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Synthesis and extraction properties of new ‘proton-switchable’ tri- and tetra-substituted calix[4]arene derivatives bearing pyridinium units

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Abstract—The article describes the syntheses and complexation properties of new calixarene-based extractants, which have been synthesized from 5,11,17,23-tetra-*tert*-butyl-25,26,27-tris(chlorocarbonylmethoxy)-28-hydroxycalix[4]arene and 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(chlorocarbonylmethoxy)calix[4]arene by treatment with isoniazid (isonicotinic acid hydrazide) in the presence of pyridine, respectively. *p*-*tert*-Butylcalix[4]arene teraamide was converted to its methyl iodide salt by refluxing with methyl iodide in acetonitrile. In this synthesis it was thought to explore the role of pyridinium sites in the extraction of $HCr_2O_7^-/Cr_2O_7^{2-}$ anions. The complexing properties of the extractants toward selected alkali/transition metal cations and $HCr_2O_7^-/Cr_2O_7^{2-}$ anions are reported. It has been observed that both receptors do not extract alkali metal cations but show excellent selectivity toward transition metals. The protonated pyridinium forms of the receptors are effective for transferring the $HCr_2O_7^-/Cr_2O_7^{2-}$ anions from an aqueous into a dichloromethane layer.

1. Introduction

Toxic heavy metals like copper, mercury, chromium, lead, nickel, and cadmium can have a serious impact on the aqueous environment, animals, and humans. Chromium and its compounds are widely used in plating, leather tanning, dye, cement, and photographic industries, producing large quantities of toxic pollutants.[1] Chromium can exist in several oxidation states, however, only the trivalent and hexavalent forms are environmentally important.[2] 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.[3] Therefore, treatment of wastewater containing Cr(VI) prior to discharge is essential. Conventional techniques for removing metal ions from wastewater include chemical precipitation, membrane separation, reverse osmosis, evaporation and electrochemical treatment, and solvent extraction. Among them, solvent extraction is one of the most commonly used treatment methods and employs a selective complexant especially for ions in aqueous solution. Although there are numerous examples of molecules that act as hosts and complexants for cations, relatively fewer molecules have been reported as hosts for anions.[4–7] Thus, the development of efficient extractants for anions has received considerable attention in recent years.[8]

Calixarenes, cyclic oligomers of phenolic units linked through the *ortho* positions, are a fascinating class of macrocycle. Chemical modification of the upper or lower rim has made this class of synthetic ionophores effective extractants for transferring anionic and cationic ions or neutral molecules from aqueous solution into an organic layer. 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[4]arene moiety.[9–12] Therefore, a variety of sophisticated anion complexing ligands containing a calix[4]arene backbone have been designed and synthesized for use as selective anion extractants.[13–16] These molecules are generally calix[4]arene derivatives bearing amine or amide functions, capable of interacting with anions by hydrogen bonds.[17] In recent years, we have reported calix[4]arene-based receptors that effectively bind anions and can be useful for multiple applications such as laboratory, clinical, environmental, and industrial process analyses.[18–21] In a previous study,[21] we reported a di-substituted calix[4]arene amide derivative bearing pyridinium units, which acts as a receptor for both dichromate

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Keywords: Calix[4]arene; Amide; Metal cations; Dichromate anions; Extraction.

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Table 1. Extraction percentages of metal picrates with ligands[a]

Ligand	Extracted metal cations								
	Li^+	Na^+	K^+	Cs^+	Cd^{2+}	Co^{2+}	Cu^{2+}	Hg^{2+}	Ni^{2+}
8	<1.0	<1.0	<1.0	<1.0	86.8	81.2	69.0	90.9	89.5
9	<1.0	<1.0	<1.0	<1.0	95.0	90.7	85.8	97.6	92.3
11[b]	<1.0	<1.0	<1.0	<1.0	64.7	63.5	90.0	96.9	71.9

[a] Aqueous phase: [metal nitrate]=1×10^{-2} M; [picric acid]=2.5×10^{-5} M; organic phase: dichloromethane, [ligand]=1×10^{-3} M; at 25 °C, for 1 h.

[b] Ref. 21.

anions and some selected cations and observed that pyridinium and amide units were effective binding sites for these ions. Thus, in this study, we aimed to synthesize tri- and tetra-substituted calix[4]arene amides bearing more pyridinium binding sites compared with the previous ligand, in order to observe their extraction abilities for these ions.

2. Results and discussion

2.1. Synthesis

We synthesized 5,11,17,23-tetra-*tert*-butylcalix[4]arene **1** as a starting material through base catalyzed condensation. Compound **1** was treated with ethyl bromoacetate in dry acetone in the presence of K_2CO_3 to obtain **2** and **3** in 54% and 88% yields, respectively. Compounds **4** and **5** were obtained by the hydrolysis of **2** and **3** with 15% aqueous NaOH in ethanol/THF, respectively. Then **4** and **5** were treated with thionyl chloride in dry THF under reflux to yield the corresponding acid chlorides (**6** and **7**) in quantitative yields. The acid chlorides (**6** and **7**) are useful synthetically in a number of ways. Simple replacement of chlorine can lead directly to other modifications, but due to its high reactivity, no attempts were made to purify the crude products; thus they were used in subsequent preparation without purification. Treatment of **6** and **7** with isonicotinic acid hydrazide in THF furnishes tri- and tetra-substituted calix[4]arene amides (**8** and **9**) in 82% and 64% yields, respectively.

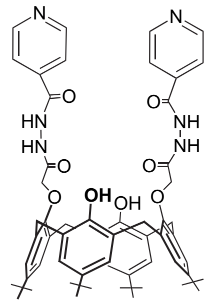
We were interested in the synthesis of calix[4]arene-based ionophores having various binding sites in order to estimate their binding ability toward cations/anions in two-phase solvent extraction systems. Compounds **8** and **9** contain pyridinyl moieties in their structures, and therefore may provide an effective binding site for anions in highly acidic media. Therefore, to reveal the mechanism of anion binding and the role of pyridinium sites, we synthesized the methyl iodide salt of **9**. Compound **9** was converted to its methyl iodide salt with methyl iodide in dry acetonitrile. After 24 h reflux, the salt derivative **10** was isolated in 85% yield.

The new compounds have been characterized by a combination of ^{1}H NMR, IR, and elemental analyses. From the ^{1}H NMR data, two signals for equivalent *tert*-butyl group are observed (two singlets at δ 0.85 and 1.17 ppm for **8** and at δ 0.91 and 1.13 ppm for **9**) and **8** and **9** exhibit a single AB system for bridging methylene groups.[22] These compounds were confirmed to be present in the cone conformation by detailed study of the ^{1}H NMR spectrum (doublets at δ 3.28 and 4.31 ppm, J=13 Hz and at δ 3.31 and 4.39 ppm, J=13 Hz for $ArCH_2Ar$ protons, respectively).

2.2. Two-phase solvent extraction

2.2.1. Metal cations. Liquid–liquid extraction experiments were performed to examine the effectiveness of compounds **8** and **9** in transferring alkali metal cations, such as Li^+, Na^+, K^+, Cs^+, and transition metals, such as Hg^{2+}, Ni^{2+}, Cu^{2+}, Co^{2+}, Cd^{2+}, and Pb^{2+} from aqueous phase into organic phase (dichloromethane). These data have been obtained using a dichloromethane solution of receptors **8** and **9** to extract metal picrates from aqueous solution. The equilibrium concentration of picrate in the aqueous phase has been determined spectrophotometrically.[21] From the data given in Table 1, it is observed that **8** and **9** only exhibited good complexation abilities toward transition metal cations. Therefore, we conclude that **8** and **9** are only selective for the transition metal cations used in the experiment. The increase in the extraction of transition metals with **8** and **9** is due to the presence of soft binding sites in **8** and **9**, which are usually provided by nitrogen atoms. This is in accordance with our previous works.[21,23,24] This characteristic enhances the utility of these receptors in various fields such as environmental, supported membrane studies, ion selective electrodes, and phase-transfer reactions. Moreover, more transition metal cation extraction ability of **9** than **8** can be attributed to the fact that **9** possesses more nitrogen atoms than **8**. When the results are compared with a previous ligand[21] (**11**) (Fig. 1), it can be seen that the new ligands (**8** and **9**) are generally more effective than the previous ligand (**11**) for transition metal cations.

2.2.2. Anions. For this purpose, we have designed extractants (**8** and **9**) having proton-switchable binding lobes for anions. A preliminary evaluation of the binding efficiencies of the extractants **8** and **9** has been carried out by solvent extraction of $Na_2Cr_2O_7$ from aqueous solution into dichloromethane at different pH values. The results are summarized in Table 2. An aqueous solution of $Na_2Cr_2O_7$ shows no extraction into a phase in the absence of the extractant. From



11

Figure 1. Previously synthesized ligand **11**.

Table 2. Extraction percentages of dichromate anions by ligands[a]

Ligand	pH			
	1.5	2.5	5.5	7.0
8	69.4	58.3	<1.0	0
9	—[b]	40.0	<1.0	0
10	0	0	0	0
11[c]	60.8	25.2	<1.0	0
12[c]	<0.1	<0.1	<0.1	<0.1

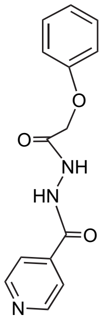
[a] Aqueous phase: [metal dichromate]$=1\times10^{-4}$ M; organic phase: dichloromethane, [ligand]$=1\times10^{-3}$ M at 25 °C, for 1 h.

[b] Could not be performed due to its water solubility in this pH.

[c] Ref. 21.

the extraction data given in Table 2, it is clear that both the extractants **8** and **9** are more effective for the extraction of dichromate anions at low pH. This is not a surprising result because extractants **8** and **9** contain appropriate proton-switchable pyridinium binding sites for aggregation of anions at low pH. Moreover, from the results in pH 2.5, it was clearly understood that **8** and **9** are better extractants than **11** for dichromate anions.

Following proton transfer to the nitrogen atom of pyridine unit in **8** and **9** from $Cr_2O_7^{2-}/HCr_2O_7^-$, an ion pair (hydrogen bonded) complex is formed in the two-phase extraction system. For the case of **10**, however, the situation is different because there is no switchable hydrogen because of the presence of CH_3 groups on the nitrogen atoms of pyridine units. As discussed previously, dichromate anions exist in aqueous solution as the $HCr_2O_7^-/Cr_2O_7^{2-}$ pair; therefore, they cannot be transferred as a hydrogen-bonded ion pair from the aqueous to the organic phase by **10**. As a consequence, dichromate anions are extracted by pyridine moieties at higher acidities. To understand the chelating effect of both pyridine fragments in the anion binding, noncyclic monomeric analog[21] (**12**) (Fig. 2) was used. It was observed that $Cr_2O_7^{2-}$ anion was only extracted in trace amounts.[21] Based on the results it has been concluded that calix[4]arene unit plays an important role in confirming the cooperative participation of the peripheral pyridine groups (Scheme 1).



12

Figure 2. Noncyclic analog (**12**) of new ligands.

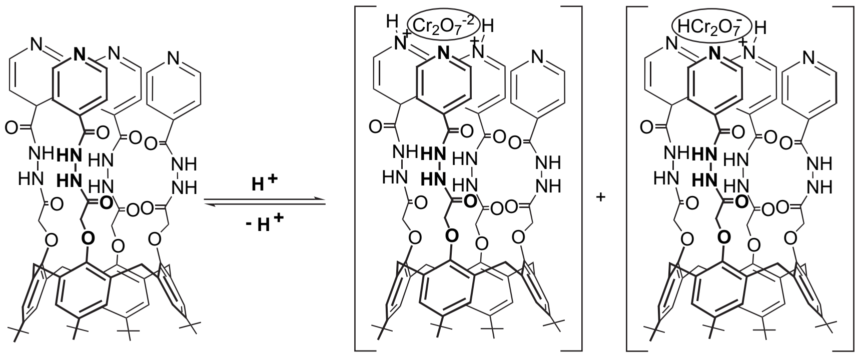
3. Conclusions

In conclusion, the synthesis and ion extraction abilities of *p-tert*-butylcalix[4]arene-based receptors **8** and **9** were studied. The spectroscopic data indicated that the new compounds are in the cone conformation. The dichromate anion complexation studies showed that compounds **8** and **9** were effective receptors for $Cr_2O_7^{2-}/HCr_2O_7^-$ anions. This work confirms the excellent selectivity of **8** and **9** toward transition metal cations, as well as being an efficient extractant for $HCr_2O_7^-/Cr_2O_7^{2-}$ anions at low pH. We have also shown that the calixarenes substituted at the lower rim with pyridine containing ionophoric moieties possess various types of proton-switchable organizations in solution at low pH. The variety of hydrogen bonding sites that occur in these calix[4]arene derivatives may be of considerable importance for the future design of novel calix[4]arene-based receptors, carriers, or supramolecular structures.

4. Experimental

4.1. General

Starting materials were obtained from commercial suppliers and used without further purification. Dry THF was distilled from the ketyl prepared from sodium and benzophenone. Acetonitrile was dried from calcium hydride and stored under N_2 over molecular sieves (4 Å). Acetone, K_2CO_3, isoniazid (all Merck), pyridine (BDH), and ethylbromoacetate (Fluka) were used as supplied. Anions were used as their sodium salts. Thin layer chromatography (TLC) was performed using silica gel on glass TLC plates (silica gel H, type 60, Merck). Generally solvents were dried by storing them over molecular sieves (Aldrich; 4 Å, 8–12 mesh). All aqueous solutions were prepared with deionized water that



Scheme 1. Proposed interactions of **9** with dichromate anions.

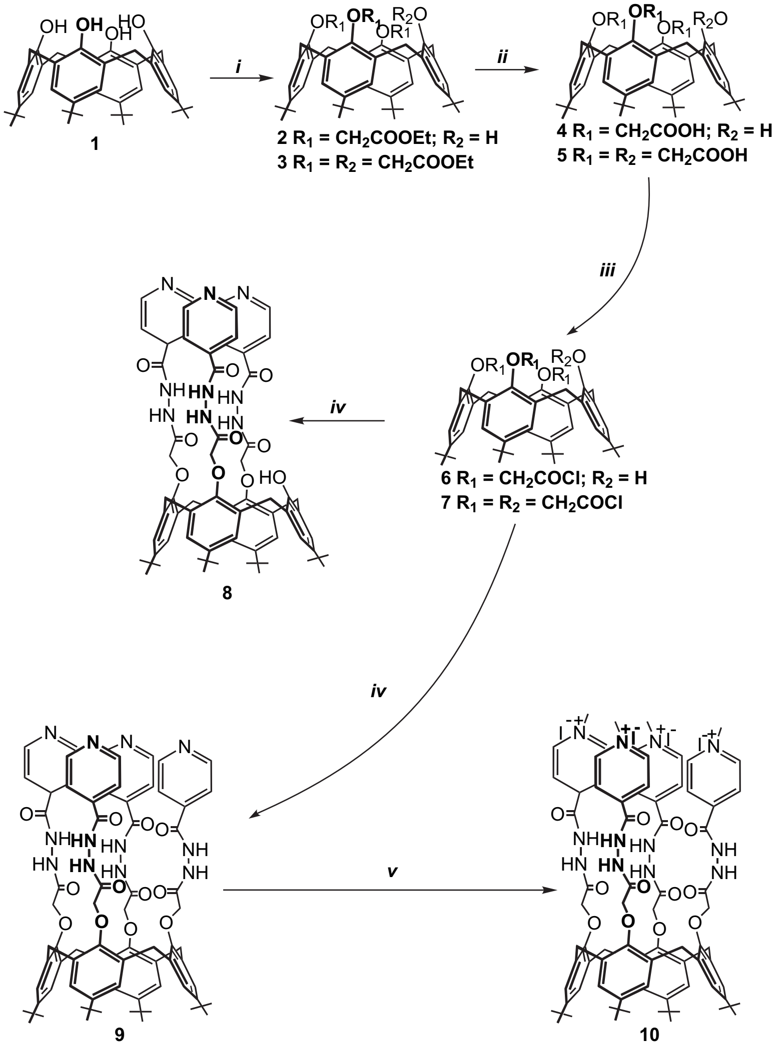
had been passed through a Millipore Milli-Q Plus water purification system. Column chromatographic separations were performed on Merck Silica gel-60 (230–400 mesh). The alkali metal picrates were prepared as described elsewhere.[21]

Melting points were determined on a Gallenkamp apparatus. ^{1}H NMR spectra were obtained using a Varian 500 MHz spectrometer operating at 500 MHz. IR spectra were recorded on a Perkin–Elmer 1605 FTIR spectrometer as KBr pellets. UV–visible spectra were obtained on Jenway 6105 and Shimadzu 160 A UV–visible recording spectrophotometers. Elemental analyses were performed using a Leco CHNS-932 analyzer. FABMS spectra were taken on a Varian MAT 312 spectrometer. An Orion 410A+ pH meter was used for the pH measurements.

4.2. Synthesis

Scheme 2 illustrates the successive synthetic steps of the compounds **1**–**10**. Compounds **1**–**7**, **11**, and **12** were synthesized according to the literature methods.[21,25,26]

4.2.1. 5,11,17,23-Tetra-*tert*-butyl-25,26,27-tris(isoniazidylcarbonylmethoxy)-28-hydroxy-calix[4]arene (8). Compound **6** (5,11,17,23-tetra-*tert*-butyl-25,26,27-tris-(chlorocarbonylmethoxy)-28-hydroxycalix[4]arene) (2.37 g, 2.7 mmol) obtained in the previous step was dissolved in dry THF (100 mL). The addition of pyridine (1 mL, 12.4 mmol) and the solution of isoniazid (2.2 g, 16.1 mmol) in THF (100 mL) was made sequentially and added dropwise in about 1 h with continuous stirring at room temperature. The reaction mixture was then stirred and refluxed for 5 h, after which most of the solvent was distilled off in vacuo. The residue was diluted with water (200 mL) and neutralized by 0.1 M HCl. The solid material was then filtered and washed with 2 M HCl, $NaHCO_3$, and distilled water sequentially. Recrystallization of the residue from ethanol/THF furnished **8** as light yellow solid. Yield: 2.6 g (82%). Mp 235–237 °C; IR: 3381 (OH), 1666–1632 cm^{-1} (NHCO); ^{1}H NMR ($CDCl_3$) δ: 0.85 (s, 18H, *tert*-butyl), 1.17 (s, 18H, *tert*-butyl), 3.28 (d, 4H, J=13 Hz, $ArCH_2Ar$), 4.31 (d, 4H, J=13 Hz, $ArCH_2Ar$), 4.51 (s, 6H, CH_2O), 6.60–7.15 (br m, 8H, ArH), 7.63 (s, 6H, PyH), 7.82 (s, 1H, OH), 8.53 (br s, 12H, PyH and NH); FABMS m/z:



Scheme 2. (i) Ethylbromoacetate, K_2CO_3, acetone; (ii) NaOH, ethanol; (iii) thionyl chloride, THF, pyridine; (iv) isonicotinic acid hydrazide, THF, pyridine; (v) CH_3I, CH_3CN.

(1203.4) [M+Na]$^+$ (calcd 1203.4). Anal. Calcd for $C_{68}H_{77}N_9O_{10}$ (1180.39): C, 69.19; H, 6.57; N, 10.68. Found: C, 69.45; H, 6.65; N, 10.87.

4.2.2. 5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis-(isoniazidylcarbonylmethoxy)calix[4]arene (9). Similar to the synthesis of **8** using compound **7** (1.08 g, 1.13 mmol) and isoniazid (0.8 g, 5.84 mmol). Yield: 5.1 g (64%) as light brown solid. Mp 352–354 °C. IR: 1660–1628 cm^{-1} (NHCO); ^{1}H NMR ($CDCl_3$) δ: 0.91 (s, 18H, *tert*-butyl), 1.13 (s, 18H, *tert*-butyl), 3.31 (d, 4H, J=13 Hz, $ArCH_2Ar$), 4.39 (d, 4H, J=13 Hz, $ArCH_2Ar$), 4.53 (s, 8H, CH_2O), 6.70–7.20 (br m, 8H, ArH), 7.57 (d, 8H, PyH), 8.58 (d, 16H, PyH and NH); FABMS *m/z*: (1380.6) [M+Na]$^+$ (calcd 1380.6). Anal. Calcd for $C_{76}H_{84}N_{12}O_{12}$ (1357.55): C, 67.24; H, 6.24; N, 12.38. Found: C, 67.45; H, 6.33; N, 12.47.

4.2.3. Treatment of compound 9 with methyl iodide (10). To a solution of **9** (0.75 g, 0.553 mmol) in CH_3CN (50 mL) was added CH_3I (0.31 mL, 5 mmol). The reaction mixture was refluxed for 24 h. After that, the solvent was evaporated in vacuo and the solid material was dried in an oven. The compound **8** was obtained as a methyl iodide salt of **7** in 85% yield (0.9 g). Mp 340–341 °C. IR: 1678–1632 cm^{-1} (NHCO); ^{1}H NMR ($CDCl_3$) δ: 0.85–1.20 (m, 36H, *tert*-butyl), 2.80 (br s, 12H, CH_3), 3.29 (d, 4H, J=13 Hz, $ArCH_2Ar$), 4.45 (d, 4H, J=13 Hz, $ArCH_2Ar$), 4.60 (s, 8H, CH_2O), 6.45–7.10 (m, 8H, ArH), 8.40 (s, 8H, PyH), 9.12 (m, 16H, PyH and NH); FABMS *m/z*: (1948.3) [M+Na]$^+$ (calcd 1948.3). Anal. Calcd for $C_{80}H_{96}N_{12}I_4O_{12}$ (1925.31): C, 69.91; H, 5.02; N, 8.73. Found: C, 70.05; H, 5.13; N, 8.82.

4.3. Analytical procedure

Picrate and/or dichromate extraction experiments were performed following Pedersen's procedure.[27] A 10 mL of 2.5×10^{-5} M aqueous picrate solution or 1×10^{-4} M aqueous dichromate solution (pH of dichromate solution has been maintained by 0.01 M KOH/HCl solution) and 10 mL of 1×10^{-3} M solution of calixarene in CH_2Cl_2 were vigorously agitated in a stoppered glass tube with a mechanical shaker for 2 min and 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/dichromate ion remaining in the aqueous phase was then determined spectrophotometrically as previously described.[21] Blank experiments showed that no picrate/dichromate extraction occurred in the absence of calixarene. The percent extraction ($E\%$) has been calculated as:

$$E\% = [(A_0 - A)/A_0] \times 100$$

where A_0 and A are the initial and final concentrations of the metal picrate/dichromate before and after the extraction, respectively.

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