Synthesis and Selective Extractant Properties of a Calixarene Thioether Derivative and its Oligomeric Analogue

Gülderen UYSAL AKKUŞ[1,*]**, Selma ASLAN**[1]**, F. Fulya TAKTAK**[1] **and**
Shahabuddin MEMON[2]

[1]*Afyon Kocatepe University, Department of Chemistry,*
Afyonkarahisar, 03200-TURKEY
e-mail: guakkus@yahoo.com
[2]*National Center of Excellence in Analytical Chemistry, University of Sindh,*
Jamshoro-76080 PAKISTAN

Herein we report the synthesis of a novel calix[4]arene thioether derivative (**4**) and its oligomeric analogue (**5**). The liquid-liquid extraction properties of these compounds towards the selected metal cations were evaluated, and it was concluded, based on our observations, that these compounds demonstrated remarkable affinity towards the selected metal cations. Nevertheless, **3** is a good extractant and very selective for Hg^{2+} ions, whereas, in the case of its oligomeric analogue **5**, the situation is quiet different. It was observed that **5** could not efficiently retain the parent selective behavior by extracting all of the selected metal ions from the aqueous to the organic phase.

Key Words: Calix, calixarene, oligomeric calixarene, liquid-liquid extraction, metal cation.

Introduction

Calixarenes are phenolic metacyclophanes with rigid cone-like structures, which posses an upper rim defined by the *para*-positions of the aromatic rings and a lower rim defined by oxygen atoms. This conformation of calixarenes allows the formation of complexes with cation, anion, and neutral molecules.[1−3] Modified calixarenes, having additional binding sites, both at the lower rim and upper rim, enhance the binding ability of the parent calixarene.[4] Various methods for functionalizing calixarenes have been developed and numerous calixarene derivatives have been synthesized during the past 2 decades.[5−15] The binding properties of these molecules appear to be highly dependent upon the nature and number of donor atoms of the calix[4]arene

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*Corresponding author

moiety.[16] For example, the presence of relatively soft base donor sites, sulfur atoms, and/or nitrile groups is indicative of selectivity for soft metal ions such as mercury.[17−21] Mercury is a toxic heavy metal, which is an environmental pollutant that poses a threat to human and animal health. In this respect it is especially important to remove this metal from the environment, including soil and underground water. For this reason in our previous research we reported a biscalix[4]arene derivative that contains nitrile groups at the lower rim and which shows selectivity towards mercury metal ions.[22,23]

Calixarene-based polymers are only now beginning to receive attention and appear in the literature. Shinkai and co-workersprepared a calix[6]arene fixed to polystyrene.[24] Harris and co-workersreported on the polymerization and Na$^+$ complexation of calix[4]arene methacrylate.[25] Gravet and Gulliet synthesized a water-soluble calixarene-containing polymer and demonstrated its photophysical properties.[26] Zhong and co-workers reported on the synthesis and properties of calixcrown telomers.[27] Ohto and co-workers presented a calix[4]arene carboxylate resin immobilized with polyallylamine.[28] Blanda and Adou prepared 3 vinyl copolymers that contain pendant calix[4]arene and reported that the copolymers were designed to take advantage of the well-established binding interactions of calixarenes with neutral molecules and ions.[29] Recently, Yilmaz and co-workers reported several polymeric calix[4]arene derivatives and investigated their extraction properties towards metal cations and anions.[30−37]

Herein we aimed to synthesize a calix[4]arene derivative with sulfur-binding sites and its oligomeric analogue, and to evaluate their extraction properties towards heavy metals.

Experimental

Apparatus

Melting points were determined with a Barnstead/Electrothermal apparatus in a sealed capillary and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DPX 400 MHz spectrometer in CDCl$_3$ with TMS as the internal standard. IR spectra were recorded on a Perkin-Elmer 1605 FTIR BX spectrometer as KBr pellets. UV-VIS spectra were obtained with a Shimadzu UV-1700 Pharma UV-Visible recording spectrophotometer. Elemental analyses were performed on an Elementar CHNS analyzer. Molecular weights were determined by gel-permeation chromatography (GPC) in THF at 30 °C using an Agilent (HP) GPC and a refractive index detector, with a solvent flow rate of 0.6 mL/min and a sample concentration of 2.0 mg/mL. Micro columns were calibrated using a set of narrow polydispersity polystyrene standards.

Materials

Analytical TLC was performed on precoated silica gel plates (SiO$_2$, Merck PF$_{254}$). Generally, solvents were dried by storing them over molecular sieves (Aldrich 4 Å, 8-12 mesh). Dichloromethane was distilled from CaCl$_2$, and MeOH was distilled over Mg and stored over molecular sieves. All materials and reagents were standard analytical grade, purchased from Fluka or Merck, and used without further purification. All aqueous solutions were prepared with deionized water that had been passed through a Millipore Milli-Q Plus water purification system.

Synthesis

The *p-tert*-butylcalix[4]arene (**1**) and *p-tert*-butyl-25,27-bis-(4-nitro-benzyloxy)-26,28-dihydroxycalix[4]arene (**2**) were synthesized according to the literature.[38,39] The other compounds, **3-5** (Figure 1), were synthesized as described below.
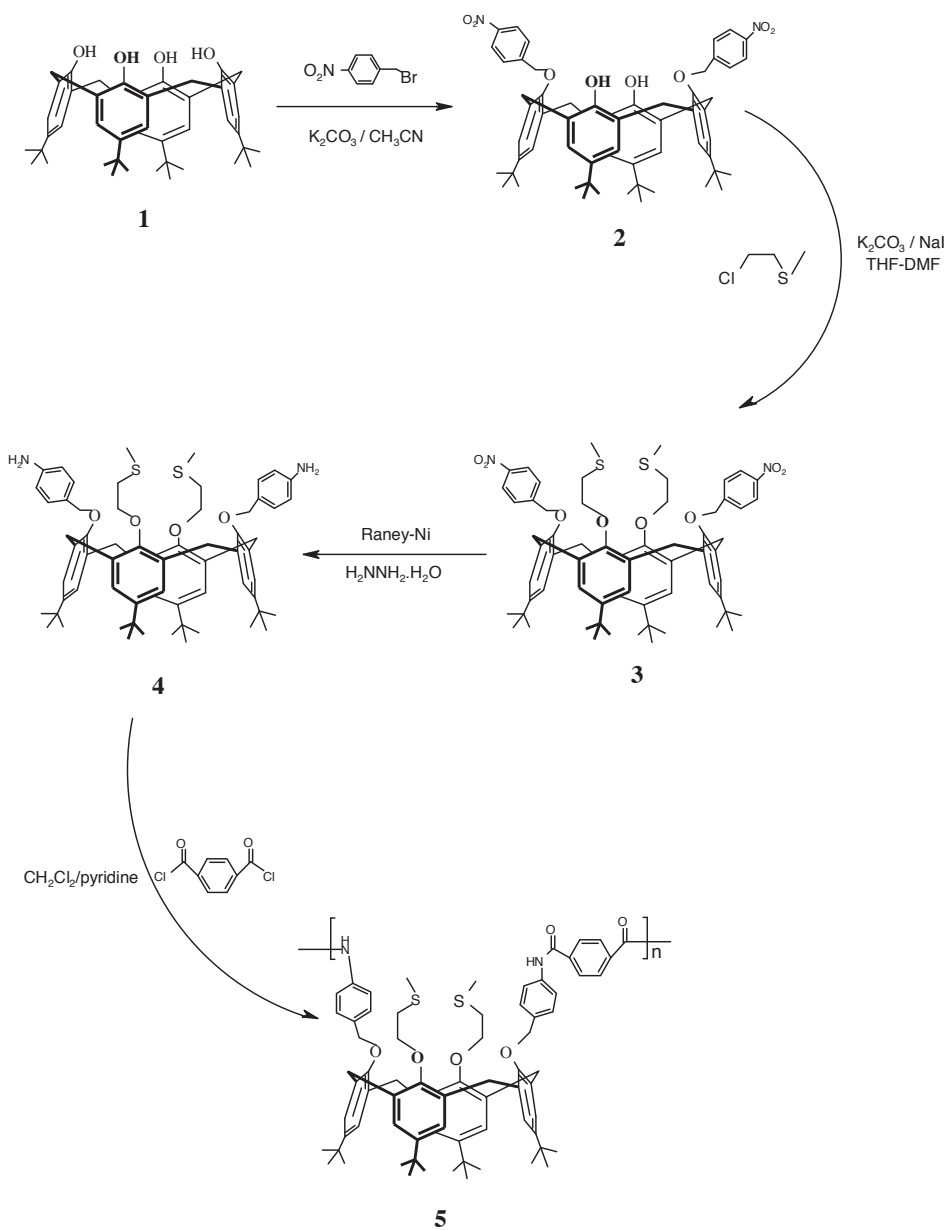

Figure 1. A schematic representation of the synthesis of *p-tert*-butylcalix[4]arene-thioether and its oligomeric derivative.

Treatment of (2) with 2-chloroethyl methyl sulfide (3)

A mixture of **2** (4.62 g, 5.10 mmol), and K_2CO_3 (2.80 g, 20.30 mmol), 2-chloroethyl methyl sulfide (2.25 g, 20.40 mmol), and NaI (3.00 g, 20.00 mmol) in dry THF-DMF (200 mL) was heated under reflux for 24 h

with continuous stirring. The cooled reaction mixture was filtered through a bed of celite and concentrated to dryness. Recrystallization of the residue from acetone furnished the bis-(2-methylthioethoxy) derivative **3**. Yield: 44%. mp: 249 °C. IR (KBr): 1522 cm^{-1} (NO$_2$). ^{1}H NMR (CDCl$_3$): 1.19 (s, 36H, Bu^t), 2.27 (s, 6H, S-CH$_3$), 3.24 (t, 4H, J= 7.1 Hz, CH$_2$S), 3.44 (d, 4H, J= 13.0 Hz, ArCH$_2$Ar), 4.25-4.30 (m, 12 H, OCH$_2$Ar, CH$_2$O, 4-nitrophenyl-H$_{3.5}$), 4.39 (d, 4H, J= 13.0 Hz, ArCH$_2$Ar), 6.98-7.09 (m, 8H, ArH), and 7.28 (s, 4H, ArH, 4-nitrophenyl-H$_{2.6}$). Calculated for C$_{64}$H$_{78}$O$_8$N$_2$S$_2$: C, 76.02; H, 7.44; N, 2.46; S, 5.64. Found: C, 75.82; H, 7.12; N, 2.03; S, 5.31%.

Reduction of compound 3 (4)

A 1.0 g sample of Raney-Ni was added to a solution of **3** (3.63 mmol, 3.84 g) in ethyl acetate (100 ml) and MeOH (75 ml) was added. To this mixture was added 10 ml of N$_2$H$_4$·H$_2$O in portions at room temperature with occasional stirring. The reaction mixture was refluxed for 5 h. Another 10 ml of N$_2$H$_4$·H$_2$O was then added and the mixture was refluxed for an additional 6 h. The mixture was allowed to cool, then it was filtered and the residue was washed with CH$_2$Cl$_2$ and acetone. The combined filtrate was concentrated under reduced pressure and poured dropwise over ice cold water with stirring to give a white precipitate (turned to light brown on exposure to air), which was removed by filtration, dried and triturated with MeOH to give **4**. Yield. 68%. mp: 235 °C. IR (KBr): 3392 cm^{-1} (N-H). ^{1}H NMR (CDCl$_3$): 1.11-1.16 (brs, 36H, Bu^t), 2.21 (s, 6H, S-CH$_3$), 3.17 (t, 4H, J= 7.2 Hz, CH$_2$S), 3.36 (d, 4H, J= 13.4 Hz, ArCH$_2$Ar), 4.18-4.23 (m, 12 H, OCH$_2$Ar, CH$_2$O, NH), 4.32 (d, 4H, J= 13.1 Hz, ArCH$_2$Ar), 6.80 (m, 8H, ArH), and 7.05 (m, 8H, ArH). Calculated for C$_{64}$H$_{82}$O$_4$N$_2$S$_2$: C, 76.30; H, 8.20; N, 2.78; S, 6.37. Found: C, 76.12; H, 8.28; N, 2.73; S, 6.14%.

Treatment of Compound 4 with Terephthaloyl Dichloride (5)

A stirred solution of compound **4** (1.50 g, 1.41 mmol) in 50 ml of CH$_2$Cl$_2$ was treated with 0.25 ml of pyridine, followed by terephthaloyl dichloride (0.32 g, 1.61 mmol). The reaction mixture was then stirred at room temperature for 6 h and the solvent was removed under reduced pressure to give a semi-solid that was stirred with ice cold water to furnish a precipitate. This precipitate was stirred with n-hexane, followed by MeOH, then it was filtrated and dried under vacuum for 12 h. Yield 72%. mp: 242 °C. IR (KBr) 3394 cm^{-1} (N–H), 1730 cm^{-1} (C=O of COOH), 1667 cm^{-1} (HNC=O).;H NMR (CDCl$_3$): 0.92-1.19 (brs, 36H, Bu^t), 2.35-2.86 (brm, 10 H, S-CH$_3$, CH$_2$S), 3.22-3.30 (d, 4H, J= 13.0 Hz, ArCH$_2$Ar), 4.13-4.28 (brm, 8H, OCH$_2$Ar, CH$_2$CH$_2$O), 4.34-4.36 (d, 4H, J= 13.2 Hz, ArCH$_2$Ar), 6.87-7.19 (brm, 18H, NH and ArH), and 7.65-8.10 (brm, 4H, ArH). Calculated for C$_{72}$H$_{84}$N$_2$O$_6$S$_2$: C, 76.02; H, 7.44; N, 2.46; S, 5.64. Found: C, 7.65; H, 7.21; N, 2.32; S, 5.23%.

Analytical procedure

Metal picrates were prepared as previously described.[40] Picrate extraction experiments were performed following Pedersen's procedure.[41] Aqueous picrate, 10 mL of 2.0 × 10^{-5}M, and 10 mL of 1 × 10^{-3}M solution of calixarene **2-4** or a 1 × 10^{-3} M solution of calix[4]arene unit/g of resin for oligomer **5** in CH$_2$Cl$_2$ were vigorously agitated in a stoppered glass tube by a mechanical shaker for 2 min, then magnetically stirred in a thermostated water bath at 25 °C for 1 h, and finally left standing for an additional 30 min. The concentration of picrate ion remaining in the aqueous phase was then determined spectrophotometrically.

Blank experiments showed that no picrate extraction occurred in the absence of calixarene. The percent extraction (E%) was calculated as:

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

where C_0 and C are the initial and final concentrations of the metal picrate before and after extraction, respectively.

Log-Log Plot Analysis

To characterize the extraction ability of compound **3**, the distribution coefficient D was calculated. If it is assumed that the general extraction equilibrium is given by equation 1,

$$M^{n+}_{(aq)} + nPic^-_{(aq)} + x[L]_{(org)} \rightleftharpoons [M(Pic)_n(L)_x]_{(org)} \tag{1}$$
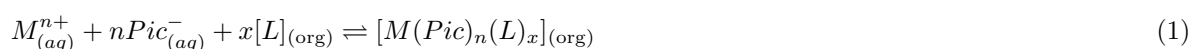
the overall extraction equilibrium constant is expressed as equation 2,

$$K_{ex} = \frac{[M(Pic)_n(L)_x]}{[M^{n+}][Pic^-]^n[L]^x} \tag{2}$$

and the distribution ratio D would be defined by equation 3,

$$D = \frac{[M(Pic^-)_n(L)_x]}{[(M^{n+})]} \tag{3}$$

equation 4 is obtained by introducing it in equation 2 and taking the log of both sides:

$$\log D = \log(K_{ex}[Pic^-]^n) + x\log[L] \tag{4}$$

With these assumptions, a plot of log D versus log[L] should be linear and its slope should be equal to the number of ligand molecules per cation in the extraction species.

Results and Discussion

Compounds **3-5** were synthesized as shown in Figure 1. The preparations of precursors **1** and **2** were based on reported procedures.[38,39] Refluxing a mixture of **2** with 2-chloroethyl methyl sulfide in THF-DMF in the presence of K_2CO_3 along with NaI afforded **3** as the cone conformer in 44% yield. The ^{1}H NMR spectrum of **3** showed an AB pattern for the methylene bridge protons at 3.44 and 4.39 ppm ($J = 13.0$ Hz) in the $ArCH_2Ar$ groups. Subsequent reduction of the nitro groups of **3** by Raney-Ni/ $H_2NNH_2 \cdot H_2O$ gave the amino-derivative **4** in 68% yield. Completion of the reaction was followed by IR spectroscopy, which showed the disappearance of the band due to the nitro groups at 1522 cm^{-1} and the appearance of a new band at 3392 cm^{-1} for the amino groups. The oligomerization reaction of **4** was performed sequentially with terephthaloyl dichloride in a minimum amount of CH_2Cl_2 in the presence of pyridine to give oligomer **5** in 75% yield after purification by reprecipitation from the n-hexane/methanol system.

The molecular weight of oligomer **5** was determined by GPC in THF against a polystyrene standard. The average molecular weight (Mn) of **5** was 5780 g/mol. This value indicates an average of 5 calix[4]arene units in the oligomeric skeleton. Oligomer **5** was characterized by a combination of FTIR, ^{1}H-NMR, and

elemental analysis. The IR spectrum of **5** showed an amide band at 1667 cm^{-1} and a band at 1730 cm^{-1} for the carbonyl group (C=O) of a carboxylic acid, showing that the oligomer has –COOH as end groups. Although the ^{1}H NMR spectrum of **5** showed rather broad signals for all protons, it is said that conformation of oligomer **5** is cone, because of the observation of a pair of doublets at 3.22-3.30 and 4.34-4.36 ppm.

Extraction Studies

We focused on synthesizing an oligomeric-type of *p-tert*-butylcalix[4]arene bearing sulfur binding sites at the lower rim, and investigated its extraction behavior for some selected transition and post-transition metal cations (Cu, Cd, Co, Ni, Hg, and Pb); therefore, the evaluation of the extraction efficiencies of compounds **1-3** and **5** were carried out by the 2-phase solvent extraction of selected metal picrates into dichloromethane under neutral conditions. The results are summarized in the Table. The data were obtained by using dichloromethane solutions of the ligands to extract metal picrates from aqueous solution. The equilibrium concentration of picrate in aqueous phase was then determined spectrophotometrically. From the extraction data given in the Table it was observed that *p-tert*-butylcalix[4]arene monomer **1** was a poor extractant for metal cations and **2** was ineffective in transferring metal cations into the organic phase, whereas its thioether derivative **3** was effective towards the transition metal cations and was especially selective for mercury ions.

Table. Liquid-liquid extraction of metal cations with ligands.*

Picrate salt extracted (%)						
Ligand	Cu^{2+}	Co^{2+}	Cd^{2+}	Ni^{2+}	Hg^{2+}	Pb^{2+}
1	9.9	8.4	9.4	12.3	15.0	< 1.0
2	< 1.0	< 1.0	< 1.0	< 1.0	25.6	< 1.0
3	12.6	17.1	21.3	18.0	76.9	36.7
5	87.0	72.5	68.3	59.6	91.1	83.5

*Aqueous phase [metal picrate] = 2.0×10^{-5}M; organic phase, dichloromethane [ligand] = 1×10^{-3}M or 1×10^{-3} M solution of calix[4]arene unit/g of resin for oligomer at 25 °C for 1 h.

This phenomenon can be explained by the hard-soft acid-base principle. The sulfur atom is a soft donor and has a stronger affinity towards soft basic metal cations than towards hard metal cations;[17,42,43,44] therefore, compound **3,** which contains sulfur atoms, showed a potential ability to form stable complexes with soft metal cations such as Hg^{2+} and Pb^{2+}. This can not be explained by the ionic radius of cations because the ionic radius of Hg^{2+} is 1.1 Å and it is very similar to that of Cd^{2+}. Yet, compound **3** failed to transfer Cd^{2+} ions from the aqueous phase to the dichloromethane phase. This difference has yet to be explained, but cavity size, polarizability effects, the number and types of donor atoms, and conformational aspects of the ligand are likely to be important factors.

Incorporation of the bis-(2-methylthioethoxy) calix[4]arene unit into a polyamide oligomer gave markedly enhanced extraction of selected transition metals, but with no apparent selectivity among them. The enhanced metal cation affinity of oligomer **5** may indicate that an important role was played by the amide bridges of the oligomeric skeleton at the water-dichloromethane interface, which would be in agreement with the literature.[39,45]

Figure 2 represents the extraction of Hg^{2+} cations into dichloromethane at different concentrations of **3** (Figure 2). A linear relationship between log D and log L was observed with the slope of 0.9858, suggesting

that **3** formed a 1:1 complex with Hg^{2+}. The analytical data of **3** shows that the complexation reactions took place according to the following equation:

$$M_{(aq)}^{n+} + nPic_{(aq)}^- + [L]_{(org)} \rightleftharpoons [M(Pic)_n(L)]_{(org)} \tag{5}$$

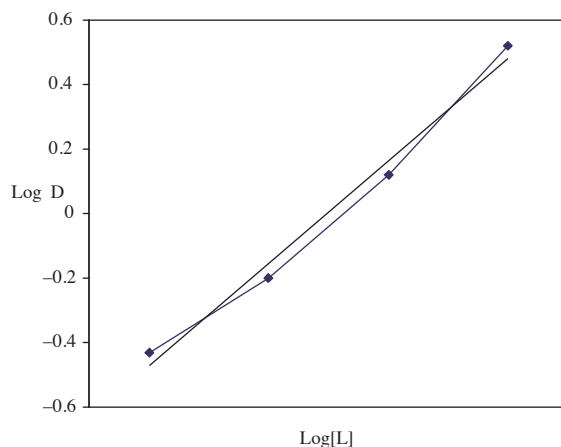By using Eq. (5) for **3**, log $K_{ex} = 3.17 \pm 0.2$.

Figure 2. Log D versus log[L] for the extraction of Hg^{2+} picrates by ligand **3** from an aqueous phase into dichloromethane at 25 °C.

Conclusion

This study described the synthesis of *p-tert*-butylcalix[4]arene derivative **3** bearing sulfur binding sites at the lower rim and its oligomeric analogue **5**. Extraction studies were performed for these compounds and it was observed that compound **3** showed good selectivity and extraction behavior towards Hg^{2+} cations, whereas its oligomeric analogue **5** showed good extraction ability without selectivity towards all of the transition metal cations, which was probably due to the influence of the amide groups of the side arms helping the metal ion-binding in a sandwich-like manner opposite to the ethyl methyl thioether part of the molecule. This strategy may enhance the utility of compound **3** in phase transfer reactions, as adsorbent in separation science and technology, or as a potential candidate material for fabricating sensors.

Acknowledgements

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