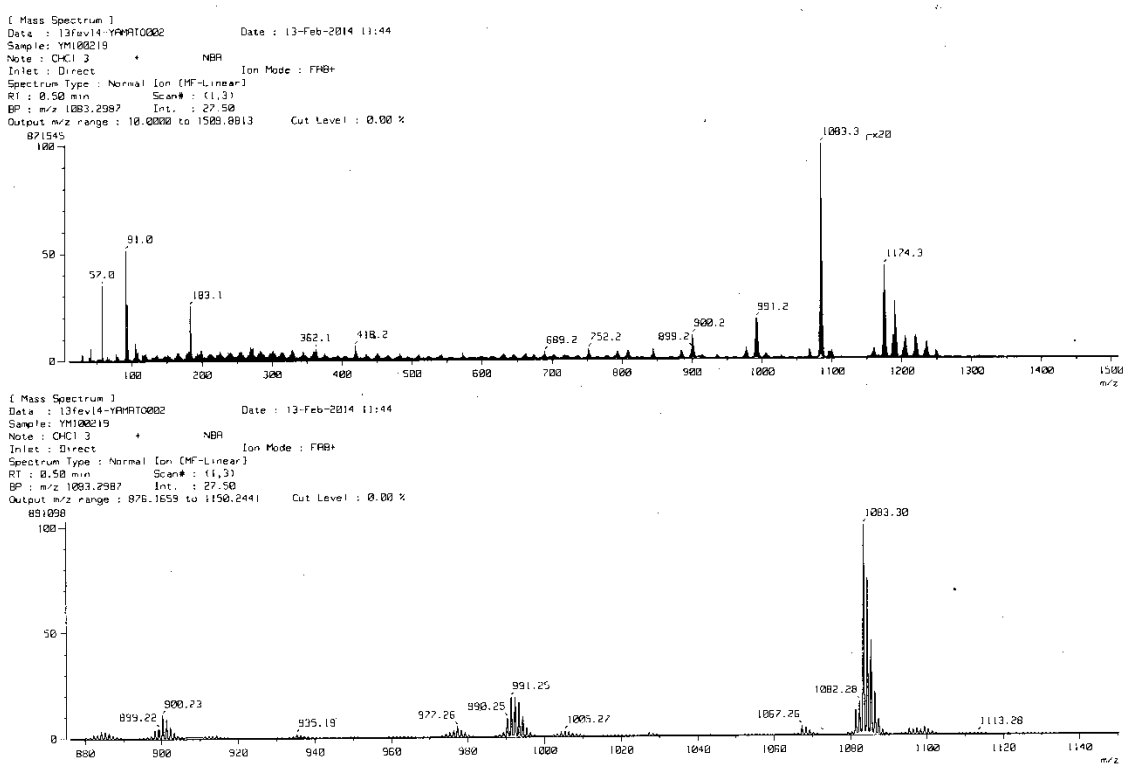

Figure S4. Mass spectrum of compound **3**.

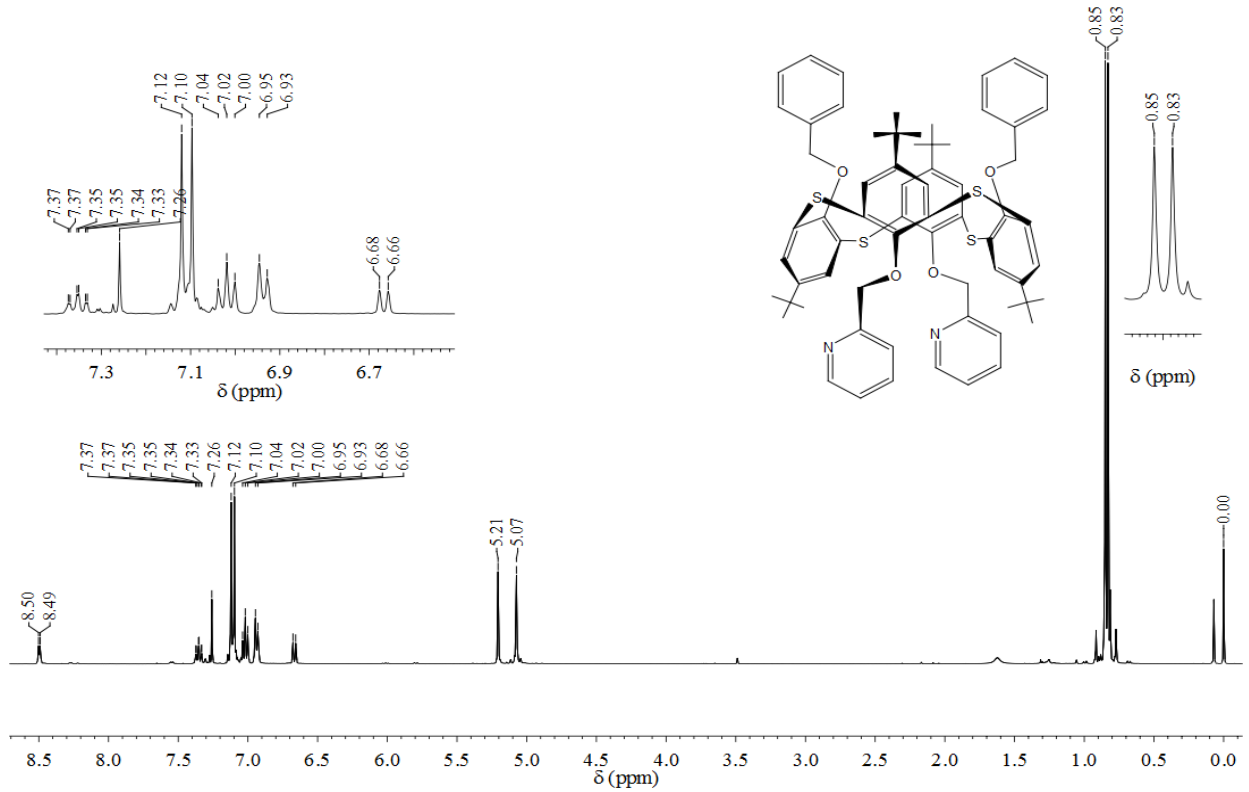

Figure S5. ^{1}H–NMR spectrum of compound **2** (400 MHz, $CDCl_3$, 293 K).

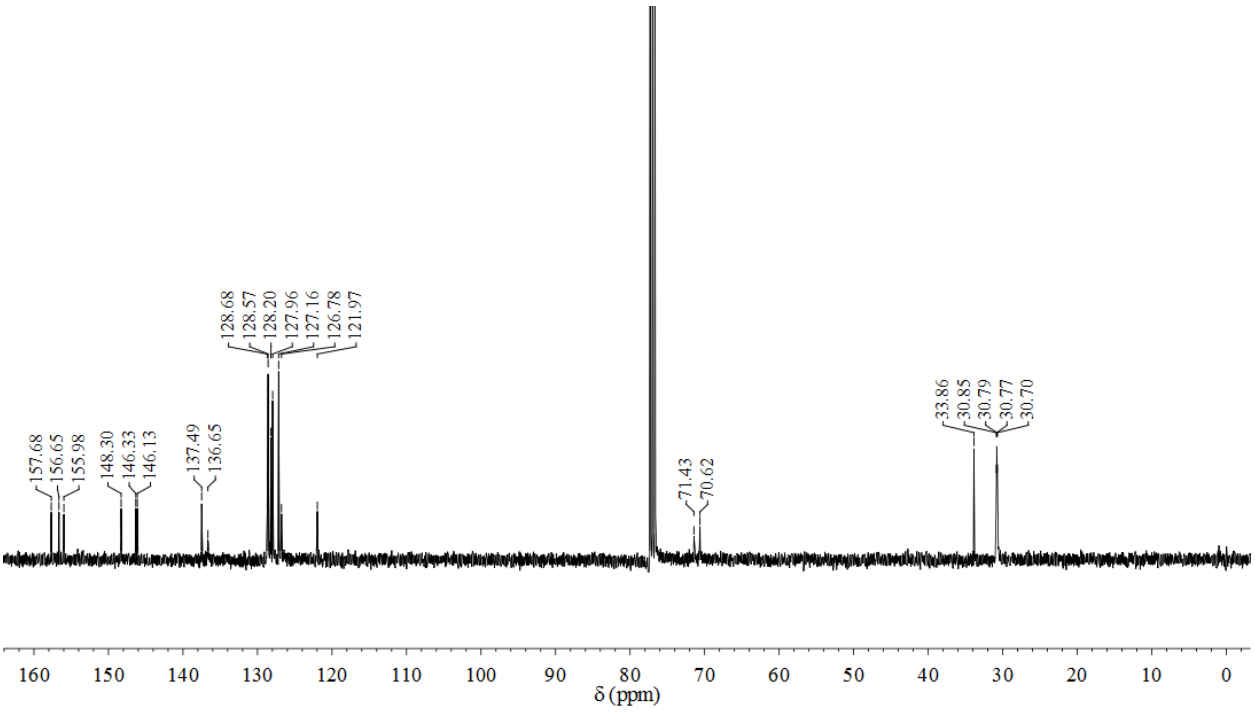

Figure S6. ^{13}C–NMR spectrum of compound **2** (100 MHz, $CDCl_3$, 293 K).

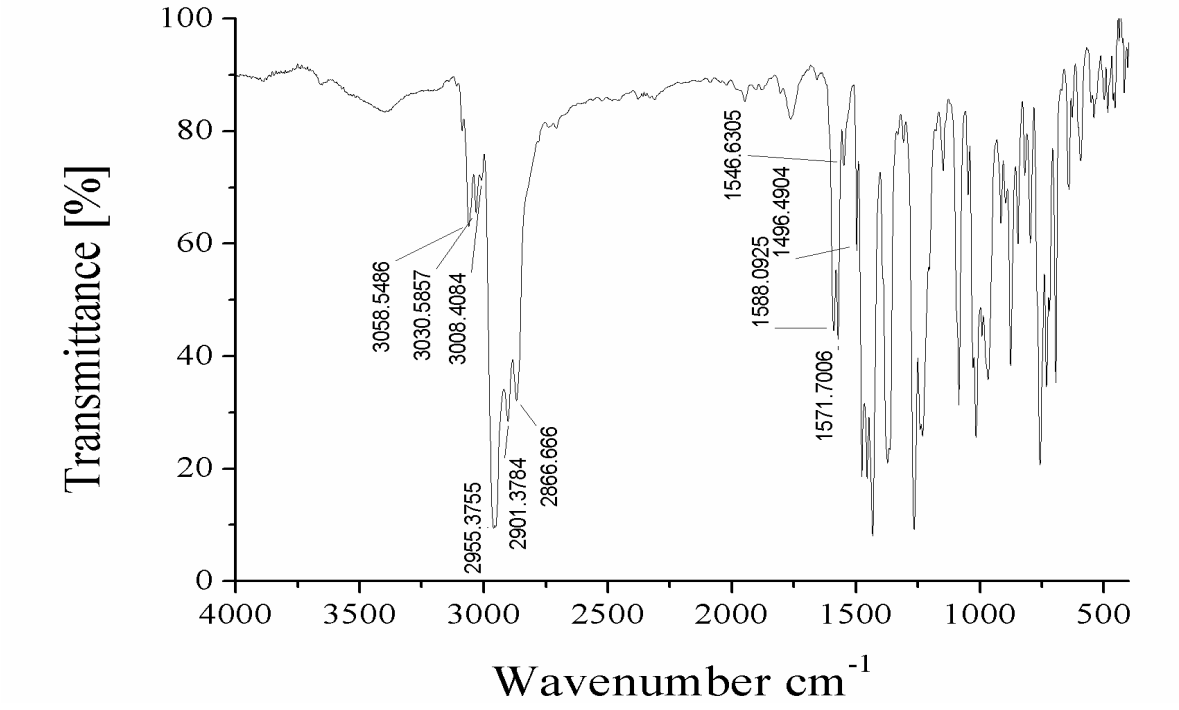

Figure S7. IR spectrum of compound **2**.

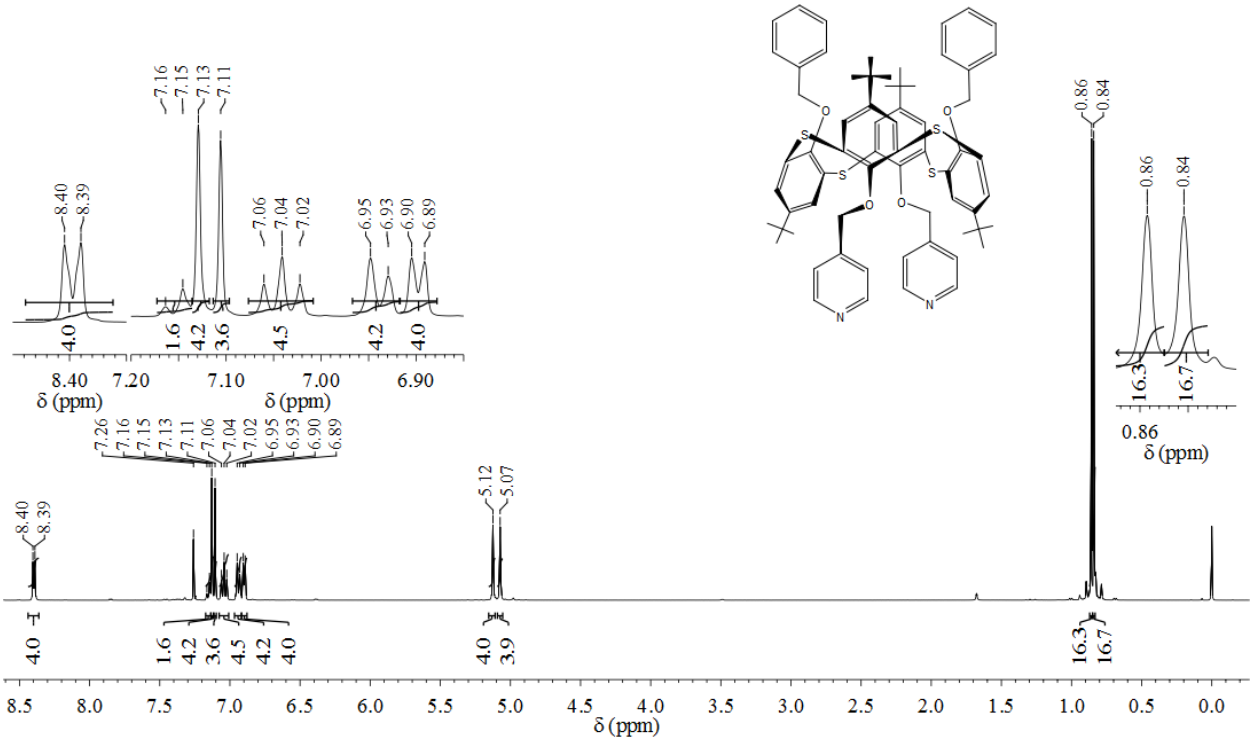

Figure S8. ^{1}H–NMR spectrum of compound **4** (400 MHz, $CDCl_3$, 293 K).

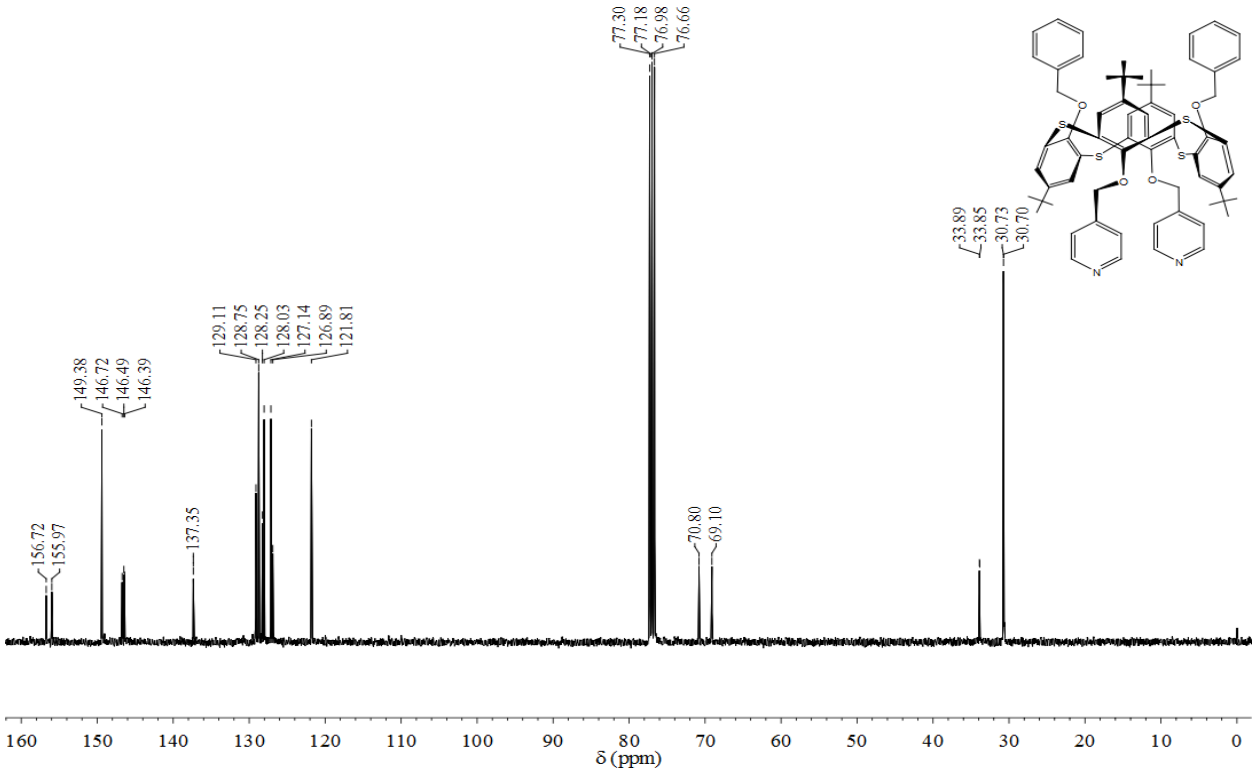

Figure S9. ^{13}C–NMR spectrum of compound **4** (100 MHz, $CDCl_3$, 293 K).

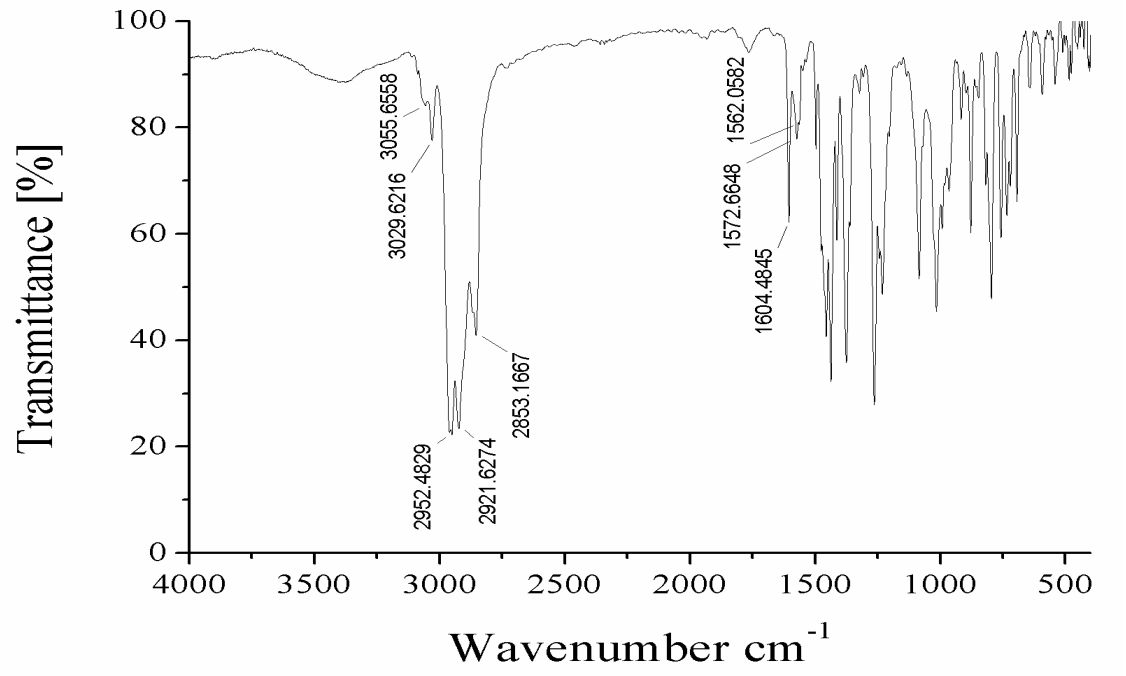

Figure S10. IR spectrum of compound **4**.

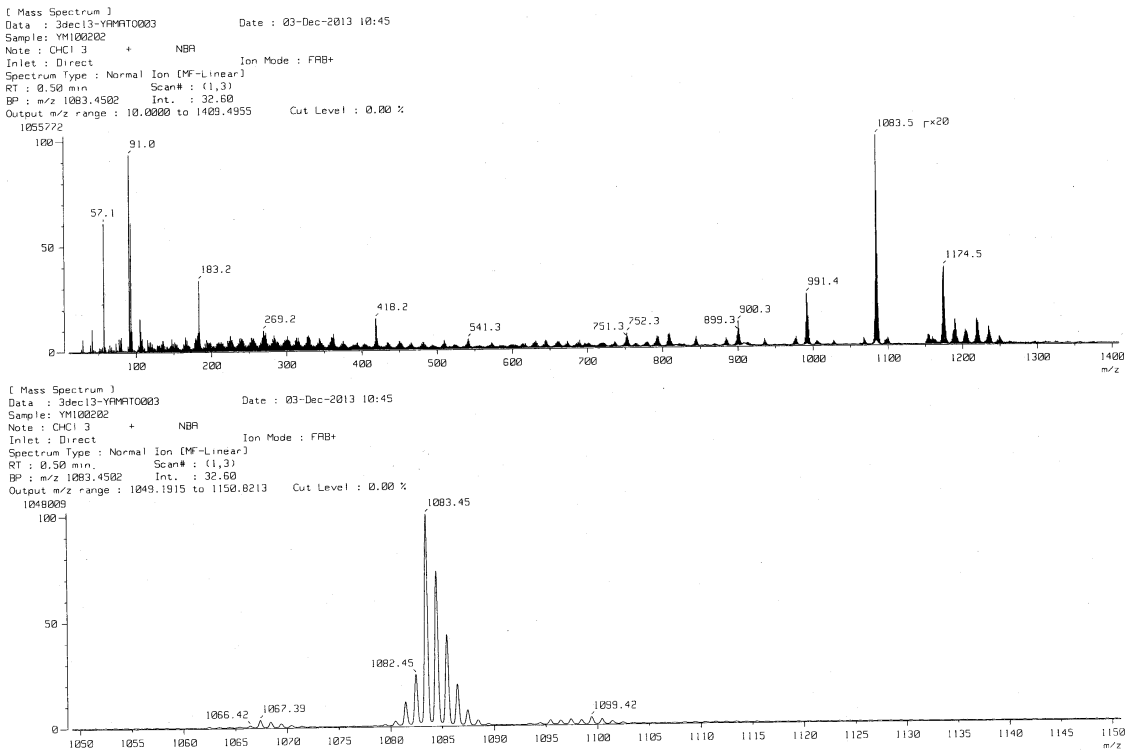

Figure S11. Mass spectrum of compound **4**.

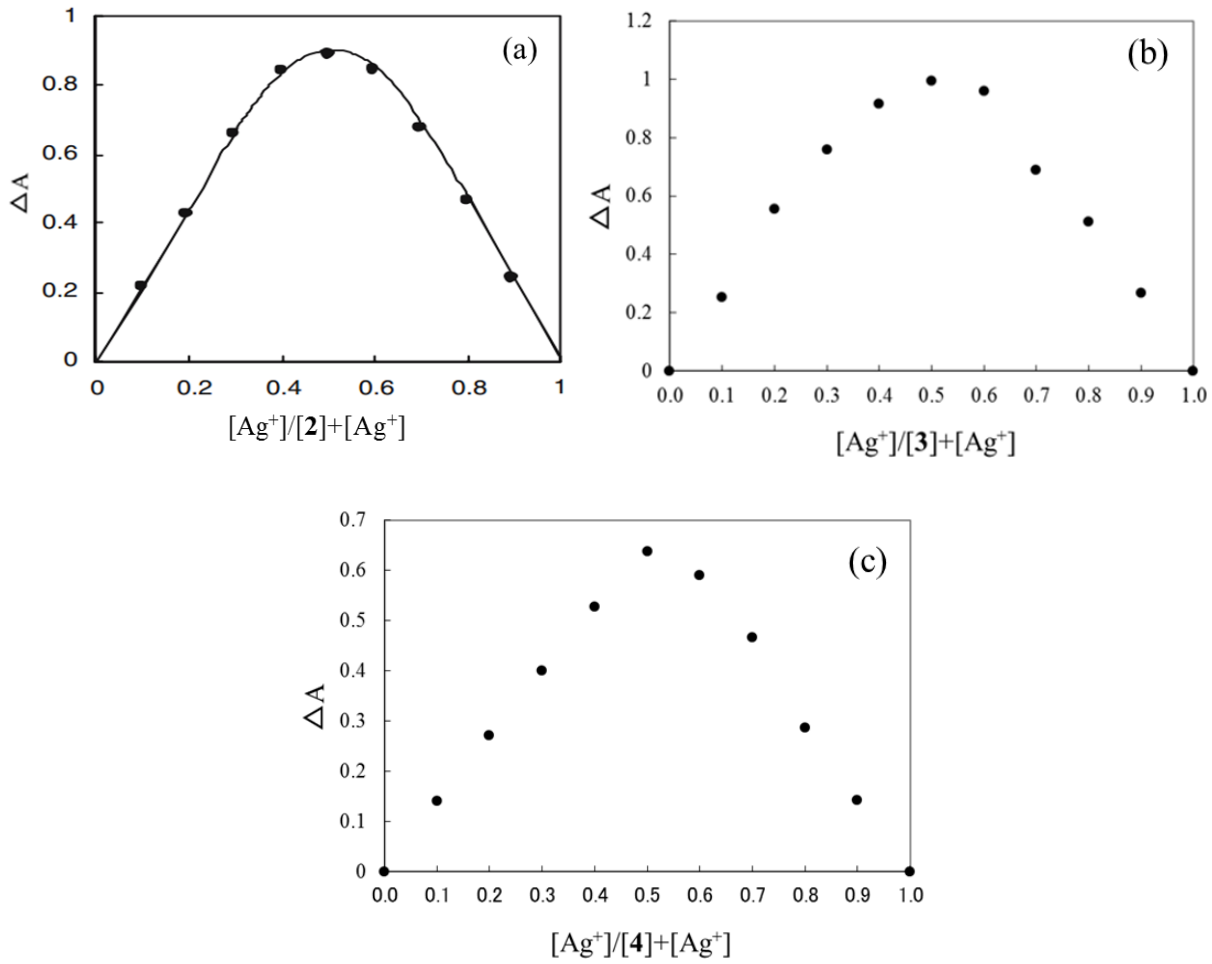

Figure S12 Job's plot for complexation of (a)[1] **2** with Ag^+, (b) **3** with Ag^+ ion and (c) **4** with Ag^+ ion.

Reference

1. T. Yamato, C. P. Casas, H. Yamamoto, M. R. J. Elsegood, S. H. Dale and C. Redshaw, *J. Incl. Phenom. Macrocycl. Chem.*, 2005, **54**, 261–269.

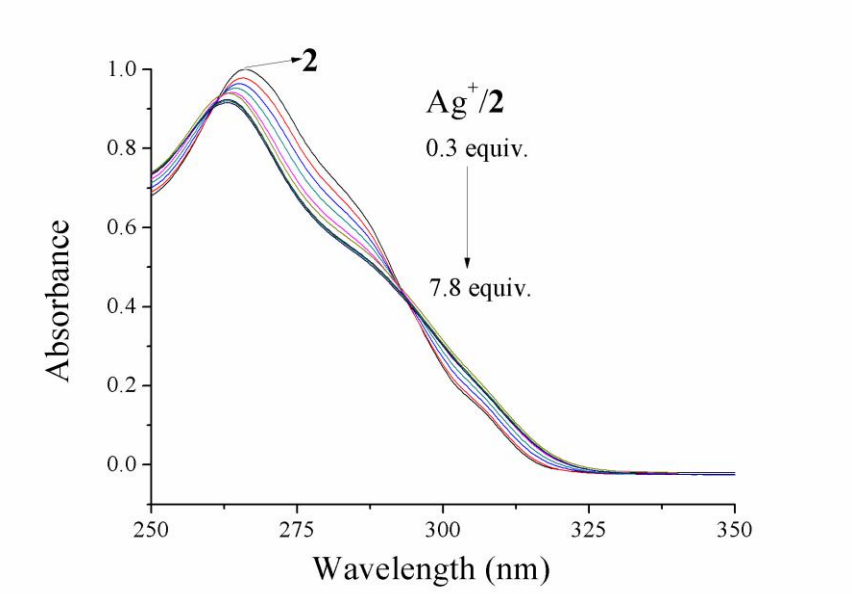

Figure S13 UV titration studies of **2** (1.5 $\times 10^5$ M/L) upon addition of $AgClO_4$ in $CHCl_3$.

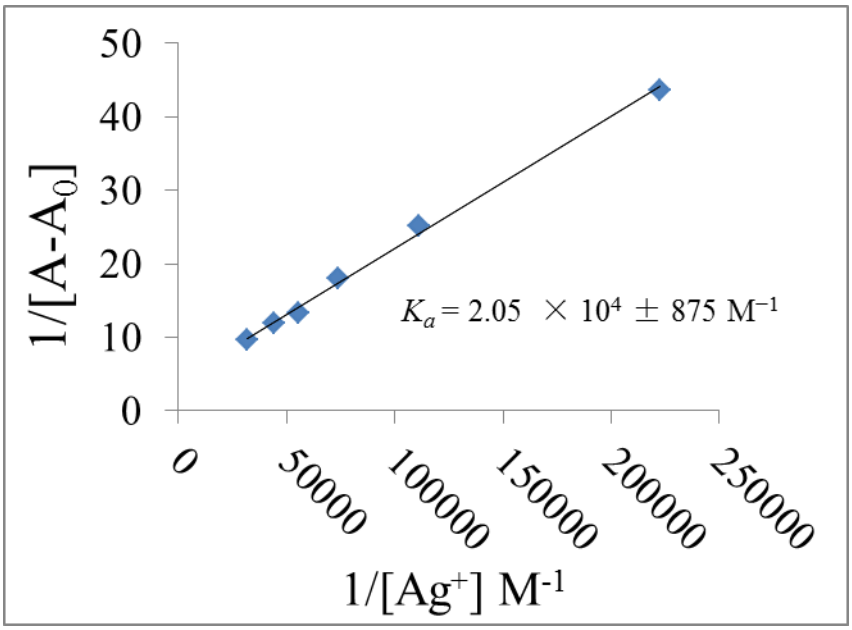

Figure S14 Bensei-Hilderbrand plot of **2** for various concentrations of Ag^+ ion at 298 K. The associate constant (*K*a) was calculated to be 2.05 $\times 10^4 \pm 875$ M^{-1}.

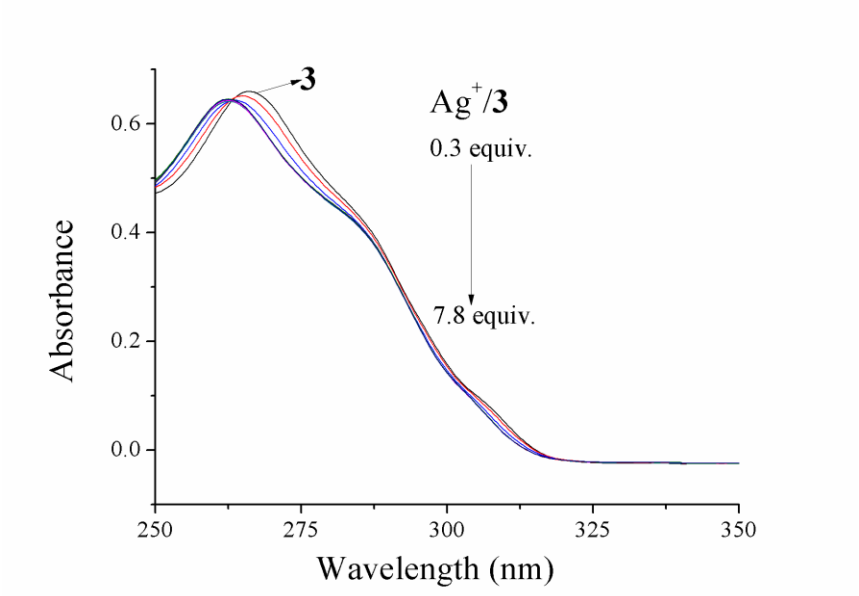

Figure S15 UV titration studies of **3** (1.5 $\times 10^5$ M/L) upon addition of $AgClO_4$ in $CHCl_3$.

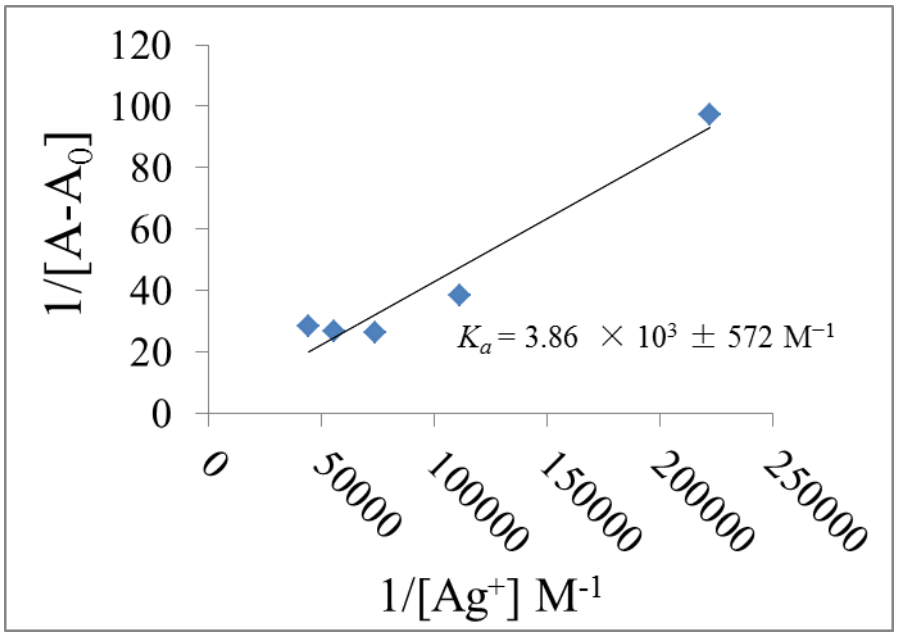

Figure S16 Bensei-Hilderbrand plot of **3** for various concentrations of Ag^+ ion at 298 K. The associate constant (*K*a) was calculated to be 3.86 $\times 10^3$ ± 572 M^{-1}.

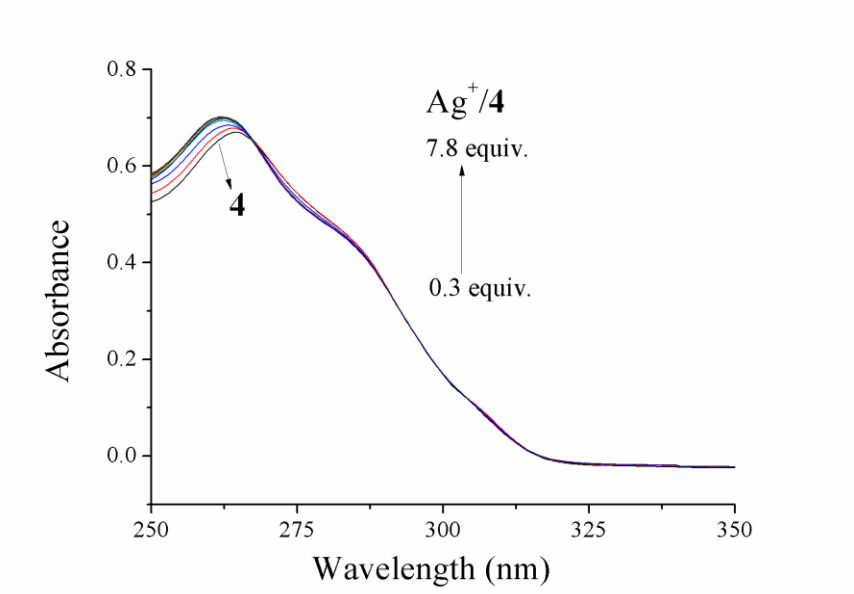

Figure S17 UV titration studies of **4** (1.5 $\times 10^5$ M/L) upon addition of $AgClO_4$ in $CHCl_3$.

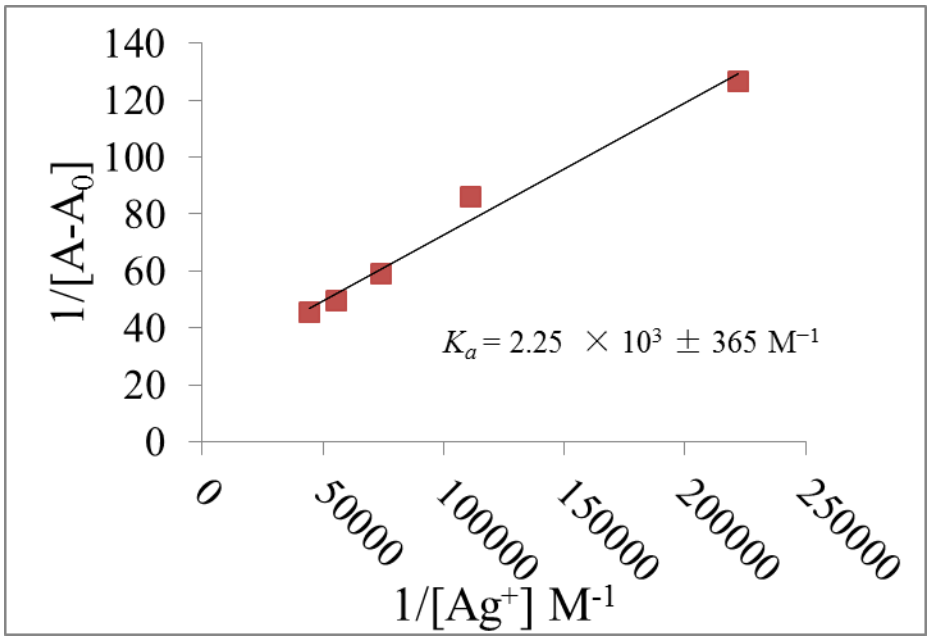

Figure S18 Bensei-Hilderbrand plot of **4** for various concentrations of Ag^+ ion at 298 K. The associate constant (*K*a) was calculated to be 2.25 $\times 10^3$ $\pm$365 M^{-1}.

General Description for Computational Study:

To better understand the binding properties of receptors **2**–**4** with Ag^+, a computation study was carried out. The molecular geometry of the individual structures in the gas-phase were fully optimized using Gaussian09,[2] with the B3LYP level of DFT and the lanl2dz basis set. Significant conformational changes were observed for the pyridine ring protons of **2**–**3** after the complexation with Ag^+. The conformation changes for **2** upon complexation with Ag^+ ion can be seen in Fig. S1 and. Fig. S2. Fig. S1 shows the structure (*right*) of the **2**⊃Ag^+ complex. The optimized molecular geometry suggests that the Ag^+ binds, in accord with the ^{1}H NMR complex study, via a N---Ag^+---S short contact distance bond, which results in the conformation change. The N---N distance between the pyridine nitrogen atoms decreases from 8.001 to 3.761 (Å) (Table 1) since the nitrogen atoms move inwards after complexing with the Ag^+. All four bridge sulphur atoms are roughly the same distance from the Ag^+ and presumably take an equal part in the coordination bonding. However, a different phenomenon was observed in the complexation of **3** with Ag^+. The N--N distance between the pyridine nitrogen atoms decreases from 9.305 to 4.234 (Å) after complexing with the Ag^+ (Fig. S3 and Fig. S4). A similar inference can also be made for the **4**⊃Ag^+complex (Fig. S5 and Fig. S6). The distance between the pyridine nitrogen atoms decrease from 10.138 to 3.798 (Å) (Table 1) after complexation with Ag^+. The optimized molecular geometry suggests that complexation of **3**–**4** with Ag^+ occurs via a N---Ag^+ short contact distance bond, which results in the conformation change.

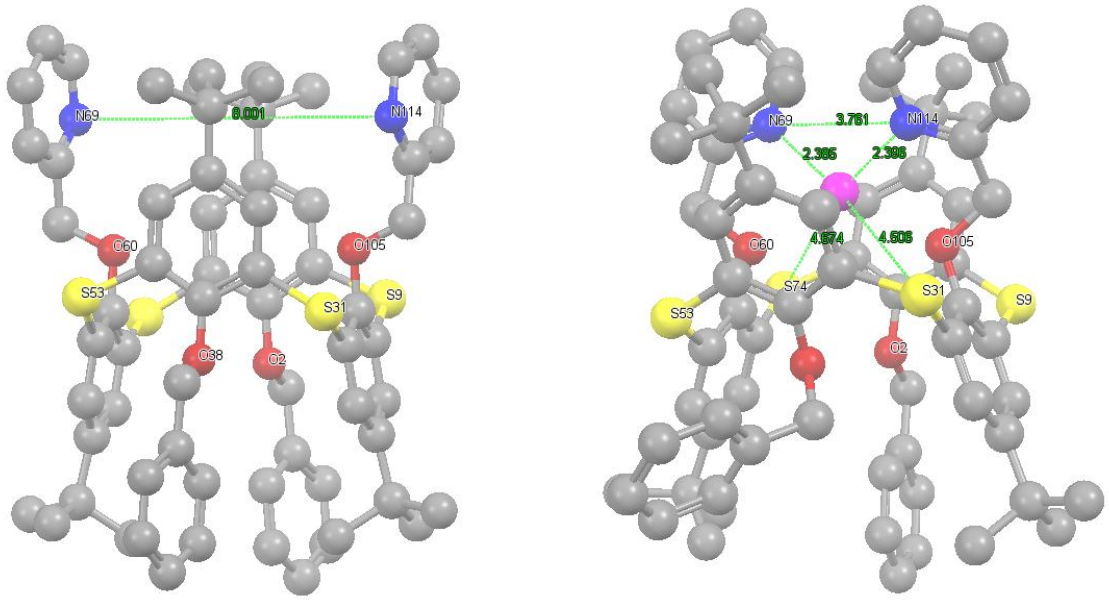

Figure S19. Geometry-optimized (ball and stick) structures of: *Left*: **2** and *Right*: **2**⊃Ag^+complex. Color code for Ag^+ = magenta, pyridine nitrogen = blue, sulphur = yellow and oxygen atom = red. Hydrogen atoms have been omitted for clarity.

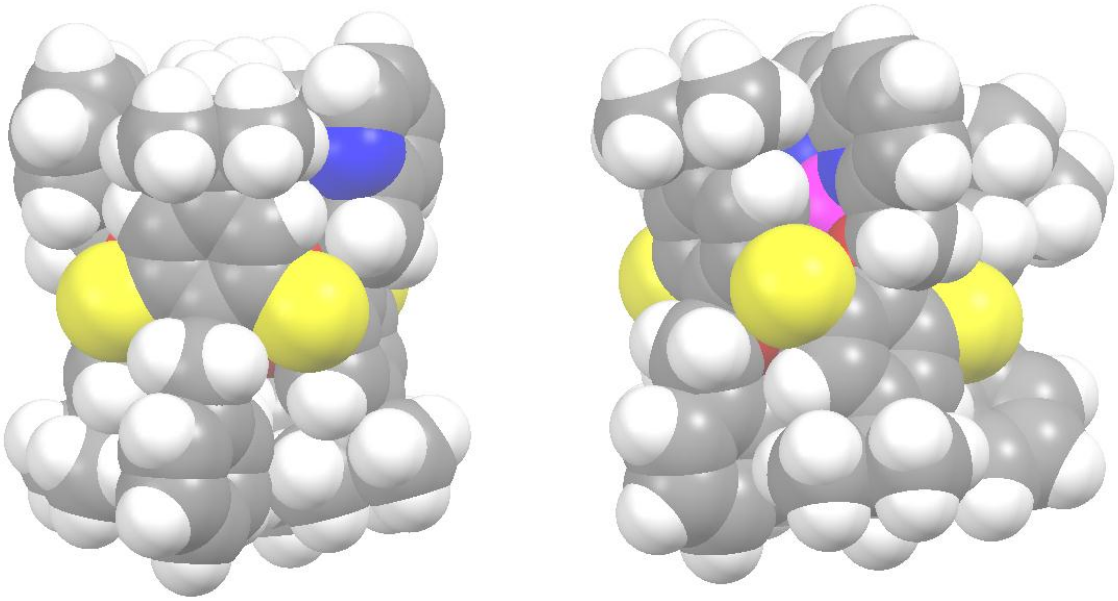

Figure S20. Geometry-optimized (space fill) structures of: *Left*: **2** and *Right*: **2**⊃Ag^+complex. Color code for Ag^+ = magenta, pyridine nitrogen = blue, sulphur = yellow and oxygen atom = red. Hydrogen atoms have been omitted for clarity.

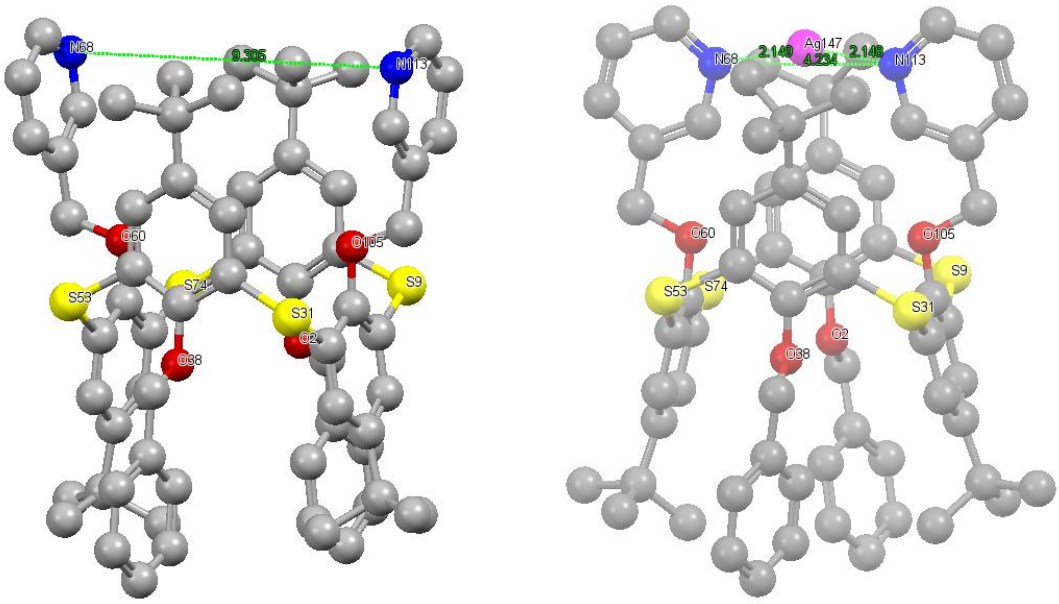

Figure S21. Geometry-optimized (ball and stick) structures of: *Left*: **3** and *Right*: **3**⊃Ag^+complex. Color code for Ag^+ = magenta, pyridine nitrogen = blue, sulphur = yellow and oxygen atom = red. Hydrogen atoms have been omitted for clarity.

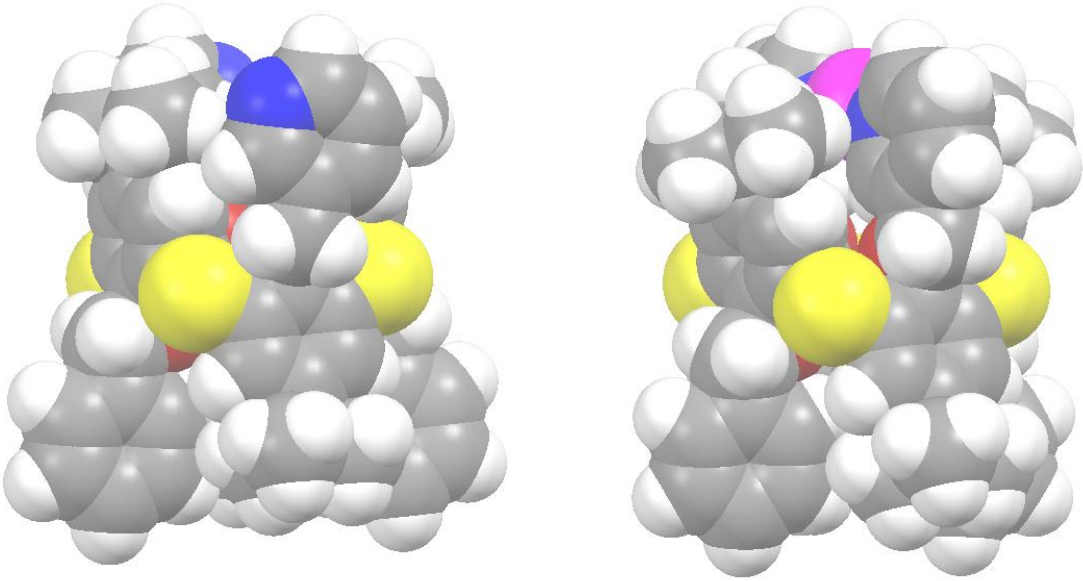

Figure S22. Geometry-optimized (space fill) structures of: *Left*: **3** and *Right*: **3**⊃Ag^+complex. Color code for Ag^+ = magenta, pyridine nitrogen = blue, sulphur = yellow and oxygen atom = red. Hydrogen atoms have been omitted for clarity.

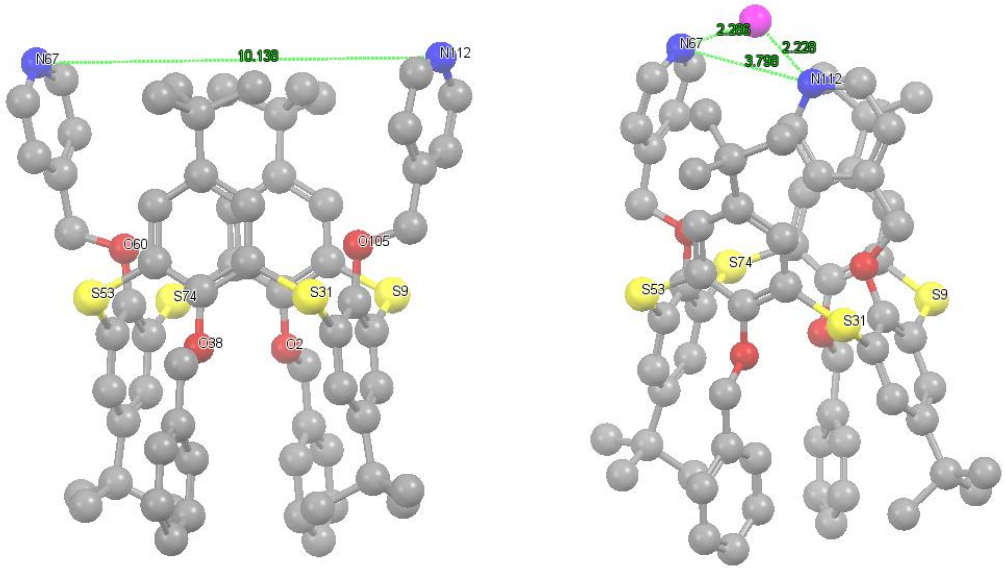

Figure S23. Geometry-optimized (ball and stick) structures of: *Left*: **4** and *Right*: **4**⊃Ag^+complex. Color code for Ag^+ = magenta, pyridine nitrogen = blue, sulphur = yellow and oxygen atom = red. Hydrogen atoms have been omitted for clarity.

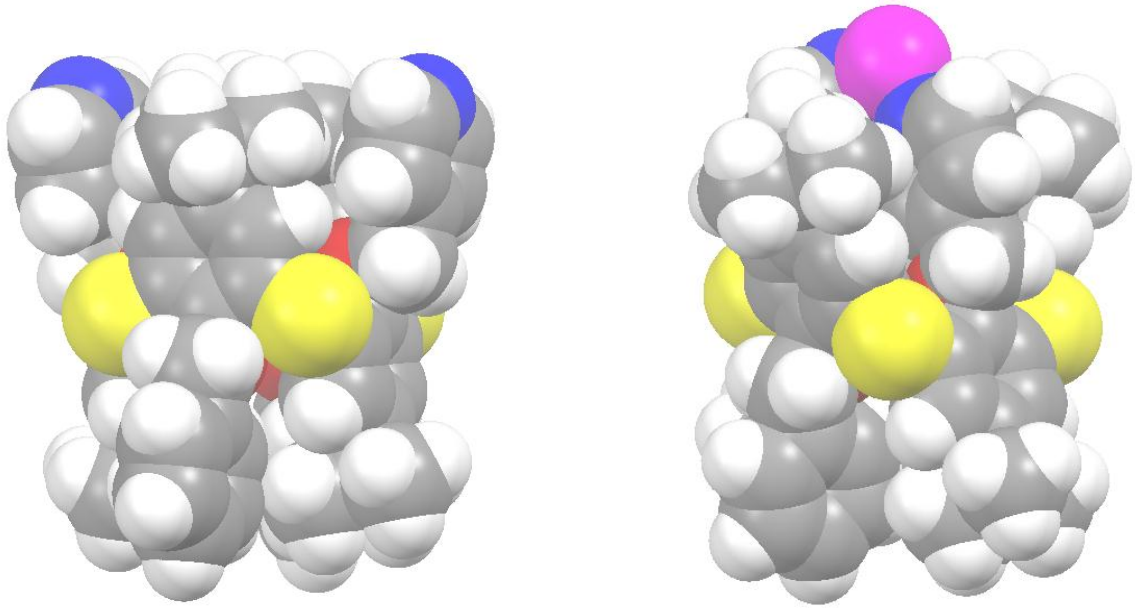

Figure S24. Geometry-optimized (space fill) structures of: *Left*: **4** and *Right*: **4**⊃Ag^+complex. Color code for Ag^+ = magenta, pyridine nitrogen = blue, sulphur = yellow and oxygen atom = red. Hydrogen atoms have been omitted for clarity.

Table S1 The calculated distance for selected parameters for the backbones of the 1,3-*alternate*-**2**–**4** and their complexes with Ag^+ optimized at B3LYP/ lanl2dz level(Distance in Å).

Parameter	**2** (Å)	**2**⊃Ag^+ (Å)	Parameter	**3** (Å)	**3**⊃Ag^+ (Å)	Parameter	**4** (Å)	**4**⊃Ag^+ (Å)
N_{69}-N_{114}	8.001	3.761	N_{68}-N_{113}	9.305	4.234	N_{67}-N_{112}	10.138	3.798
N_{69}-S_9	8.188	6.841	N_{68}-S_9	6.715	7.651	N_{67}-S_9	10.536	9.319
N_{69}-S_{31}	8.89	6.712	N_{68}-S_{31}	6.219	7.941	N_{67}-S_{31}	9.96	9.249
N_{69}-S_{53}	5.614	5.231	N_{68}-S_{53}	9.431	5.966	N_{67}-S_{53}	6.528	6.713
N_{69}-S_{74}	5.036	4.708	N_{68}-S_{74}	9.971	6.12	N_{67}-S_{74}	7.3	6.762
N_{114}-S_9	5.614	5.512	N_{113}-S_9	9.431	5.953	N_{112}-S_9	6.528	6.942
N_{114}-S_{31}	5.036	4.323	N_{113}-S_{31}	9.971	6.132	N_{112}-S_{31}	7.3	6.84
N_{114}-S_{53}	8.188	6.556	N_{113}-S_{53}	6.715	7.654	N_{112}-S_{53}	10.536	7.055
N_{114}-S_{74}	8.89	6.886	N_{113}-S_{74}	6.219	7.924	N_{112}-S_{74}	9.96	7.111
N_{69}-Ag^+	-	2.385	N_{68}-Ag^+	-	2.149	N_{67}-Ag^+	-	2.286
N_{114}-Ag^+	-	2.396	N_{113}-Ag^+	-	2.148	N_{112}-Ag^+	-	2.228
S_9-Ag^+	-	4.98	S_9-Ag^+	-	6.811	S_9-Ag^+	-	8.857
S_{31}-Ag^+	-	4.506	S_{31}-Ag^+	-	7.069	S_{31}-Ag^+	-	8.749
S_{53}-Ag^+	-	4.699	S_{53}-Ag^+	-	6.818	S_{53}-Ag^+	-	7.725
S_{74}-Ag^+	-	4.674	S_{74}-Ag^+	-	7.056	S_{74}-Ag^+	-	7.8

Calculated binding energies

The DFT B3LYP/ lanl2dz basis set-calculated binding energies (ΔE) of the Ag^+ complexes of thiacalix[4]arene derivatives **2-4** ($L_{free} + Ag^+_{free} \rightarrow L/Ag^+_{complex}$) formed between the Ag^+ ion and the free thiacalix[4]arene derivatives **2-4** in the gas phase at 298 K are based on the equation (1), are listed in Table S2.

For this system, the binding energy ΔE can be express as follows:

$$\Delta E = E(L/Ag^+_{complex}) - E(L_{free}) - E(Ag^+_{free}) \quad (1)$$

Table S2 Calculated binding energies for the thiacalix[4]arene derivatives with Ag^+.

Parameter	**2**⊃**Ag**$^+$ ΔE (KJ/mole)	**3**⊃**Ag**$^+$ ΔE (KJ/mole)	**4**⊃**Ag**$^+$ ΔE (KJ/mole)
Binding energy for thiacalix[4]arene derivatives with **Ag**$^+$	-488.096	-464.022	-372.966

Reference

2. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, Jr. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox. *Gaussian 09, Revision D.01*; Gaussian, Inc., Wallingford CT, 2013.

Dear editor

Thank you very much for your E-mail about our manuscript, manuscript ID: OB-ART-11-2014-002393. We deeply appreciate your attention and we benefit a lot from the comments offered by the reviewers. We have revised our manuscript according to reviewers' comments. Changes against each point which is being raised and corresponding comments are listed as follows.

Thank you very much for your time and consideration.

Yours sincerely,

Prof. Dr. Takehiko Yamato (corresponding author)
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Reviewer(s)' Comments to Author:

Referee: 1

Comments to the Author

The manuscript "A study of the position of nitrogen atoms in pyridyl ring to affect the ability of thiacalix[4]arene derivatives to interact with ions" by Yamato described about Three 1,3-*alternate* thiacalix[4]arenes bearing pyridyl moieties (ortho for **2**, meta for **3** and para **4**) at the lower rim and their solvent extraction experiments. Authors claimed that mode of binding of the C_2V-symmetrical dipyridyl substituted thiacalix[4]arenes, **2** – **4** with Ag^+ was elucidated clearly using a ^1H NMR titration method. The DFT computational studies were consistent with the experimental findings. Reading the manuscript thoroughly, the current manuscript can be recommended to be accepted for publication in "OBC" with minor revision requested as follows.

1. *Authors need to calculate binding constant of the ligand for the metal ions and binding ratio using Job plotting.*
   The experiments of binding constant and binding ratio have been added. (For more detail information, please see the manuscript, page 3 and the supporting information, page 8–11, Figure S12–S18). The binding constants (K_a) value for the complexation with Ag^+ ion was determined to be $2.05 \times 10^4 \pm 875$ M^{-1} (**2**) , $3.86 \times 10^3 \pm 572$ M^{-1} (**3**), $2.25 \times 10^3 \pm 365$ M^{-1} (**4**) based on the Benesi–Hildebrand equation. Job's plot showed that Ag^+ formed 1:1 complexes with **2** – **4**.
2. *For the new compounds, authors are recommended to provide ^{13}C NMR spectral data in experimental section.*
   We have added the ^{13}C NMR, ^1H NMR, IR and Mass for all compounds. (For more detail information, please see the manuscript, page 6 and the supporting information, page 2–7, Figure S1–S11).

Referee: 2

Comments to the Author

The work is devoted to solvent extraction study of the metal ions and dichromate anions by thiacalix[4]arene derivatives bearing two pyridyl coordinating moieties (ortho, meta and para). The relationship between the position of the nitrogen atoms of the pyridyl ring and the ability of these derivatives to interact with various ionic species were evaluated. This work is of interest in that it presents new perspectives in the field of thiacalixarene chemistry, especially the finding that macrocycle **3** containing two pyridyl (meta) substituents could be meaningful for applying a solvent extraction method for the selective treatment of waste water containing Cr (VI) and Cr (III) ions prior to discharge.

It is well known that thiacalix[4]arene derivatives can form aggregates with Ag+ ions but in the article didn't written about the character of interaction between studied thiacalixarenes and Ag+. Metal ion and anions binding by thiacalixarene derivatives is well known in the literature and these studies are ongoing for many years. For this reason, the novelty of the research and

applicability of the conclusions should be substantiated and discussed in more detail. Thus, this article cannot be published in this view and should be rejected.

Notes:

1) *Why in the abstract is written that new organic ionophores (**2–4**) based on the p-tert-butylthiacalix[4]arene have been synthesized if compounds **2** and **4** are described according to previous reports (6,10)?*
Thank you for your kindly reminding. I am sorry for my thoughtless. We have revised it. (Please see the manuscript, Page 1.)

2) *P.1 In the Abstract in the first sentence is a printing mistake: "synthesised and characterised" should be changed by "synthesized and characterized". Also in Conclusion it should write "synthesized".*
The grammatical mistakes have been revised. (Please see the manuscript, Page 1and page 5.) Thank you.

3) *P.1. In the introduction in the sentence "Recently, our lab has reported the regioselective synthesis of distal-bis[(2-pyridylmethyl)oxy]tetra-thiacalix[4]arene in the 1,3-alternate conformation by using a protection-deprotection method using benzyl groups as protecting groups" is a repetition of "using".*
Thank you for your suggestion. The "using" is deleted. (Please see the manuscript, Page 1.)

4) *P.1. Introduction. What is the name "Pyridinothiacalix[4]arenes"? It should be better to change by "pyridine derivatives of thiacalix[4]arene" or "pyridyl containing thiacalix[4]arenes".*
"Pyridinothiacalix[4]arenes" have been replaced by "pyridine derivatives of thiacalix[4]arene". (Please see the manuscript, Page 1.) Thank you for your suggestion.

5) *P.3 (Results and discussions) In the sentence "As a result, since the pyridine moieties orientated inwards, the ring current shielding effect[14] operating in the two thiacalix benzene rings is destroyed, forcing the steric conformation change" it should be better to write "in the two thiacalixarene benzene rings".*
"in the two *thiacalix* benzene rings" has been revised to "in the two *thiacalixarene* benzene rings ". (Please see the manuscript, Page 3.) Thank you for your suggestion.

6) *P.3-4 (Results and discussions) In the sentence "This maybe attribute that when 3 complexes with Ag+, the Ag+ is trapped in the cavity formed by the nitrogen atoms in pyridine, induce the proton H_2 become folded into the π-cavity formed by the two thiacalix benzene rings and are thus shifted strongly upfield (-0.38 ppm)" what is the name "thiacalix benzene rings"? It should write as "thiacalixarene benzene rings".*
"the two *thiacalix* benzene rings" has been revised to "the two *thiacalixarene* benzene rings ". (Please see the manuscript, Page 4.) Thank you for your suggestion.

7) *It is well known that thiacalix[4]arene derivatives can form aggregates with Ag^+ ions. What is the character of interaction between studied thiacalixarenes and Ag^+? Inclusion complex or aggregates are formed?*

The character of interaction between studied thiacalix[4]arenes, **2 – 4** with Ag^+ have been elucidated clearly by using a ^1H NMR titration method and DFT computational studies. Two different complexation modes were observed: **2** armed with two *ortho* pyridyl groups, complexed with Ag^+ via N···Ag^+···S interactions whereas **3** and **4**, complexed with Ag^+ through N···Ag^+ interactions. The DFT computational studies were also consistent with the experimental findings. (For more detail information, please see the manuscript, page 3–4 and the supporting information, page 12–17, Figure S19–S24).

8) *Metal ion binding by thiacalixarene derivatives is well known in the literature and these studies are ongoing for many years. This also applies to the dichromate anion. For this reason, the novelty of the research and applicability of the conclusions should be substantiated and discussed in more detail.*

As you said "Metal ion binding by thiacalixarene derivatives is well known in the literature and these studies are ongoing for many years." However, it is still unknown whether the metal extractability can be affected by the position of the coordination binding sites of the substituents themselves. Therefore, it is necessary to find out this relationship which can help us to design a best thiacaixarene ionophore in the further study. In this paper, a series of 1,3-*alternate* thiacalix[4]arenes bearing pyridyl moieties (*ortho*, *meta* and *para*) at the lower rim were targeted for synthesis. The relationship between the position of the nitrogen atoms of the pyridyl ring and the ability of these derivatives to interact with various ionic species were evaluated by solvent extraction experiments. Finally, it is clearly that the extractability of thiacalix[4]arene receptors are dependent on the position of the binding sites.

This is the first case which focus on studying the relationship between the extractability of thiacalix[4]arene derivatives and the position of the coordination binding sites. With this study, it will provide us an important reference to design an appropriate thiacaixarene ionophore in the future.

Referee: 3

Comments to the Author

I have read over the manuscript by Yamoto and coauthors and after careful consideration, recommend publication of the work with some minor revisions and or re-framing of the work.

My challenge in reviewing this work was picking up on the thesis of the work since it seemed to be telling the story for cations (with the major discovery being binding mode for silver) and then the application was geared towards a very specific anion. I am unsure if either the title, the way the introduction was framed, or the conclusion really link the work together in the best way.

That said, the work looks very solid, professional and thorough. I urge the authors to find a better way to emphasize the more significant aspects of their work through a more specifically descriptive title and through weaving the components together in a more intentional way.

Thank you for your kindly suggestion. We have improved this paper as possible as we can. The title has been improved to “The first study about the relationship between the extractability of thiacalix[4]arene derivatives and the position of the coordination binding sites”. (For more detail information, please see the manuscript.)

Actually, as you saw, this work was divided to two sides. First, we focused on studying the relationship between the extractability of thiacalix[4]arene derivatives and the position of the coordination binding sites by solvent extraction experiments. Due to there are still nobody known whether the metal extractability can be affected by the position of the coordination binding sites of the substituents themselves. This is the main part of this work. With this study, it will provide us an important reference to design an appropriate thiacalixarene ionophore in the future. This is the most meaningful application of ionophores **2 – 4**. And then, we explored ionophore **3** was meaningful for applying solvent extraction method in selective treatment of waste water containing Cr (VI) and Cr (III) prior to discharge.

The discovery of the extractability of thiacalix[4]arene derivatives **2 – 4** are largely dependent on the position of the binding sites is very important for the thiacalixarene chemistry. It will provide us an important rule to design an appropriate thiacalixarene ionophore. That is why we pay a lot’s of comments on the first side.

Journal Name

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ARTICLE

The first study about the relationship between the extractability of thiacalix[4]arene derivatives and the position of the coordination binding sites †

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Three organic ionophores (**2 – 4**) based on the *p-tert*-butylthiacalix[4]arene backbone, blocked in the 1,3-*alternate* conformation, bearing two pyridyl coordinating moieties (*ortho* for **2**, *meta* for **3** and *para* for **4**), have been synthesized and characterized in the solid state. The solvent extracted experiments of the metal ions showed that the ability of these derivatives to complex with Ag^+ appeared to be largely dependent on the position of the nitrogen atoms of the pyridyl ring. Two different complexation modes have been confirmed by ^1H NMR titration, ionophore **2** armed with two pyridyl, complexed with Ag^+ cation through N···Ag^+···S interactions; however, ionophore **3** and ionophore **4**, complexed with Ag^+ through metal-nitrogen (N···Ag^+) interactions. The DFT computational studies were consistent with the experimental findings. These findings will provide us an important rule to design an appropriate thiacaixarene ionophore in the future. Another studied on the possibility for application of ionophores **2 – 4** to the treatment of waste water containing Cr (VI) and Cr (III), showed that ionophore **3** was meaningful for applying solvent extraction method in selective treatment of waste water containing Cr (VI) and Cr (III) prior to discharge.

Introduction

Thiacalix[4]arene is widely used as a macrocyclic platform for designing and building synthetic receptors toward metal cations.[1] The complexation properties of these molecules appear to be highly dependent upon the nature and number of donor atoms and also upon the conformation of the calix[*n*]arene moiety.[2] It is found that thiacalix[4]arene has a very high ability to bind transition metal ions,[3] which has been quite unexpected considering the poor binding ability of calix[4]arene. The 1,3-*alternate* stereoisomer, which shows an allosteric effect in metal cation binding, or offers divergently oriented binding sites, is of special interest.[1,4] For the synthesis of macrocycles with controlled (switchable) binding sites of metal cations,[5] there is a need for the development of novel approaches to the design of tetrasubstituted thiacalix[4]arenes with various groups with specific conformations. Recently, our lab has reported the regioselective synthesis of distal-bis[(2-pyridylmethyl)oxy]tetra-thiacalix[4]arene in the 1,3-*alternate* conformation by a protection-deprotection method using benzyl groups as protecting groups.[6] Pyridine derivatives of thiacalix[4]arene can exist as positional isomers which differ by the positions of the nitrogen (N) atom on the pyridyl unit which can be *ortho*, *meta* and *para* to the phenolic oxygen attachment position. The N-hetero atoms can serve as additional coordination sites due to their electron lone pairs and can also undergo facile further modifcation. Given that the position of the nitrogen atoms of the pyridyl ring can differ in thiacalix[4]arene derivatives, it is interesting to assess what kind of ability these derivatives will provide to interact with metal cations (hard or soft).

Chromium (III) has been reported to be biologically essential to mammals as it maintains effective glucose, lipid, and protein metabolisms. However, chromium (VI) can be toxic, as it can diffuse as $Cr_2O_7^{2-}$ or $HCr_2O_7^-$ through cell membranes and oxidize biological molecules.[7] Therefore, selective treatment of waste water containing Cr (VI) and Cr (III) prior to discharge is essential. Solvent extraction is one of the most commonly used treatment methods and employs a selective complexant especially for ions in aqueous solution. Thus, the development of efficient extractants for anions has received considerable attention in recent years.[8] The dichromate ($Cr_2O_4^{2-}$ 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). Thiacalix[4]arene derivatives with nitrogen functionalities such as pyridine, amino, or imino groups on their lower rim have been shown to be capable of interacting with anions by hydrogen bonds as efficient extractants for oxoanions.[9] Thus, the introduction of a pyridyl moiety to thiacalix[4]arene would potentially lead to an effective extractant for dichromate anions.

In this study, a series of 1,3-*alternate* thiacalix[4]arenes bearing pyridyl moieties (*ortho*, *meta* and *para*) at the lower rim which should have the appropriate encapsulating ionophilic cavity were

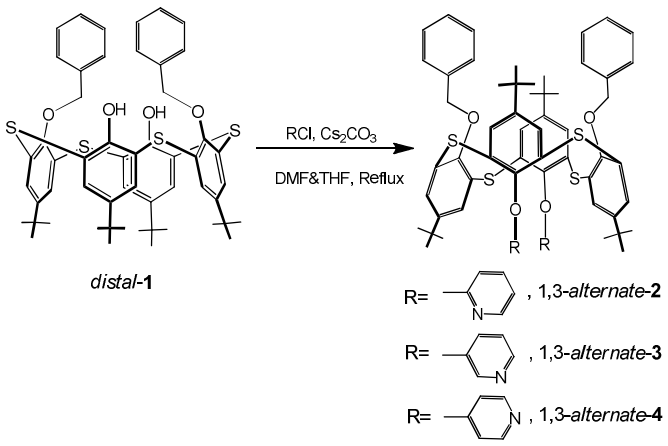
targeted for synthesis. The relationship between the position of the nitrogen atoms of the pyridyl ring and the ability of these derivatives to interact with various ionic species were evaluated.

Results and discussions

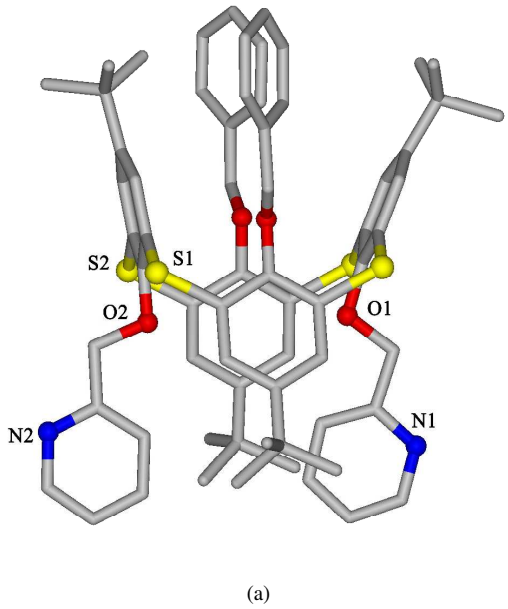
The synthesis of the new thiacalix[4]arene derivatives is given in Scheme 1. For the synthesis of thiacalix[4]arene derivatives based on different functional units (1,3-*alternate*-**2**, 1,3-*alternate*-**3** and 1,3-*alternate*-**4**), the parent compound (*distal*-**1**) was prepared according to published literature procedures.[6] The reaction of bisbenzylated compound *distal*-**1** with 3-(chloromethyl)pyridine in THF-DMF in the presence of Cs_2CO_3 as base yielded 1,3-*alternate*-**3** in 59% yield. 1,3-*alternate*-**2** and 1,3-*alternate*-**4** were prepared as following a published procedure.[6,10] All of the structures were confirmed by their ^{1}H- and ^{13}C-NMR and IR spectra, MS, elemental analyses and by X-ray crystallography.

The ^{1}H NMR spectrum of 1,3-*alternate*-**3** shows two singlets for *tert*-butyl protons, in which both *tert*-butyl protons were observed at higher field, at δ 0.85 and 0.86 ppm due to the ring current effect arising from the two benzyl benzene rings and the two pyridine rings introduced; two singlets for the methylene protons at δ 5.06 ppm (O*CH*$_2$Benzyl) and 5.19 ppm (O*CH*$_2$Pyridyl), respectively, indicating a C_2-symmmetric structure for the 1,3-*alternate*-**3** (Figure S1).

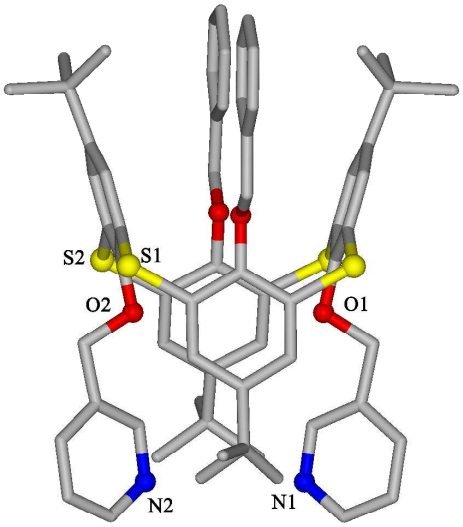
X-ray quality colourless crystals of 1,3-*alternate*-**2**, and 1,3-*alternate*-**3** were obtained by recrystallizations from mixed MeOH and $CHCl_3$ solutions. The single crystal X-ray diffraction Ortep (Pluto) representations of **2** and **3** are shown in Figure 1. It is clear that these compounds adopt 1,3-*alternate* conformations. Interestingly, both of the pyridine nitrogen atoms in **2** are orientated outwards, the distance between them being 9.079 Å. However, the pyridine nitrogen atoms in **3** are orientated inwards, the distance between them being only 3.883 Å. This may be attributed to the distances between the pyridine nitrogen atoms and the oxygen atoms (N1···O1 and N2···O2). In the case of compound **2**, the distances between N1···O1 and N2···O2 are shorter; but for **3** the corresponding N1···O1 and N2···O2 distances are longer enough.



Scheme 1 *O*-Alkylation of *distal*-**1** with (chloromethyl)pyridine in the presence of Cs_2CO_3.



(a)



(b)

Fig. 1 X-ray structures of (*a*) **2**[6] and (*b*) **3**. Hydrogen atoms have been omitted for clarity.

The shorter distances and hence, the stronger electron repulsion could therefore be the factors which control the different orientations of the nitrogen atoms toward each other.

Recently, the synthesis of calix[4]arenes bearing pendant pyridine groups at the lower rim as potential ligands for transition metal cations have been reported.[11] A similar investigation has also been conducted using hexahomotrioxacalix[3]arene and homocalix-[3]arene-based derivatives.[12] It is well-known that the metal selectivity and extractability of these types of receptors are dependent on the ring size and the nature of the *O*-alkyl substituents. However, it is still unknown whether the metal extractability can be affected by the position of the coordination binding sites of the substituents themselves. Therefore, it is of importance to assess the

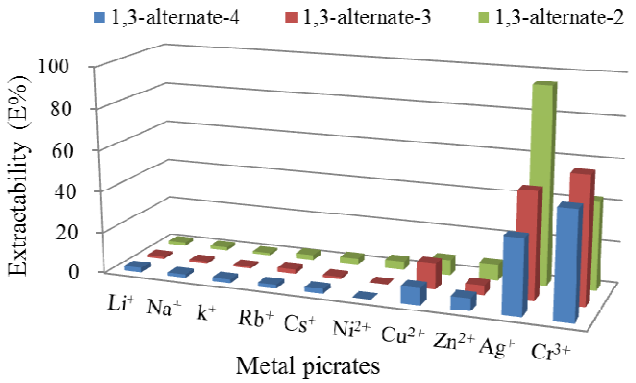


Fig. 2 Extraction percentages of metal picrates with ionophores **2** – **4** ([Host] = 4.0×10^{-5} M in CH_2Cl_2, [Guest] = 4.0×10^{-5} M in water at 25 °C).

relationship between the position of the nitrogen atoms of the pyridyl ring and the ability of these derivatives (**2 – 4**) to interact with ions. Experiments for solvent extraction of aqueous phase metal ions to the organic phase were therefore undertaken with **2 – 4**. The results showed that the extraction of transition metals by all three receptors **2 – 4** was higher than for the extraction of alkali metals, especially for Cr^{3+} and Ag^+ (Fig. 2). The E% values of Cr^{3+} *i.e.* 43%, 61% and 52% for **2 – 4**, respectively, showed that a higher Cr^{3+} affinity exists for these molecules. However, what is surprising is that the extractability for Ag^+, the E% values of 95%, 52% and 36% for **2 – 4**, respectively, showed that the extractability of Ag^+ by **2** to **4**, decreased gradually. These compounds are positional isomers differing only by the position of the nitrogen atom on the pyridyl ring. The position of the N atoms on the pyridyl rings (*ortho* for **2**, *meta* for **3** and *para* for **4**), which determines the distances between the nitrogen and the diaryl thiaether linkages were also reduced gradually. Recently, Ferlay has reported a 1,3-*alternate* conformation thiacalix[4]arene armed with four pyridyl (*ortho*), complexed with Ag+ cation through N···Ag^+···S interactions.[13] Thus, the extractability (E%) of **2 – 4** which followed the order of **2 > 3 >4**, may be attributed to the shorter distance, the stronger N···Ag^+···S interactions, the higher extractability (E%). This hypothesis is supported by the stability constants, which follow the same order of **2 > 3 >4**. The binding constants (K_a) value for the complexation with Ag^+ ion was determined to be $2.05 \times 10^4 \pm 875$ M^{-1} (**2**) , $3.86 \times 10^3 \pm 572$ M^{-1} (**3**), $2.25 \times 10^3 \pm 365$ M^{-1} (**4**) based on the Benesi–Hildebrand equation[23], respectively (Figure S13–18).

Due to the existence of the two potential metal-binding sites, namely, the pyridine moieties and two benzyl moieties, there are several possibilities for the metal complexation for compounds **2 – 4**. Both 1:1 and 1:2 metal complexation might be possible, attributable to electrostatic interactions as well as cation-π interactions. Job plots of **3** and **4** were carried out in the H_2O/CH_2Cl_2 phases. The E% values reach maxima at 0.5 mole fraction when **3** or **4** with Ag^+ are changed systematically. (Figure S12) Similar 1:1 coordination of **2** with Ag^+ was shown by Job plots in our previous study. (Figure S12) [6] Thus, it can be concluded that Ag^+ forms 1:1 complexes with **2 – 4**. These results suggest the major contribution of receptors **2 – 4** to Ag^+ binding are from the nitrogens of the pyridine rings, and not from the alternative cation-π-interactions.

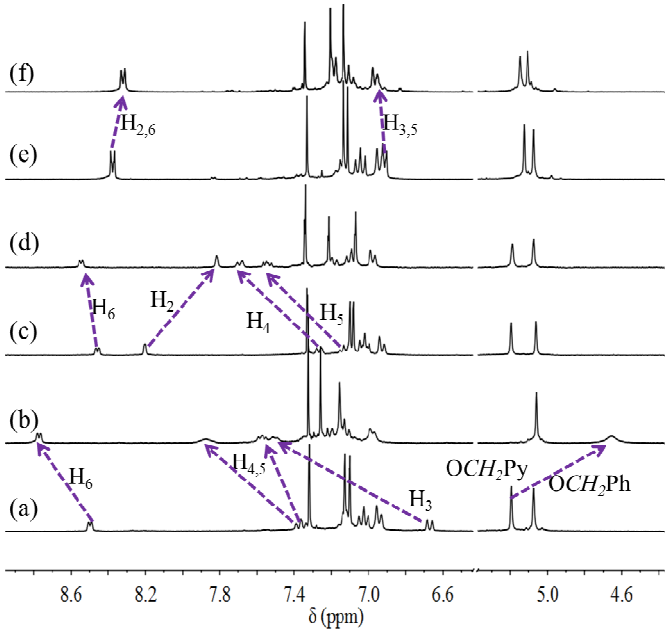


Fig. 3 ^{1}H NMR spectral changes of ionophores **2 – 4** (5×10^{-3} M) on addition of $AgClO_4$ (300 MHz, $CDCl_3$:CD_3CN = 10 : 1, [ionophores **2 – 4**] = 5×10^{-3} M). (a) Free **2**; (b) **2** in the presence of 1.0 equiv. of $AgClO_4$; (c) Free **3**; (d) **3** in the presence of 1.0 equiv. of $AgClO_4$; (e) Free **4**; (f) **4** in the presence of 1.0 equiv. of $AgClO_4$.

Furthermore, in order to look further into the binding properties of receptors **2 – 4** with Ag^+, ^{1}H NMR titration experiments were carried out in CD_3Cl : CD_3CN = 10 : 1 solution. The chemical shift changes for compound **2 – 4** on complexation with Ag^+ are illustrated in Figure 3 and are summarized in Figure 4.

Significant changes were observed for the pyridine ring protons after the complexation of each of **2 – 4** with 1.0 equiv. Ag^+. In the case of **2,** the protons in the pyridine rings were shifted to lower field with Δδ = +0.27, +0.21, +0.52 and +0.83 ppm for H_6, H_5, H_4, and H_3 protons, respectively. In contrast, the O*CH*$_2$Py methylene protons were shifted dramatically to-up field, with Δδ = -0.53. This may be due to both pyridine nitrogens of **2** close to the diaryl thiaether linkages (N2···S1= N2···S2 = 5.333 Å, Fig. 1a). Thus, when **2** complexes with Ag^+, the Ag^+ is easily captured through N···Ag^+···S interactions.[13] As a result, since the pyridine moieties orientated inwards, the ring current shielding effect[14] operating in the two thiacalixarene benzene rings is destroyed, forcing the steric conformation change. This affects the protons H_6, H_5, H_4 and H_3 of the pyridine rings which shift to lower field, due to the deshielding effect. Also, the O*CH*$_2$Py methylene protons become folded into the thiacalix[4]arene-cavity and are thus shifted strongly upfield (-0.53 ppm), due to the steric conformation changes.

However, a different phenomenon was observed in the complexation of **3** with Ag^+. From the X-ray results, both pyridine nitrogen atoms in **3** were orientated inwards and far from the diaryl thiaether linkages (N2···S1 = 6.360 Å and N2···S2 = 5.847 Å, Fig. 1b), which is exactly opposite to what is seen with **2**. The ^{1}H NMR spectrum of the Ag^+ of **3** reveals that the protons in the pyridine rings were shifted to lower field with Δδ = +0.09, +0.42 and +0.43 ppm for H_6, H_5 and H_4, protons, respectively. In contrast, a remarkable shielding effect experienced by proton H_2 (–0.38 ppm)

was observed. This maybe attribute that when **3** complexes with Ag^+, the Ag^+ is trapped in the cavity formed by the nitrogen atoms in pyridine, induce the proton H_2 become folded into the π-cavity formed by the two thiacalixarene benzene rings and are thus shifted strongly upfield (-0.38 ppm). Thus, **3** complexes Ag^+ through the metal-nitrogen interactions and thus, due to the interaction of the nirogens and the Ag^+, the H_6, H_5 and H_4 protons of the pyridine rings shift to lower fields.[15]

Similar phenomena were observed for the complexation of **4** with Ag^+; protons H_3 and H_5 in the pyridine rings of **4** shifted to lower field after complexation (+0.05 ppm), which are deshielded due to the N···Ag^+ interactions. Pyridine ring protons H_2 and H_6 in **4** shifted upfield after complexation (-0.06 ppm), which may be attributed to the weaker repulsion between the nitrogen atoms in the pyridine rings.[15]

The chemical shift changes of the thiacalixarene benzene protons and benzyl protons may also be attributed to the conformational changes of **2 – 4** upon complexation. The chemical shift changes (Δδ) of **2 – 4** upon complexation are in the order **2 > 3 > 4**, which corresponds with the extractability of Ag^+ which found to be in the same order.

To better understand the binding properties of receptors **2 – 4** with Ag^+, a computation study were carried out. The molecular geometry of the individual structures in the gas-phase were fully optimized using Gaussian09,[22] with the B3LYP level of DFT and the lanl2dz basis set. Significant conformational changes were observed for the pyridine ring protons of **2 – 4** after the complexation with Ag^+. The conformation changes for **2** on complexation with Ag^+ ion can be seen in Fig. 5 (See the Supporting Information for details of the computational study, Figure S19–24). Fig. 5 shows the structure (*right*) of the **2**⊃Ag^+ complex. The optimized molecular geometry suggests that the Ag^+ binds, in accord with the ^{1}H NMR complex study, via a N···Ag^+···S short contact distance bond, which results in the conformation change. The N···N distance between the pyridine ring nitrogens decreases from 8.001 to 3.761 (Å) since the nitrogen atoms move inwards after complexing with the Ag^+. All four bridge sulphur atoms are roughly the same distance from the Ag^+ and presumably take an equal part in the coordination bonding.

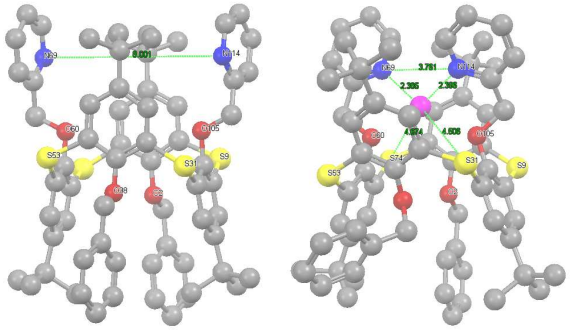


Fig. 5. Geometry-optimized (ball and stick) structures of: *Left*: **2** and *Right*: **2**⊃Ag^+complex. Color code for Ag^+ = magenta, pyridine nitrogen = blue, sulphur = yellow and oxygen atom = red. Hydrogen atoms have been omitted for clarity.

However, a different phenomenon was observed in the complexation of **3** – **4** with Ag^+. The N···N distance between the pyridine ring nitrogens decreases from 9.305 to 4.234 (Å) for **3** and 10.138 to 3.798 (Å) for **4** after complexing with the Ag^+. (Figure S19 – S24, Table S1) The optimized molecular geometry suggests that complexation of **3 – 4** with Ag^+ occurs via a N···Ag^+ interactions. The calculated complexation energies (ΔE kJ/mole) of the Ag^+ complexes of **2 – 4** are -488.096, -464.022 and -372.966 kJ/mole respectively (Table S2), which is in agreement with the trend observed for the experimentally observed complexation data.

A preliminary evaluation of the anion binding efficiencies of **2 – 4** as potential extractants for the dichromate anion has been carried out by solvent extraction of aqueous solution of $K_2Cr_2O_7$ into dichloromethane at different pH values according to reported procedure.[15,16] The extraction results summarized in Fig. 6, indicate that **3** showed a higher effective for the extraction of dichromate anions at low pH (pH 1.5) than either **2** and **4**. This is also consistent with the solvent extraction results seen with Cr^{3+} (Fig. 2). This could be attributed to the closer (3.883 Å) distance (Fig. 1) between the pyridine nitrogen atoms in **3**, which was easily formed an efficient ion-pair (hydrogen bonded) complex in the two-phase extraction

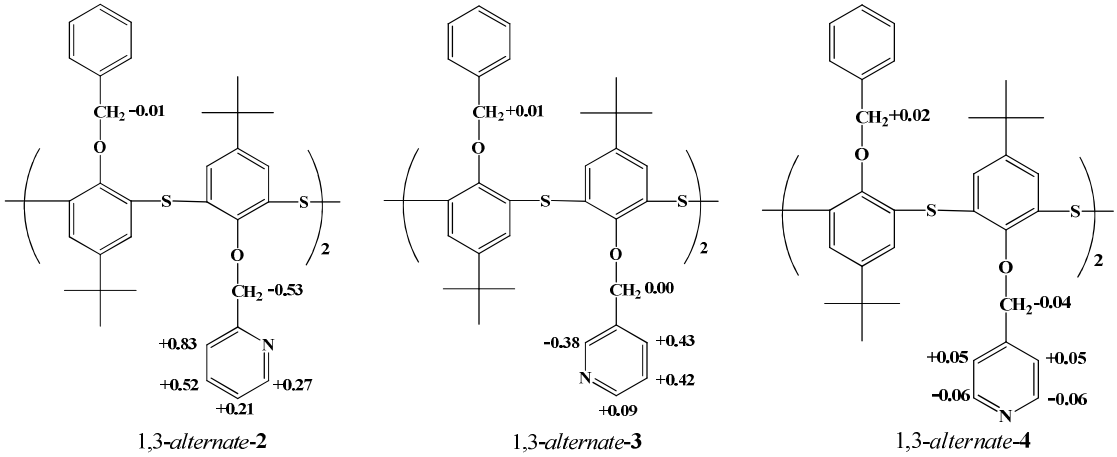


Fig. 4. Chemical shift changes of **2**, **3** and **4** induced in the presence of $AgClO_4$; + denotes the downfield and – denotes the upfield shift.

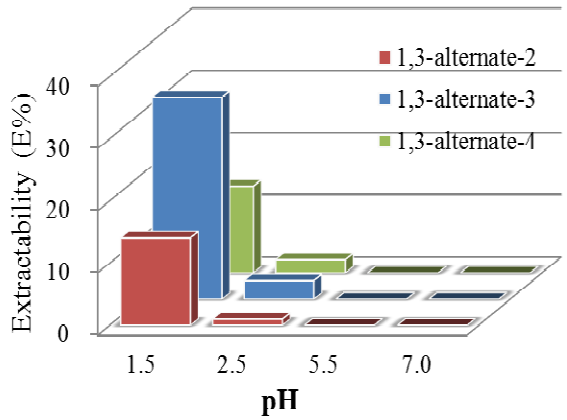


Fig. 6. E% values of dichromate anion with ionophores **2 – 4** (2.0×10^{-4} M, 2 h at 25 °C) at pH 1.5–7.0 (H_2O/CH_2Cl_2:10/10 (v/v); $K_2Cr_2O_7 = 1 \times 10^{-4}$ M).

system following proton transfer to the nitrogen atoms. As the pH of the solution increased from 1.5 to 2.5 to 5.5 to 7.0, the E% for all three receptor ionophores decreased. This may directly be attributed to decreased proton concentrations in the solution.[17] In other words, **3** showed a high extractability with dichromate anions only at lower pH, but another high extractability of Cr^{3+} at higher pH. Since, Cr(VI) is highly toxic, carcinogenic and harmful to human beings because it can diffuse as $Cr_2O_7^{2-}$ or $HCr_2O_7^-$ through cell membranes and oxidize biological molecules,[7] whereas Cr(III) is an essential ion for mammals as it maintains effective glucose, lipid, and protein metabolisms[18] Thus, **3** could be a meaningful extractant when applying a solvent extraction method for the selective treatment of waste water containing Cr (VI) and Cr (III) prior to discharge.

Conclusion

Three 1,3-*alternate* thiacalix[4]arenes bearing pyridyl moieties (*ortho* for **2**, *meta* for **3** and para **4**) at the lower rim were regioselectively synthesized. The solvent extraction experiments of the metal ions showed that the ability of these derivatives to complex with Ag^+ (95%, 52% and 36% for **2, 3** and **4**, respectively) appeared to be largely dependent on the position of the pyridine nitrogen atoms. The mode of binding of the C_{2V}-symmetrical dipyridyl-substituted thiacalix[4]arenes, **2 – 4** with Ag^+ was elucidated clearly using a ^{1}H NMR titration method. Two different complexation modes were observed: **2** armed with two *ortho* pyridyl groups, complexed with Ag^+ via N···Ag^+···S interactions whereas **3** and **4**, complexed with Ag^+ through N···Ag^+ interactions. The DFT computational studies were consistent with the experimental findings. These findings will provide us an important rule to design a appropriate thiacaixarene ionophore in the future.

Another studies aimed at the potential for application of these extractants to the treatment of waste water containing Cr (VI) and Cr (III) were initiated. The combination of the two-phase solvent extraction data of Cr^{3+} and the results of the dichromate anion extraction by **3**, suggest that **3** could be meaningful for applying a solvent extraction method for the selective treatment of waste water containing Cr (VI) and Cr (III) ions prior to discharge.

Experimental Section

General

All melting points were determined using a Yanagimoto MP-S1. ^{1}H-NMR spectra were determined at 300 MHz with a Nippon Denshi JEOL FT-300 NMR spectrometer with $SiMe_4$ as an internal reference; *J*-values are given in Hz. IR spectra were measured as KBr pellets or as liquid films on NaCl plates in a Nippon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by a Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 mass spectrometer at an ionization energy of 70 eV using a direct inlet system through GLC. Elemental analyses were performed by a Yanaco MT-5.

Materials

25,27-Dibenzyloxy-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetra thiacalix[4]arene-26,28-diol (*distal*-1) was prepared from 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25, 26,27,28-tetraol in one step according to a reported procedure.[6]

O-Alkylation of 1 *distal*-1 with 3-(chloromethyl)pyridine in the presence of Cs_2CO_3.

A mixture of *distal*-**1** (400 mg, 0.44 mmol) and Cs_2CO_3 (1.60 g, 4.92 mmol) in dry tetrahydrofuran (THF) (8 mL) was heated at reflux for 1 h under N_2. A solution of 3-(chloromethyl)pyridine (4.92 mmol) [prepared by neutralization of 3-(chloromethyl)pyridine hydrochloride (807 mg, 4.92 mmol) in DMF (8 mL) with a solution of triethylamine (0.68 mL, 4.92 mmol) in THF (8 mL) at room temperature.] was then added and the mixture heated at reflux for an additional 24 h. After cooling the reaction mixture to room temperature, it was acidified with 1 M HCl (10 mL) and extracted with CH_2Cl_2 (100 mL × 2). The combined extracts were washed with water (50 mL × 2), and dried ($MgSO_4$) and condensed under reduced pressure to give a yellow oil. The residue was washed with methanol to give a mixture of tetra-*O*-alkylated products as a colorless precipitate. The precipitate was washed with ether (5 mL) to give a colourless solid. Recrystallization from MeOH:$CHCl_3$ (1:3) gave **3** as a colorless prisms (280 mg, 59%).

25,27-Dibenzyloxy-26,28-bis[(3-pyridylmethyl)oxy]-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene (3): Colourless prisms [MeOH:$CHCl_3$ (1:3)], m.p. 285.4–286.6 °C. IR ν_{max} (KBr)/cm^{-1}: 3058, 3030, 2958, 2902, 2868, 1575, 1546 and 1496. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.85 (s, 18H, tBu), 0.86 (s, 18H, tBu), 5.06 (s, 4H, Ar–O*CH*$_2$Ph), 5.19 (s, 4H, Ar–O*CH*$_2$Py), 6.92 (d, *J* = 7.2 Hz, 4H, Ph–*H*), 7.02 (t, *J* = 7.6 Hz, 6H, Ph–*H*), 7.07 (s, 4H, Ar–*H*), 7.10 (s, 4H, Ar–*H*), 7.12 (t, *J* = 7.6 Hz, 2H, Py–*H*$_5$), 7.24 (d, *J* = 8.0 Hz, 2H, Py–*H*$_4$), 8.22 (s, 2H, Py–*H*$_2$) and 8.46 (d, *J* = 4.8 Hz, 2H, Py–*H*$_6$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.77, 30.78, 33.89, 33.90, 67.74, 70.64, 122.99, 126.83, 127.18, 127.98, 128.38, 128.42, 128.48, 128.60, 133.20, 134.81, 137.47, 146.31, 146.58, 148.33, 148.92, 155.59 and 156.61 ppm. FABMS: *m/z*: 1083.30 (M^+). Anal. calcd. for $C_{66}H_{70}N_2O_4S_4$ (1083.53): C 73.16, H 6.51, N 2.59%. Found: C 71.85, H 6.56, N 2.38%.

Preparation of 25,27-Dibenzyloxy-26,28-bis[(2-pyridylmethyl)oxy]-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (**2**) was carried out as following our previous report.[6]

25,27-Dibenzyloxy-26,28-bis[(2-pyridylmethyl)oxy]-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (2): Colourless prisms [MeOH:$CHCl_3$ (1:3)], m.p. 274.8–275.5 °C. IR ν_{max} (KBr)/cm^{-1}: 3058, 3029,3008, 2955, 2901, 2866, 1571,1588, 1546, 1496. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.83 (s, 18 H, tBu), 0.85 (s, 18 H, tBu), 5.07 (s, 4 H, Ar–OCH_2Ph), 5.20 (s, 4 H, Ar–OCH_2Py), 6.66 (d, *J* = 7.2 Hz, 2 H, Py–H_3), 6.94 (d, *J* = 7.0Hz, 4 H, Ph–*H*), 7.02 (t, *J* = 7.5 Hz, 6 H, Ph–*H*), 7.09 (4 H, s, Ar–*H*), 7.12 (4 H, s, Ar–*H*), 7.35(t, *J* = 6.9 Hz, 4 H, Py–$H_{4,5}$) and 8.49 (d, *J* = 4.8 Hz, 2 H, Py–H_6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.73, 30.82, 30.88, 33.88, 70.65, 71.46, 121.99, 126.80, 127.19, 127.99, 128.23, 128.60, 128.71, 137.52, 146.15, 146.35, 148.33, 156.01, 156.67 and 157.70 ppm.

Preparation of 25, 27-Dibenzyloxy-26,28-bis[(4-pyridylmethyl)oxy]-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (**4**) was carried out as following our previous report.[10]

25,27-Dibenzyloxy-26,28-bis[(4-pyridylmethyl)oxy]-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (4): Colourless prisms [MeOH:$CHCl_3$ (1:3)], m.p. 283–285 °C. IR ν_{max} (KBr)/cm^{-1}: 3055, 3029, 2952, 2921, 2853, 1604, 1572, 1562. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.84 (s, 18 H, tBu), 0.86 (s, 18 H, tBu), 5.07 (s, 4 H, Ar–OCH_2Ph), 5.12 (s, 4 H, Ar–OCH_2Py), 6.90 (d, *J* = 5.5 Hz, 4 H, Py–$H_{3,5}$), 6.94 (d, *J* = 7.4 Hz, 4 H, Ph–*H*), 7.04 (t, *J* = 7.6 Hz, 4 H, Ph–*H*), 7.10 (s, 4 H, Ar–*H*), 7.12 (s, 4 H, Ar–*H*), 7.13 ~ 7.18(m, 2 H, Ph–*H*) and 8.40 (d, *J* = 5.8 Hz, 4 H, Py–$H_{2,6}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.70, 30.73, 33.86, 33.89, 69.10, 70.80, 121.80, 126.90, 127.14, 128.03, 128.26, 128.75, 129.11, 137.35, 146.39, 146.50, 146.71, 149.38, 155.97 and 156.72 ppm. FABMS: *m/z*: 1083.45 (M^+).

Extraction experiments and stoichiometry of metal complexation.

Metal picrates (4.0×10^{-5} M) were prepared *in situ* by dissolving the metal hydroxide (0.02 mol) in 4.0×10^{-5} M picric acid (1000 mL); triply distilled water was used for all aqueous solutions. Two-phase solvent extraction was carried out between aqueous picrates (10 mL, [metal picrate] = 4.0×10^{-5} M) and host (10 mL, [host] = 4×10^{-5} M in CH_2Cl_2). 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. This was repeated 3 times. The absorbance of each solution was determined by UV spectroscopy (λ = 356 nm). The method of continuous variation was employed to determine the stoichiometry in the complexes involving the host receptors **2**, **3** or **4**. The molar ratios of both the host and metal picrate were varied from 0 to 1, while the total concentration was kept at several constant levels. Job plots were generated by plotting the extracted [M^+] versus the mole fraction of metal. We confirmed that this period was sufficient to attain the distribution equilibrium. The extractability was determined spectrophotochemically from the decrease in the absorbance of the picrate ion in the aqueous phase, as described by Pedersen.[19]

^{1}H-NMR complexation experiments

To a $CDCl_3$–CH_3CN (10:1, v/v) solution (5×10^{-3} M) of **2, 3** or **4** in an NMR tube was added a CD_3CN solution (5×10^{-3} M) of $AgClO_4$. The spectra were recorded after the additions. The temperature of the NMR probe was kept constant at 27 °C. The ^{1}H NMR data of the most-representative complexes are given below:

2: ^{1}H NMR (300 MHz, $CHCl_3$–CH_3CN, 10:1, v/v): δ = 0.83 (s, 18H, tBu), 0.85 (s, 18H, tBu), 5.07 (s, 4 H, CH_2–Ph), 5.19 (s, 4H, CH_2–Py), 6.67 (d, *J* = 7.8 Hz, 2H, Py–H_3), 6.94 (d, *J* = 7.6 Hz, 4H, Ph–*H*), 7.03 (t, *J* = 6.6 Hz, 6H, Ph–*H*), 7.10 (s, 4H, Ar–*H*), 7.13 (s, 4H, Ar–*H*), 7.36 (t, *J* = 7.8 Hz, 4H, Py–$H_{4,5}$) and 8.49 (d, *J* = 4.7 Hz, 2H, Py–H_6) ppm.

2 ⊃Ag^+: ^{1}H NMR (300 MHz, $CHCl_3$–CH_3CN, 10:1, v/v): δ = 0.85 (s, 18H, tBu), 0.98 (s,18H, tBu), 4.65 (s, 4H, CH_2–Py), 5.06 (s, 4H, CH_2–Ph), 6.98 (d, *J* =7.5 Hz, 4H, Ph–*H*), 7.10–7.14 (m, 4H, Ph–*H*), 7.16 (s, 4H, Ar–*H*), 7.21 (t, *J* = 6.6 Hz, 2H, Ph–*H*), 7.26 (s, 4H, Ar–*H*), 7.50 (d, *J* = 7.8 Hz, 2H, Py–H_3), 7.57 (t, *J* = 5.7 Hz, 2H, Py–H_4), 7.82–7.92 (m, 2H, Py–H_5) and 8.77 (d, *J* = 4.9 Hz, 2H, Py–H_6) ppm.

3: ^{1}H NMR (300 MHz, $CHCl_3$–CH_3CN, 10:1, v/v): δ = 0.85 (s, 18H, tBu), 0.86 (s, 18H, tBu), 5.06 (s, 4H, CH_2–Ph), 5.19 (s, 4H, CH_2–Py), 6.93 (d, *J* = 7.2 Hz, 4H, Ph–*H*), 7.00–7.05 (m, 6H, Ph–*H*), 7.08 (s, 4H, Ar–*H*), 7.10 (s, 4H, Ar–*H*), 7.13 (m, 2H, Py–H_5), 7.27 (d, *J* = 7.8 Hz, 2H, Py–H_4), 8.20 (s, 2H, Py–H_2)*and* 8.46 (d, *J* = 3.9 Hz, 2H, Py–H_6) ppm.

3 ⊃Ag^+: ^{1}H NMR (300 MHz, $CHCl_3$–CH_3CN, 10:1, v/v): δ = 0.84 (s, 18H, tBu), 0.91 (s, 18H, tBu), 5.07 (s, 4H, CH_2–Ph), 5.19 (s, 4H, CH_2–Py), 6.98 (d, *J* = 7.5 Hz, 4H, Ph–*H*), 7.07 (s, 4H, Ar–*H*), 7.08–7.12 (m, 4H, Ph–*H*), 7.17–7.20 (m, 2H, Ph–*H*), 7.21 (s, 4H, Ar–*H*), 7.52–7.57 (m, 2H, Py–H_5), 7.69 (d, *J* = 7.9 Hz, 2H, Py–H_4), 7.82 (s, 2H, Py–H_2) and 8.55 (d, *J* = 5.1 Hz, 2H, Py–H_6) ppm.

4: ^{1}H NMR (300 MHz, $CHCl_3$–CH_3CN, 10:1, v/v): δ = 0.84 (s, 18H, tBu), 0.85 (s, 18H, tBu), 5.07 (s, 4H, CH_2–Ph), 5.13 (s, 4H, CH_2–Py), 6.91 (d, *J* = 5.5 Hz, 4H, Py–$H_{3,5}$), 6.94 (d, *J* = 7.4 Hz, 4H, Ph–*H*), 7.02–7.07 (m, 4H, Ph–*H*), 7.11 (s, 4H, Ar–*H*), 7.13 (s, 4H, Ar–*H*), 7.14–7.18 (m, 2H, Ph–*H*) and 8.38 (d, *J* = 5.9 Hz, 4H, Py–$H_{2,6}$) ppm.

4 ⊃Ag^+: ^{1}H NMR (300 MHz, $CHCl_3$–CH_3CN, 10:1, v/v): δ = 0.86 (s, 18H, tBu), 0.91 (s, 18H, tBu), 5.11 (s, 4H, CH_2–Ph), 5.15 (s, 4H, CH_2–Py), 6.94–6.99 (m, 4H, Py–$H_{3,5}$) 7.09 (d, *J* = 7.3 Hz, 2H, Ph–*H*), 7.13 (s, 4H, Ar–*H*), 7.16–7.21(m, 6H, Ph–*H*), 7.21 (s, 4H, Ar–*H*)and 8.32 (d, *J* = 6.0 Hz, 4H, Py–$H_{2,6}$) ppm.

Crystallographic analyses of 3

Diffraction data were collected on a Bruker APEX 2 CCD diffractometer equipped with graphite-monochromated Mo-Kα

radiation at 150(2)K.[20] Data were corrected for Lorentz and polarisation effects and for absorption.[20] The structures were solved by direct methods and refined by full-matrix least-squares methods, on F^2.[21] H atoms were refined using a riding model except for those on hetero atoms in **3** which were freely refined.

Crystal data for 3. $C_{66}H_{70}N_2O_4S_4$, M = 1083.48. Orthorhombic, space group $Pmn2_1$, a = 15.1668 (6), b = 14.7772 (7), c = 12.7612 (6) Å, V = 2860.1 (2) Å^3. Z = 2, Dc = 1.258 g.cm^{-3}, F(000) = 1152, T = 100 K, μ(Mo-Kα) = 0.17 mm^{-1}, λ(Mo-Kα) = 0.6525 Å, colourless crystal of size 0.20 × 0.20 × 0.06 mm^3. The total number of reflections measured, to θ_{max} = 30.3°, was 345676 of which 11331 were unique (R_{int} = 0.087); 10920 were 'observed' with $I > 2\sigma(I)$. For the 'observed' data only, R_1 = 0.037; wR_2 = 0.101 for all 11331 reflections and 400 parameters. Residual electron density within +/– 0.48 eÅ^{-3}.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 245644 for **2**[6] and 1021161 for **3**, respectively. 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].

Supporting information: ^{1}H, ^{13}C NMR, MS and IR spectra of **3,** computational study of **2** – **4** with Ag^+.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Details of single-crystal X-ray crystallographic data. For ESI and crystallographic data in CIF see DOI: 10.1039/b000000x/

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