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A convenient single step synthesis of *p*-thiomethylmethylcalixarenes and metal ion extraction studies

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Abstract—A facile synthesis of *p*-thiomethylmethylcalixarenes through a [2,5] sigmatropic rearrangement and extraction of soft heavy metal ions using the prepared calix[4]arene derivative is reported here.

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1. Introduction

Sulfur containing calixarenes are an important class of compounds because they can be used for selective extraction of soft heavy metal ions against alkali, alkaline earth, or other common metal ions.[1,2] Calixarenes with sulfur-derivatized functionalities potentially meet these requirements because they are multidentate preorganized macrocyclic type ligands with appended arms. Our chosen calix[*n*]arenes have sulfur groups appended to the upper rim. Previously, thiomethylether derivatives have been synthesized by Gutsche et al.[3] through the Mannich base, which on subsequent conversion to an ammonium salt and reaction with ethyl mercaptan yield ethylthiomethyl ether derivatives of calix[4]arene, whereas the Roundhill[4] method passes through a chloromethylation step followed by treatment with sodium thiomethoxide to yield the product. Since both processes involve a number of steps, these therefore lead to low yield of the thiomethyl derivative of calixarene and are time consuming. In our synthesis, we have utilized activated dimethyl sulfoxide as the source of the methylthiomethyl moiety (using Moffatt methodology). The valuable Moffatt[5] technique employing dimethylsulfoxide–dicylohexylcarbodiimide with, for example, pyridinium trifluoroacetate, has been found to cause alkylation of certain phenols.[6] The most important feature of this route is the effective generation of the unstable sulfonium salt. Although the latter has been made by the reaction of phenol either with an activated sulphoxide or an aza or halogenosulfonium salt,[7] these reactions are reversible and hence tend not to go to completion. These drawbacks were easily overcome by the use of appropriate electrophiles, derived from phenol, as an activator of $(CH_3)_2SO$. We have used thionyl chloride and acetic anhydride as activators of $(CH_3)_2SO$. Thionyl chloride and $(CH_3)_2SO$ were used previously by Sato et al. for *ortho*-thiomethylation of phenols[7] while Brown and Pettit[8] have utilized acetic anhydride–dimethyl sulfoxide for this purpose. In both these methods the substitution takes place at the *ortho* position through a [2,3] sigmatropic rearrangement.

We have decided to use thiomethylmethylcalixarene derivatives for extraction of soft heavy metal ions (Mn(II), Co(II), Ni(II), Cu(II), Cd(II), Pb(II), Zn(II)), since the extraction of heavy metal ions like, Ag(I), Au(III), Pd(II), Pt(II) and Hg(II) have been carried out by Roundhill and co-workers[4] and also on the promise that the uncharged thiomethyl group may show higher selectivity towards soft heavy metal ions. This idea is supported by the literature search which reveals the use of thiomethylmethyl substituted calix[4]arenes as silver selective chemically modified field effect transistors.[9]

In this paper we report a facile synthesis of *p*-thiomethylmethylcalixarenes through a [2,5] sigmatropic rearrangement and extraction of soft heavy metal ions using the prepared calix[4]arene derivative.

2. Results and discussion

In the present methodology for the introduction of methylthiomethylether functionality to upper rim of calix[*n*]arene two procedures were used viz. one involving reaction of acetic anhydride as the activator of $(CH_3)_2SO$ with calix[*n*]arene and the other involving thionyl chloride as the activator of $(CH_3)_2SO$. After a series of reactions, it was found that reaction of calix[*n*]arene with acetic anhydride and $(CH_3)_2SO$ lead to some acetylation of calix[*n*]arene units which leads to a mixture of products

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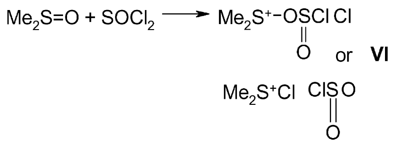
from which the methylthiomethylether derivative of calix[*n*]arene was separated in small amounts. The other products of the mixture could not be isolated by usual chromatographic techniques. However, the reaction of thionyl chloride does not suffer from this disadvantage and a good yield of the desired product was obtained by simple filtration of the crude reaction product through the silica gel column (silica gel used for TLC). The reaction possibly follows the path shown in Scheme 1, which involves initial formation of intermediate **I** by the reaction of thionyl chloride and calix[*n*]arene. The intermediate **I** reacts with $(CH_3)_2SO$ to give another intermediate **II** which rearranges to intermediate **III**. The intermediate **III**, in the presence of base (triethylamine), can attack the *para* position of the phenolic unit of calix[*n*]arene over the plane of the benzene ring ([2,5] sigmatropic shift) to give the desired compound. Some of the product was formed from the decomposition of the intermediate **III** and also through salt **VI** (Fig. 1) which is formed by prior reaction of $(CH_3)_2SO$ and thionyl chloride which react directly with calix[*n*]arene in the presence of base. However, the major product is formed through the process shown in Scheme 1.

Extraction of metal ions. Extraction studies were carried out to determine the extraction conditions for soft heavy metal ions and optimization was carried out using Cd^{2+} ion (as $Cd(NO_3)_2{\cdot}6H_2O$) solution. The concentration of **2**[4] required to extract 2 ppm Cd^{2+} solution was determined by using different concentrations ranging from 5×10^{-6} mol dm^{-3} to 5×10^{-4} mol dm^{-3} (Fig. 2). The time required to extract was determined by varying time from 10 min to 24 h (Fig. 3). It was determined that a concentration of 2×10^{-4} mol dm^{-3} and a stirring time of 16 h is enough to extract 2 ppm cadmium solution from aqueous phase to organic phase containing compound **2**[4].

Table 1 provides the extraction data for compound **2**[4] under optimized conditions. From Table 1 it is clear that Cd(II) and Pb(II) are extracted completely at pH 8, while the



$$Me_2S{=}O + SOCl_2 \longrightarrow Me_2S^{+}\text{-}O\underset{\underset{O}{\|}}{S}Cl\ Cl^{-} \text{ or } \mathbf{VI}\ \ Me_2S^{+}Cl\ Cl\underset{\underset{O}{\|}}{S}O$$

Figure 1.

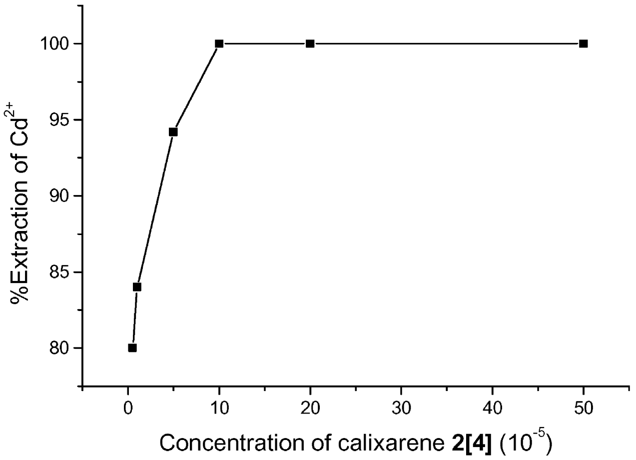
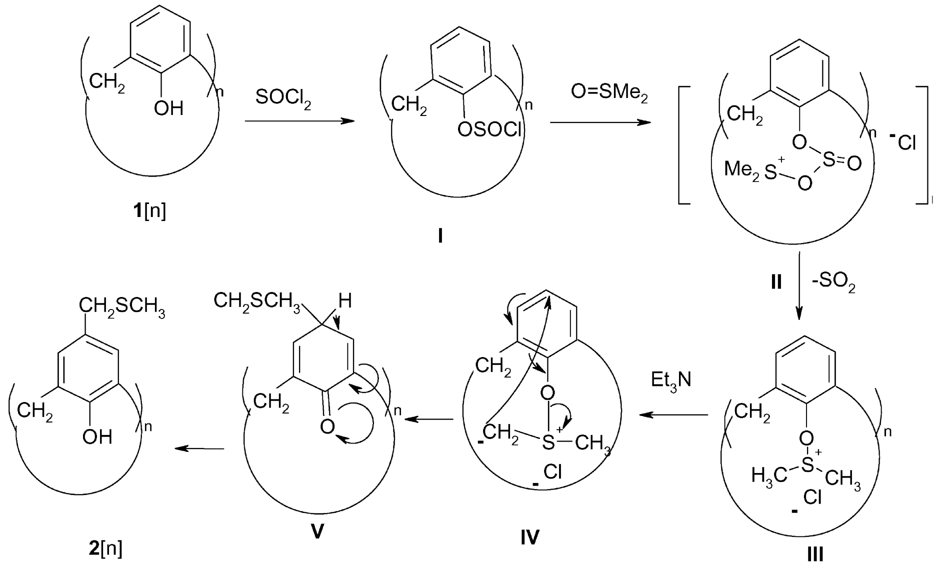


Figure 2. Effect of tetra-*p*-thiomethylmethylcalix[4]arene (**2**[4]) concentration for extraction of aqueous Cd^{2+} (2 ppm) into CCl_4.

Table 1. %Extraction of M^{2+} after 16 h into CCl_4 containing 2×10^{-4} mol dm^{-3} **2**[4] (column pH, row metal ions)

pH	M^{2+}						
	Cu^{2+}	Co^{2+}	Ni^{2+}	Mn^{2+}	Cd^{2+}	Pb^{2+}	Zn^{2+}
3.7	0	0[a]	14.5	8.5	18.0	0[a]	0[a]
5.5	9	4	19	12.5	50.5	12.5	38.2
6.8	31	68.5	24	14	65.1	25.7	48.1
8	54	71	40	29	100	100	59.7
9	85.5	75.5	73	48	100	100	81.0
10	86	85	94.5	65.5	100	100	95.9

[a] Less than 1%.



Where n =4, 6, 8

Scheme 1. Methylthiomethylation of calixarenes.

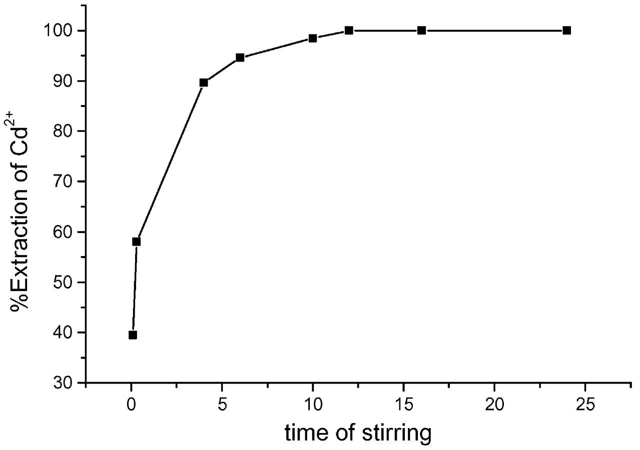


Figure 3. Effect of stirring time for extraction of aqueous Cd^{2+} (2 ppm) into CCl_4.

other metals were not extracted completely up to pH 10 under the conditions used for extraction.

3. Experimental

Equipment. NMR spectra were recorded on a 300 MHz Bruker DPX 300 instrument, IR spectra were recorded on a Nicolet Protégé 460 spectrometer in KBr disks while CHN analysis were obtained using a Perkin–Elmer 240C elemental analyzer. Mass spectra were recorded on a Jeol SX-102 spectrometer.

All absorbance measurements were measured using an ECIL atomic absorption spectrometer with air–acetylene burner head. Hollow cathode lamps manufactured by Pye Unicam were used in all the experiments. The parameters used were; current=6.0 mA, monochromator band pass=0.2 nm; flow of acetylene 2, 10 min^{-1}. Wavelengths used for the determination of metal ion concentrations were; Cd 228.8 nm; Co, 204.6 nm; Ni, 232.0 nm; Mn, 279.5 nm; Zn, 213.9 nm; Pb, 283.3; Cu, 324.8 nm.

3.1. General procedure of synthesis: 2[*n*]

Calix[*n*]arene (*n*=4, 6, 8) (0.5 g) was taken in a two necked 250 ml round bottom flask and dry dichloromethane (20 ml), dry $(CH_3)_2SO$ (15 ml) [for calix[8]arene $(CH_3)_2SO$ (25 ml) was used] was added to it. The whole reaction mixture was cooled with the help of ice–salt mixture. $SOCl_2$ (15 ml) [for calix[8]arene thionyl chloride (25 ml) was used] in dry dichloromethane (15 ml) was added over a period of 1.5 h keeping the solution below 0°C while N_2 gas was bubbled through the solution. When all the solution was added, it was stirred for 30 min and then triethylamine (15 ml) in dry dichloromethane (10 ml) was added slowly over a period of 40 min. The reaction mixture was stirred for 3 h at this temperature and then added slowly to cold water (500 ml). The dichloromethane layer was separated, washed with water, dried over anhydrous sodium sulphate and concentrated to give crude product which was filtered through silica gel and the first dichloromethane fraction was collected. The dichloromethane was evaporated under reduced pressure to give colorless product in 54–61% yield.

3.1.1. Synthesis of tetra-*p*-thiomethylmethylcalix[4]arene: 2[4]. Compound **2**[4] was synthesized using the procedure described above and eluted with dichloromethane. Yield 61%. mp 142–143°C. IR (KBr, ν/cm^{-1}): 3162 (OH), 2911, 1603, 1463, 1489, 1377, 1217, 1162, 752. ^1H NMR ($CDCl_3$, 300 K, δ): 7.02 (s, 8H, ArH), 4.13 (d, 4H, *J*=12 Hz, $ArCH_2Ar$), 3.47 (m, 12H, $ArCH_2Ar$, CH_2S), 1.96 (s, 13H, SCH_3), 10.12 (s, 4H, OH). ^{13}C NMR ($CDCl_3$, 300 K, δ): 15.1, 31.1, 37.7, 127.8, 129.0, 131.7, 147.7. FAB-Mass (*m/z*): 664 M^+, 661 $(M\text{-}3H)^+$. Anal. calcd for $C_{36}H_{40}O_4S_6\cdot(CH_3)_2SO\cdot H_2O$: C, 59.98; H, 6.36; found: C, 61.10; H, 6.38.

The second fraction was eluted using ethylacetate/hexane (2:8) to give a colorless product in 17% yield (recrystallized once with chloroform/methanol) which was characterized by using spectroscopic techniques as tri-*p*-thiomethylmethyl calix[4]arene.

mp 247–249°C, IR (KBr, (KBr, ν/cm^{-1}): 3446 (OH), 2922, 1626, 1592, 1485, 1424, 1306, 1284, 1085, 1012, 821. ^1H NMR ($CDCl_3$, 300 K, δ):7.23–6.72 (m, 9H, ArH), 4.19–3.97 (m, 4H, $ArCH_2Ar$), 3.67–3.47 (m, 10H, $ArCH_2Ar$, CH_2S), 1.96 (s, 9H, SCH_3), 10.15, 10.12, 10.08 (3s, 4H, OH). FAB-Mass (*m/z*): 603 $(M-H)^+$. Anal. calcd for $C_{32}H_{36}O_4S_3\cdot CHCl_3$: C, 58.05; H, 5.11; found: C, 58.47; H, 4.99.

3.1.2. Synthesis of hexa-*p*-thiomethylmethylcalix[6]arene: 2[6]. Yield 61%. mp>300°C. IR (KBr, ν/cm^{-1}): 3306 (OH), 2921, 2852, 1604, 1476, 1447, 1226, 919. ^1H NMR ($CDCl_3$, 300 K, δ): 7.09 (s, 12H, ArH), 3.66 (s, 12H, $ArCH_2Ar$), 3.62 (s, 12H, CH_2S), 1.96 (s, 13H, SCH_3), 10.33 (s, 6H, OH). ^{13}C NMR ($CDCl_3$, 300 K, δ): 15.0, 30.9, 37.7, 127.8, 129.8, 131.4, 148.5. FAB-Mass (*m/z*): 997 M^+, 1093 $(M+(CH_3)_2SO+H_2O)$. Anal. calcd for $C_{54}H_{60}O_6S_6\cdot(CH_3)_2SO\cdot H_2O$: C, 61.50; H, 6.26; found: C, 61.08; H, 6.50.

3.1.3. Synthesis of octa-*p*-thiomethylmethylcalix[8]arene: 2[8]. Yield 54%. mp 299–301°C. IR (KBr, ν/cm^{-1}): 3154 (OH), 2932, 2866, 1607, 1592, 1466, 1413, 1243, 1196, 1145, 1076. ^1H NMR ($CDCl_3$, 300 K, δ): 7.07 (s, 16H, ArH), 3.87 (s, 16H, $ArCH_2Ar$), 3.53 (s, 16H, SCH_2), 1.92 (s, 24H, SCH_3), 9.44 (s, 8H, OH). ^{13}C NMR ($CDCl_3$, 300 K, δ): 15.1, 29.7, 38.3, 126.6, 131.4, 147.4. Anal. calcd for $C_{72}H_{80}O_8S_8\cdot(CH_3)_2SO$: C, 53.56; H, 5.56; found: C, 53.07; H, 5.38.

3.1.4. Synthesis of 5-thiomethylmethyl-25,26,27,28-tetra hydroxycalix[4]arene. Calix[4]arene (0.37 g, 0.8 mmol) was taken in a two necked 150 ml round bottom flask and dry dichloromethane (10 ml), dry $(CH_3)_2SO$ (3 ml) was added to it. The whole reaction mixture was cooled with the help of ice–salt mixture. $SOCl_2$ in (6 ml) dry dichloromethane (10 ml) was added over a period of 35 min keeping the solution below 0°C while N_2 gas was bubbled through the solution. When all the solution was added, then 6 ml of triethylamine in dry dichloromethane (10 ml) was added slowly over a period of 20 min. The reaction mixture was worked up as reported in general procedure. The product was eluted with ethylacetate. The ethylacetete was evaporated under reduced pressure to give colorless product in 35% yield.

mp>280°C. IR (KBr, ν/cm^{-1}): 3162 (OH), 2911, 1603, 1463, 1489, 1377, 1217, 1162, 752. ^{1}H NMR ($CDCl_3$, 300 K, δ): 7.06–6.88 (m, 8H, ArH), 6.75, 6.73 (d, 3H, J=6 Hz, ArH), 4.23 (d, 4H, J=7.2 Hz, $ArCH_2Ar$), 3.47–3.37 (m, 6H, $ArCH_2Ar$, CH_2S), 1.96 (s, 3H, SCH_3), 10.16, 10.12, 10.00 (3s, 4H, OH). FAB-Mass (*m/z*): 581 (M^+-3H). Anal. calcd for $C_{30}H_{28}O_4S$.: C, 61.64; H, 4.7; found: C, 61.52; H, 4.90.

Liquid–liquid extraction. The synthesized compound **2**[4] was used for the extraction of metal ions from aqueous solution. Carbon tetrachloride was chosen as solvent for this purpose. A stock solution of **2**[4] (2×10^{-3} mol dm^{-4}) was prepared and this solution was diluted to appropriate concentrations. Similarly, stock solutions (100 ppm) of metal ions (Cu^{2+}, Pb^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, Cd^{2+}, Zn^{2+}) were prepared in distilled water and this solution was diluted to make solutions of different concentrations for extraction studies. The pH was maintained by using buffer solutions of pH 3.7 and 5.5, these were prepared by mixing appropriate composition of 0.2 M CH_3COOH and 0.2 M CH_3COONa. The solution of pH 6.8 buffer was prepared from 0.5 M KH_2PO_4 and 0.5 M K_2HPO_4. Buffer solutions of pH 8, 9 and 10 were prepared by mixing appropriate volumes of 0.5 M ammonia and 0.5 M ammonium acetate.

A stock solution of calixarene derivative was prepared by mixing 10^{-4} mol of tetra-*p*-thiomethylmethylcalix[4]arene in CCl_4 in a 100 ml round bottom flask, which was diluted appropriately for use in liquid–liquid extraction. Similarly, solutions of 10 ppm were prepared from stock solution of 100 ppm, which in turn was prepared by mixing appropriate amount of metal salts in a 100 ml volumetric standard flask and making up the volume with distilled water. The metal salts used were $Cd(NO_3)_2\cdot4H_2O$, $Co(NO_3)_2\cdot6H_2O$, $Zn(NO_3)\cdot6H_2O$, $MnCl_2\cdot4H_2O$, $CuCl_2\cdot2H_2O$, $Pb(NO_3)_2$, $NiNO_3\cdot6H_2O$.

A solution of 2 ml of metal ion solution (10 ppm) was taken in a reagent bottle and the pH was adjusted with 1 ml buffer solution. The total volume was made to 10 ml with distilled water. The two-phase mixtures were stirred with a magnetic stirrer for 16 h. The two phases were separated with the help of a separating funnel and the residual metal ion concentration was determined using AAS.

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