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Synthesis and Extraction Studies of a Versatile Calix[4]arene-Based "Proton-Switchable Extractant" for Toxic Metals and Dichromate Anions

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Abstract

The article describes the syntheses and extraction properties of a new calixarene based extractant **5**, which has been synthesized from 5,11,17,23-tetra-*tert*-butyl-25,27-bis(chlorocarbonyl-methoxy)-26,28-dihydroxycalix[4]arene (**4**) by treatment with isoniazid (isonicotinic acid hydrazide) in the presence of pyridine. The compound **5** was converted to its methyl iodide salt (**6**) by refluxing **5** 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 5 toward selected alkali/transition metal cations and $HCr_2O_7^-/Cr_2O_7^{2}-$ anions are reported. It has been observed that receptor **5** does not extract alkali metal cations but shows an excellent selectivity toward transition metals. The protonated pyridinium form of **5** is an effective form for transferring the $HCr_2O_7^-/Cr_2O_7^{2-}$ anions from an aqueous into a dichloromethane layer.

Introduction

In the field of supramolecular chemistry, the calix[4]arene platform displays interesting organizing properties for the building of various ligating sites to recognize various species including cations, anions and neutral molecules [1–2]. Anionic coordination has received little attention over the last few decades, when compared to that devoted to the coordination chemistry of cations. However, as the realization of the important roles that anions play in biology [3, 4], medicine [5], catalysis [6], and the environment [7–9] has grown, so interest in anion coordination has become more widespread [10–12].

Several excellent studies on anion coordination have reported using calixarene based chelating units. Synthetic receptors containing two individual recognition sites for a cation and anion have attracted chemists attention. Application of such receptors may be found in metal controlled anion sensing devices. Reinhoudt and coworkers [13] have elegantly demonstrated that a calix[4]arene derivative with cation binding ester groups on the lower rim and anion binding ureas on the upper rim can efficiently bind Cl^- only in the presence of Na^+. Beer and co-workers [14–16] have synthesized a number of ditopic receptors that can undergo selective ion pair recognition. Tuntulani et al. [17] have synthesized tripodal azacrown ether calix[4]arenes containing both cation and anion binding sites, and have shown that these compounds can bind Br^- and I^- to a different extent depending on counter cations. Hagege and coworkers [18] have reported solvent extraction of selenate and chromate using a diaminocalix[4]arene. Roundhill et al. [19–20] have demonstrated that the lower rim alkylammonium-substituted calix[4]arenes act as "proton-switchable" extractants for chromate and dichromate anions. Recently, we have reported [21, 22] a bifunctional receptor based on calix[4]arene for the recognition of cations and $Cr_2O_7^{2-}$ anions.

Chromate and dichromate anions are important because of their high toxicity [23–26] and because of their presence in soils and waters [27]. In designing complexants for these particular guest anions a number of structural features can be incorporated into the host molecule that may be important in achieving selective binding. For such a molecule to be effective as a host it is necessary that its structural features are compatible with those of the guest anion. The chromate and dichromate (CrO_4^{2-} and $Cr_2O_7^{2-}$) ions are dianions with oxide functionalities at their periphery. Since the metal center does not bind to additional ligands there is no advantage in designing a host that can act as a complexant to it. Nevertheless, since the periphery of the anions have oxide moieties, these are potential sites for hydrogen bonding to the host molecule. It would be a better strategy if the host molecule contains two sites in its structure for the recognition of cations and anions. Thus, following the previous studies [22] we have extended the field of research to design elaborate structures based on calix[4]arene platform for the extraction of alkali/transition metal cations and chromate/dichromate anions. We now report the synthesis of a chemically modified p-*tert*-butylcalix[4]arene that is an extractant for both

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cations and anions. The compound is 5,11,17,23-*tetra*-tert-butyl-25,27-bis(isoniazidylcarbonylmethoxy)-26,28-dihydroxycalix[4]arene having amido and pyridinium binding sites that can potentially form associations with the ions.

Experimental

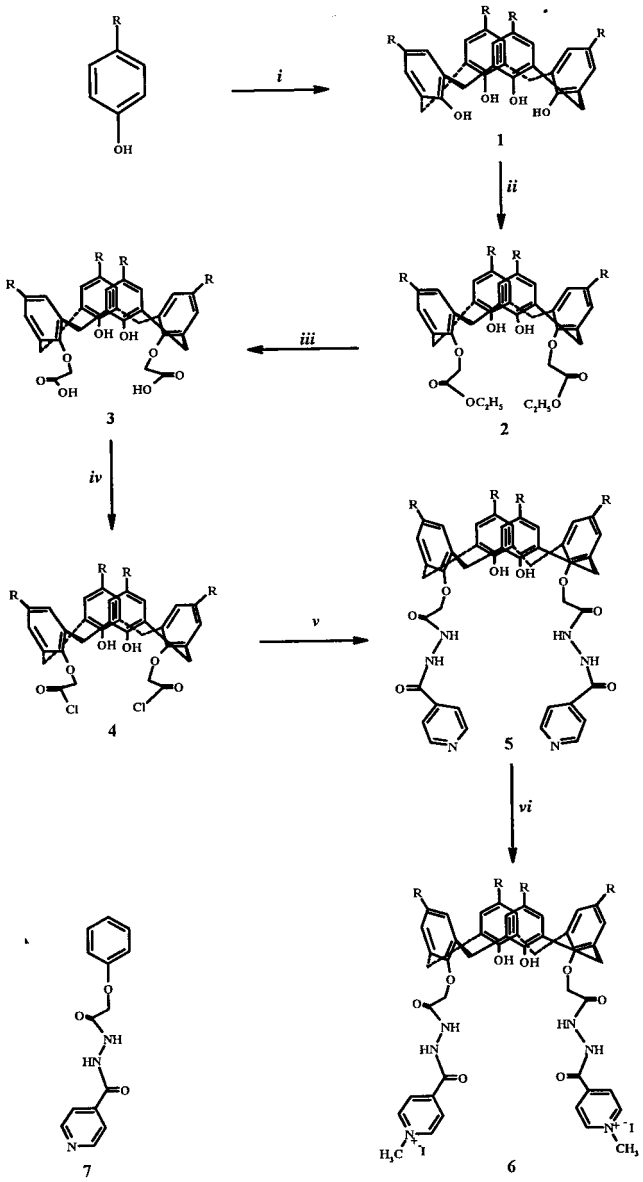
Reagents

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, isoniazide (all Merck), pyridine (BDH), ethyl-bromoacetate (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 had been passed through a Millipore Milli-Q Plus water purification system. Column chromatography separations were performed on Merck Silica gel-60 (230-400 Mesh).

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 a Shimadzu 160 A UV-visible recording spectrophometer.

Scheme 1 illustrates the successive synthetic steps of the extractants (**1–6**) used. 5,11,17,23-tetra-tert-butyl-25,26,27,28-tetrahydroxy calix(4)arene (**1**) and compounds **1–4** were synthesized according to the literature methods [28, 29]. The synthesis of compounds **4** and **5** is illustrated as follows:



Scheme 1. R= *tert-butyl*, (i) HCHO, NaOH, (ii) Acetone, Ethly bromoacetate, K_2CO_3, (iii) NaOH: EtOH, (iv), $SOCl_2$, THF, (v) 4-Pyridinecarboxylic acid hydrazide, THF, Pyridine (vi) MeCN, MeI.

5,11,17,23-tetra-*tert*-butyl-25,27-bis(isoniazidylcarbonylmethoxy)-26,28-dihydroxycalix-[4]arene (5)

The compound **4** (5,11,17,23-tetra-*tert*-butyl-25,27-bis(chlorocarbonyl-methoxy)-26,28-dihidroxycalix[4]arene) (1.66 g; 1.89 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 (1.3 g; 9.5 mmol) in THF (25 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 under vacuo. The residue was diluted with water (200 mL) and neutralized by 0.1 M HC1. The solid material was then filtered and washed with 2 N HCl, $NaHCO_3$ and distilled water sequentially. Recrystallization of residue from ethanol-THF furnished **5**. Yield 1.6 g (85%), m.p. 213–215 °C; IR: 3400 cm^{-1} (OH), 1670–1654 cm^{-1} (NHCO); ^{1}H NMR ($CDCl_3$) + (DMSO-d_6) δ: 0.95 (s, 18H, *tert*-butyl), 1.15 (s, 18H, *tert*-butyl), 3.25 (d, 4H, J = 12.8 Hz, $ArCH_2Ar$), 4.35 (d, 4H, J = 12.8 Hz, $ArCH_2Ar$), 4.45 (s, 4H, CH_2O) 6.70–7.10 (brm, 8H, ArH), 7.50 (d, 4H, PyH), 7.80 (s, 2H, OH), 8.50 (d, 8H, PyH and NH). Anal. Calcd for $C_{60}H_{70}O_8N_6$: C, 71.83; H, 7.03; N, 8.37. Found: C, 71, 45; H, 7.25; N, 8.07.

Treatment of compound 5 with methyl iodide (6)

To a solution of **5** (1 g; 0.998 mmol) in CH3CN (75 mL) was added CH_3I (0.31 mL; 5 mmol). The reaction mixture was refluxed for 24 h. After that, the solvent was evaporated under vacuo and the solid material was dried in an oven. The compound **6** was obtained as a methyl iodide salt of **5** in 86%

yield (1.1 g), m.p. 228–230 °C; IR: 3421 cm^{-1} (OH), 1684–1640 cm^{-1} (NHCO); ^{1}H NMR ($CDCl_3$) + (DMSO-d_6) δ: 0.85 (s, 18H, *tert*-butyl), 1.10 (s, 18H, *tert*-butyl), 2.45 (s, 6H, CH3), 3.50 (d, 4H, J = 12.8 Hz, $ArCH_2Ar$), 4.15 (d, 4H, J = 12.8 Hz, $ArCH_2Ar$), 4.45 (s, 4H, CH_2O), 6.40–6.80 (m, 8H, ArH), 7.30 (s, 2H, OH), 8.30 (d, 4H, PyH), 8.90 (m, 8H, PyH and NH). Anal. Calcd for $C_{62}H_{76}O_8N_6I_2$: C, 57.85; H, 5.95; N, 6.53; I, 19.72. Found: C, 57.55; H, 6.05; N, 6.30; I, 19.85.

Analytical procedure

Picrate and/or dichromate extraction experiments were performed following Pedersen's procedure [30]. 10 mL of a 2.5×10^{-5} M aqueous picrate solution or 1×10^{-4} M aqueous dichromate solution (pH of dichromate solution has been maintained by 0.01M 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 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 [31]. 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.

The alkali picrates were prepared as described elsewhere [32] by stepwise addition of a 2.0×10^{-2} M aqueous picric acid solution to a 0.14 M aqueous solution of metal hydroxide until neutralization, which was checked by pH control with a glass electrode. They were then rapidly washed with ethanol and ether before being dried in vacuo for 24 h. Transition metal picrates were prepared by stepwise addition of a 1×10^{-2} M of metal nitrate solution to a 2.5×10^{-5} M aqueous picric acid solution and shaken at 25 °C for 1 h.

Results and discussion

The main focus of this work is the design of new calixarene based ionophores that are easily accessible, that have effective binding character for a particular set of cations/anions, and could be useful for multiple applications; such as laboratory, clinical, environmental and industrial process analysis. To achieve the desired goal, we have synthesized 5,11,17,23-tetra-*tert*-butylcalix[4]arene **1** as a starting material through the base catalyzed condensation reaction [28]. The compound **1** is treated with ethyl bromacetate in dry acetone in the presence of K_2CO_3 to obtain **2** in 77% yield. The compound **3** is obtained by the hydrolysis of the compound **2** with 15% aqueous NaOH in ethanol-THF. Then **3** is treated with thionyl chloride in dry THF under reflux to yield the acid chloride in quantitative yield. The acid chloride **4** is 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 product; thus it was used in subsequent preparation without purification. Treatment of **4** with isoniazid in THF furnishes the 5,11,17,23-tetra-*tert*-butyl-25,27-bis(isoniazidylcarbonylmethoxy)-26,28-dihydroxycalix-[4]arene **5**, in 85% yield.

We were interested in the synthesis of calix[4]arene-based ionophores having various binding sites in order to estimate their binding ability toward cation/anions through the two phase solvent extraction systems. The compound **5** contains pyridinyl moieties in its structure, and therefore may be an effective binding site for anions in highly acidic medium. Therefore, to reveal the mechanism of anion binding and the role of pyridinium sites we have synthesized the methyl iodide salt of **5**. The compound **5** is converted to its methyl iodide salt with methyl iodide in dry CH_3CN. After 24 h reflux the salt derivative **6** is isolated in 86% yield.

The new compounds have been characterized by a combination of ^{1}H NMR, IR and elemental analysis. From the ^{1}H NMR data, the broad signals of not equivalent *tert*-butyl group are observed (two singlet at δ 0.95 ppm, 1.15 ppm for **5** and at δ 0.85 ppm, 1.10 ppm for **6**) and **5** and **6** exhibit a single AB system for bridging methylene groups [33]. These compounds were confirmed to be present in the cone conformation by detailed study of the ^{1}H NMR spectrum (doublets at δ 3.25 ppm, 4.35ppm, J = 12.8 Hz and at δ 3.50 ppm, 4.15 ppm, J = 12.8 Hz for $ArCH_2Ar$ protons respectively).

Two-phase solvent extraction

Metal cations

The present work is focused on elaborating the strategic requirements for the two-phase extraction measurements. Solvent extraction experiments were performed to ascertain the effectiveness of the compounds **1**, **2** and **5** in transferring the 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). The results of the picrate extraction studies are summarized in Table 1. These data have been obtained using a dichloromethane solution of the receptors **1**, **2** and **5** to extract metal picrates from aqueous solution. The equilibrium concentration of picrate in the aqueous phase has been determined spectrophotometrically. From the data given in Table1, it is observed that neither alkali nor transition metal cations are significantly extracted by starting material **1**. However, the introduction of two esteric groups onto the 1,3-position of the lower rim of **1**, induces a small change in its extraction behavior; whereas **2** shows a selective nature toward Na^+ among alkali metals, and a better extraction ability for transition metal cations as compared to **1**. By contrast, the replacement of ethoxy groups in **2** with isoniazid has improved the complexation ability of **5** toward transition metal cations only. Therefore, we conclude that **5** is only selective for the transition metal cations used in the experi-

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

	Picrate salt extracted (%)								
Ligand	Li^+	Na^+	K^+	Cs^+	Cd^{2+}	Co^{2+}	Cu^{2+}	Hg^{2+}	Ni^{2+}
1b	18.9	8.9	3.4	2.8	9.4	7.9	9.9	15.5	6.3
2b	<1.0	16.3	4.3	2.2	23.6	25.4	51.2	33.3	37.4
5	<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]Reference [31].

Table 2. Percentage extraction of dichromate by extractant **5**[a]

Compound	Dichromate anion extracted (%) pH			
	1.5	2.5	5.5	7.0
5	60.8	25.2	<1.0	0
6	<1.0	<1.0	<1.0	<1.0
7	<1.0	<1.0	<1.0	<1.0

[a]Aqueous phase, [metal dichromate] = 1×10^{-4} M; organic phase, dichloromethane, [ligand] = 1×10^{-3} M at 25 °C, for 1 h.

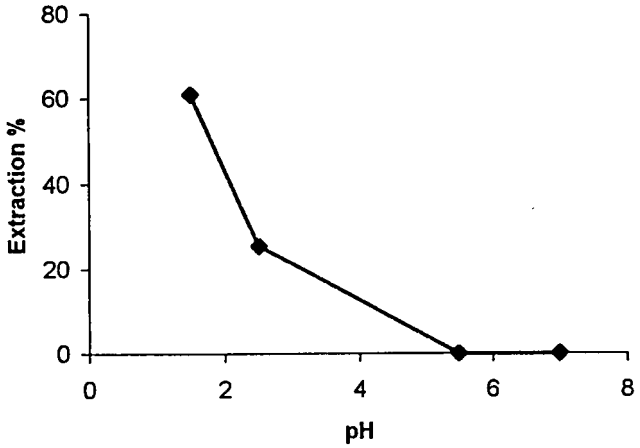


Figure 1. Plots of extraction (E %) vs. pH following the two phase solvent extraction of dichromate with compound **5**.

ment. The increase in the extraction of transition metals with **5** is due to the presence of soft binding sites in **5** which is usually provided by nitrogen atoms. This is in accordance with our previous work [34, 35]. This characteristic enhances its utility in various fields such as environmental, supported membrane studies, ion selective electrodes, and phase-transfer reactions.

Anions

Recently a number of chemically modified calixarenes have been synthesized that can be used as host for simple anions [36]. This has occurred because the periphery of a chemically modified calixarene can be made structurally compatible with these ions. Thus we have targeted the synthesis of an extractant based on a calix[4]arene framework especially for dichromate anion. Dichromate anions in particular are important because of their high toxicity [11, 24–26] and their presence in soils and waters [27]. For this purpose we have designed an extractant (**5**) having proton-switchable binding lobes for anions (Scheme 2). A preliminary evaluation of the binding efficiencies of the extractant **5** has been carried out by solvent extraction of $Na_2Cr_2O_7$ from aqueous into dichloromethane at different pH values. The results are summarized in Table 2. Aqueous solution of $Na_2Cr_2O_7$ show no extraction into a phase in the absence of the extractant. From the extraction data given in Table 2 (Figure 1), it is clear that the extractant **5** is more effective for the extraction of dichromate anions at low pH. This is not a surprising result because the extractant **5** contains a proton-switchable pyridinium binding site appropriate for aggregation of anions at low pH.

Observations show that the extraction ratio decreases as the pH increases, showing that the protonated form of **5** is an effective host for the dichromate anion (Figure 1, Table 2). All data have been analyzed by using the classical slope analysis method. Assuming the extraction of an anion An- by the anion receptor L occurs according to the following equilibrium:

$$n(\mathrm{LH}^{n+})_{\mathrm{org}} + nA^{n-}_{\mathrm{aq}} \rightleftharpoons ((\mathrm{LH}^{n+})_n, A^{n-}_n)_{\mathrm{org}}. \qquad (1)$$

The extraction constant K_{ex} is then defined by:

$$K_{\mathrm{ex}} = \frac{[((\mathrm{LH}^{n+})_n, A^{n-}_n)]_{\mathrm{org}}}{[A^{n-}]^n_{\mathrm{aq}}[\mathrm{LH}^{n+}]^n_{\mathrm{org}}}. \qquad (2)$$

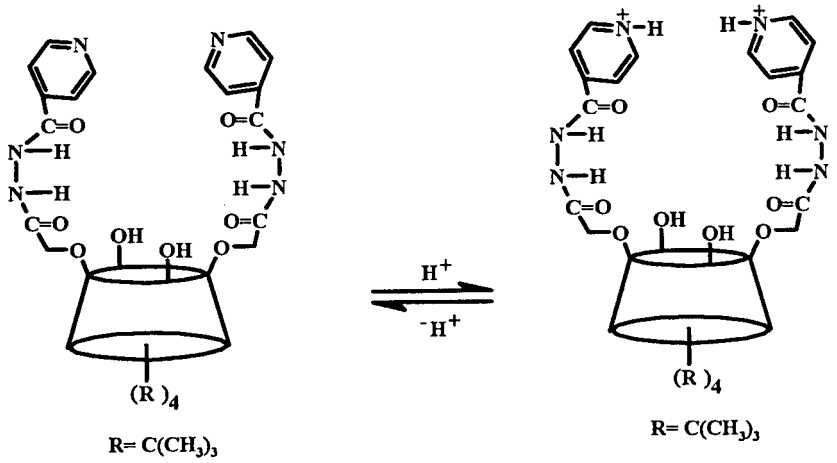
Equation (2) can be re-written as

$$\log D_A = \log K_{\mathrm{ex}} + n \log[\mathrm{LH}^{n+}]_{\mathrm{org}}, \qquad (3)$$

where D_A is defined as ratio of the analytical concentration of the anion A^{n-} in both phases:

$$D_A = [A]_{\mathrm{org}}/[A]_{\mathrm{aq}}.$$

Consequently a plot of the log D_A vs log[L] may lead to a straight line whose slope allows to access the stoichiometry of the extracted species. Figure 2, represents the extraction into dichloromethane at different concentrations of the extractant **5** for dichromate anion. A linear relationship between log D_A versus log[L] is observed with a slope of line for the dichromate anion by the ligand **5** which is roughly equal to 1.29 at pH 1.5 suggesting that the ligand **5** forms a 1:1 complex with dichromate anion. This was attributed to the presence of following equilibrium.



Scheme 2.

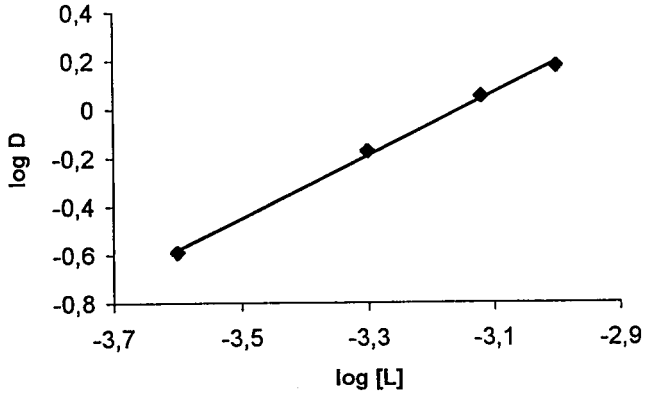


Figure 2. Log D versus log $[L]$ for the extraction of dichromate by the ligand **5** from an aqueous phase into dichloromethane at 25 °C.

$$HCr_2O_7^- \rightleftharpoons Cr_2O_7^{2-} + H^+. \quad (4)$$

However, it is well known that at higher acidic conditions $Na_2Cr_2O_7$ is converted into the $H_2Cr_2O_7$ form, and after the ionization in aqueous solution it exists in the $HCr_2O_7^-/Cr_2O_7^{2-}$ form. This has allowed us to consider this simultaneous extraction of 1:1 complexes, according to the following equilibria:

$$(LH^+)_{org} + HCr_2O_{7\,aq}^- \rightleftharpoons^{K_{ex}} (LH^+, HCr_2O_7^-)_{org}, \quad (5)$$

$$(LH_2^{2+})_{org} + Cr_2O_{7\,aq}^{2-} \rightleftharpoons^{K'_{ex}} (LH_2^{2+}, Cr_2O_7^{2-})_{org}, \quad (6)$$

According to these assumptions, a conditional constant has been calculated from the experimental data with similar K_{ex} and K'_{ex} values using Equation (3). Calculations of these constant values lead to Log K_{ex} = log K_{ex} = 3.18 ± 0.2.

Following proton transfer to the nitrogen atom of pyridine unit in **5** from $HCr_2O_7^-$, an ion pair (hydrogen bonded) complex is formed in the two phase extraction system (Scheme 3). For the case of **6**, 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 $HCr_2O_7^-/Cr2O_7^{2-}$ pair, therefore they cannot be transferred as a hydrogen-bonded ion pair from the aqueous to the organic phase by **6**. 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, non cyclic monomeric analog (**7**) was used. It was observed that $Cr_2O_7^{2-}$ anion was extracted only in trace amount. Based on the results it has been concluded that calix[4]arene unit plays a very important role in confirming the cooperative participation of the both peripheral pyridine groups.

Conclusion

The work reported here allows further conclusions to be made about the description of simple calixarene host-guest compounds. For example, a newly synthesized isoniazid derivative of calix[4]arene (**5**) and its methyl iodide salt (**6**) have been employed for the systematic complexation studies presented here for some alkali/transition metal cations and $HCr_2O_7^-/Cr_2O_7^{2-}$ anions. This work confirms the excellent selectivity of 5 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 motifs 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.

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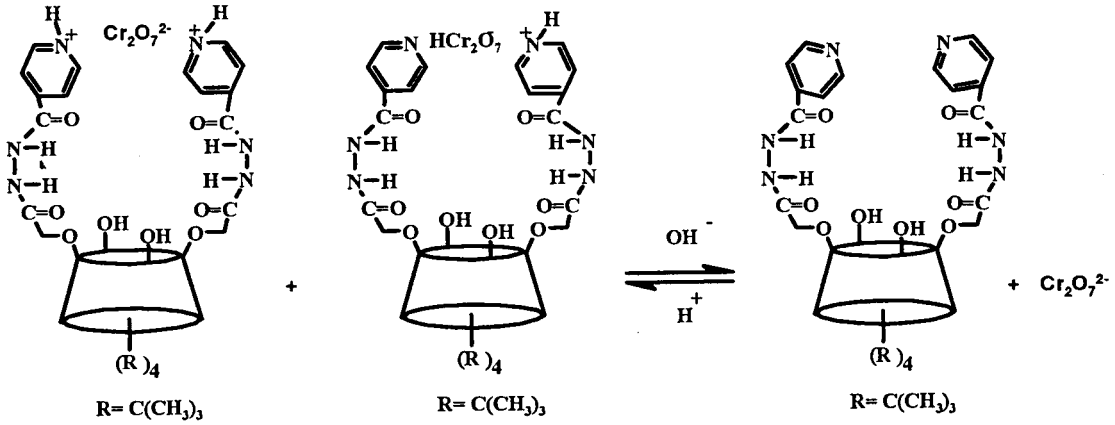

Scheme 3.

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