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# Synthesis and study of allosteric effects on extraction behavior of novel calixarene-based dichromate anion receptors

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**Abstract**—In this study the selective derivatization of *p-tert*-butylcalix[4]arene was carried out and two new calix[4]arene-based azacrown ionophores, 5,17-di-*tert*-butyl-11, 23-di-(methyl-3,5-dioxaoctane-1,8-diimine)-25,26,27,28-tetrahydroxycalix[4]arene (**6**), and 5,17-di-*tert*-butyl-11,23-di-(methyl-3,5-dioxaoctane-1,8-diimine)-25,27-diethoxyformyl-methoxy-26,28-dihydroxycalix[4]arene (**7**) have been synthesized. Treatment of 5,17-di-*tert*-butyl-11,23-diformylcalix[4]arene-25,26,27,28-tetrol (**5**) with 1,8-diamino-3,6-dioxaoctane gave the ionophore **6** which was converted to its diester derivative **7** by reaction with ethylbromoacetate in the presence of potassium carbonate. In the synthesis, the upper and lower rims of *p-tert*-butylcalix[4]arene were modified in order to acquire binding sites for the recognition of metal cations and dichromate anions. It was observed that receptor **7** is a better extractant for $Cr_2O_7^{2-}$ anions than receptor **6**. The protonated alkylinium form of **7** is an effective extractant for transferring the $Cr_2O_7^{2-}$ anions from aqueous into a dichloromethane layer and failed in transferring $Na^+$ cations due to the allosteric effect produced by the crown part of the calix moiety present at the *p*-position. © 2002 Elsevier Science Ltd. All rights reserved.

## 1. Intoduction

Calix[*n* ]arenes have been made in the design and synthesis of artificial receptors for cations, anions and neutral organic molecules. In particular, the lower or upper rim of the calix[4]arene unit can be modified to achieve more sophisticated structures to bind specific guest species.[1–4] Di- or polytopic receptors are thus constructed with two or more binding subunits within the same macrocycle structure. Once recognition of each binding subunit has been identified, the ability of multiple recognition and mutual effects of binding subunit occupation provide entries to higher forms of molecular behavior such as cooperativity, allostery and regulation, as well as communication or metal transfer.[5]

The molecular recognition of anionic guest species by positively charged or electron deficient neutral abiotic receptor molecules is an area of intense current interest.[6,7] The importance of favorable amide or protonated imine hydrogen bonding interactions for anion binding has recently been exploited in the design of calix[4]arene anion receptors which are still relatively rare.[8,9] Several excellent studies on anion coordination have been reported using calixarene based chelating units.[10–16] Synthetic receptors containing two individual recognition sites for a cation and anion have potential application in metal controlled anion sensing devices. However, chromate and dichromate anions are important because of their high toxicity[20–22] and because of their presence in soils and waters.[23] In designing complexants for these particular guest anions a number of structural features can be incorporated in to 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. 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 previous studies[8] we have extended the field of research to design elaborate structures based on calix[4]arene platform for the extraction of dichromate anions. Herein we report the synthesis and extraction studies of two novel host–guest inclusion compounds designed on a *p-tert*-butylcalix[4]-arene platform with an azacrown ring on their upper rim. Both compounds provide specific information about the guest-size host cavity interactions and ability to extract dichromate anions at different pH.

## 2. Results and discussion

### 2.1. Synthesis and characterization

Calixarenes have been widely used as three-dimensional building blocks for the construction of artificial molecular receptors capable of recognizing neutral molecules, cations

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*Keywords*: *p-tert*-butylcalix[4]arene; Schiff-base; phase transfer; extractant; dichromate anions; supramolecular chemistry.

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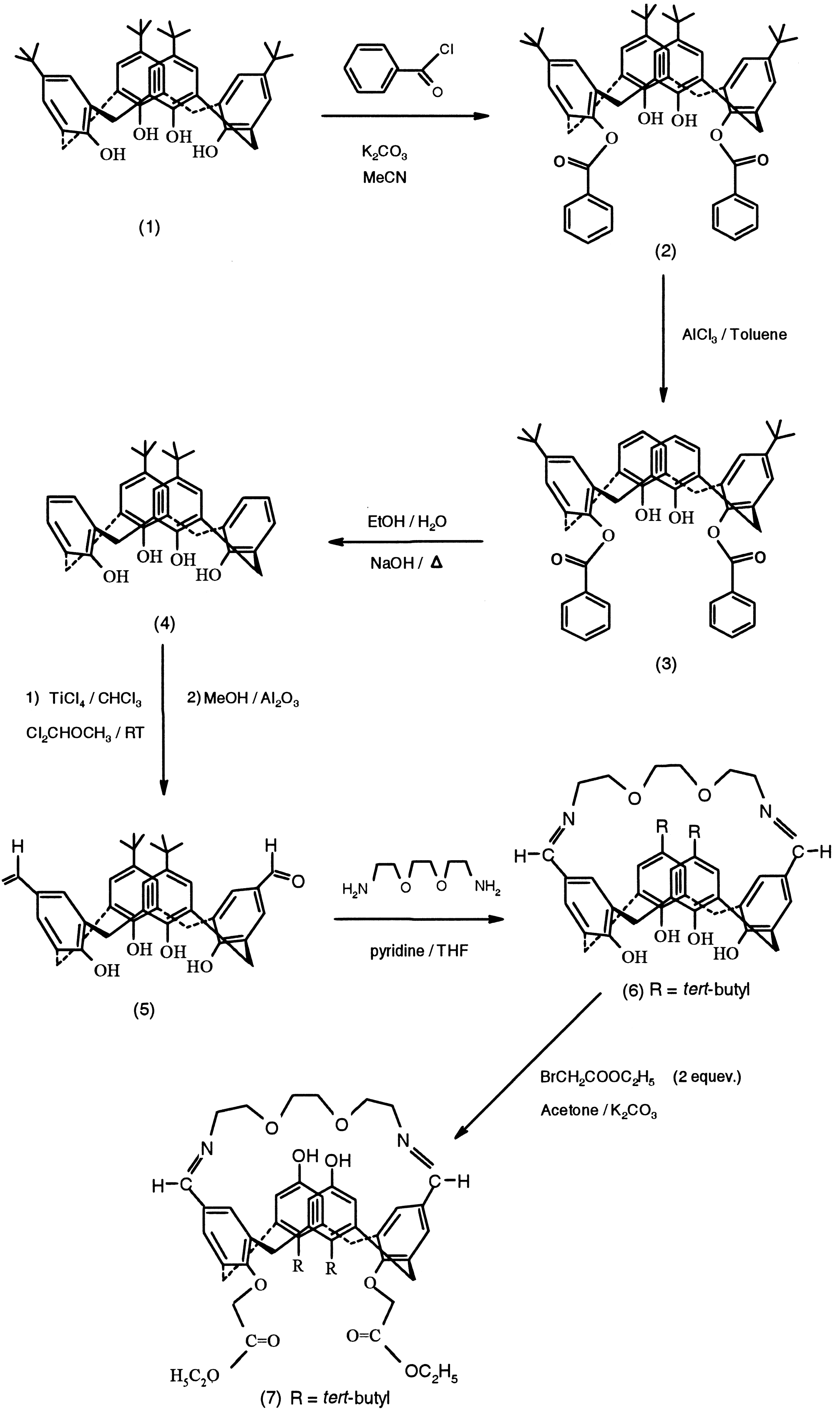
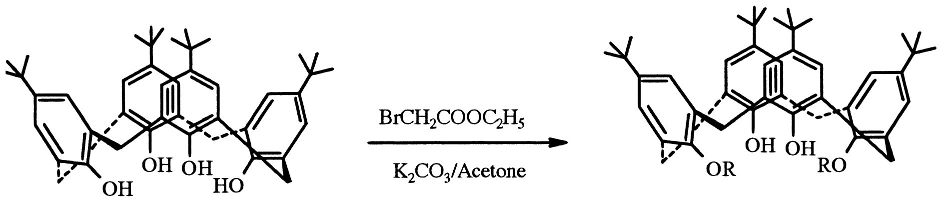

(1)
K$_2$CO$_3$
MeCN
(2)
AlCl$_3$ / Toluene
(3)
EtOH / H$_2$O
NaOH / Δ
(4)
1) TiCl$_4$ / CHCl$_3$
Cl$_2$CHOCH$_3$ / RT
2) MeOH / Al$_2$O$_3$
(5)
pyridine / THF
(6) R = *tert*-butyl
BrCH$_2$COOC$_2$H$_5$ (2 equev.)
Acetone / K$_2$CO$_3$
(7) R = *tert*-butyl

**Scheme 1.**



(1)

(8) R=$CH_2COOC_2H_5$

**Scheme 2.**

and more recently anions.[7–19] Thus, having chosen the *p-tert*-butylcalix[4]arene as the basis for derivatives, a synthetic scheme had to be developed to enable the derivatization of the molecule. Such a synthetic route is shown in Scheme 1. The ionophores reported here were designed to take advantage of the well-established binding interactions of ionophore molecules and dichromate anions. The syntheses of compounds **1**–**5** and **8** (Schemes 1 and 2) were based on the previously published procedures,[24,25,27] while reaction steps leading from **5** to **7** (Scheme 1) are reported for the first time.

The synthetic utility of the *p*-diformyl derivative of calix[4]arene is well known and can be bridged across the upper rim. Therefore, compound **5** was treated with 1,8-diamino-3,6-dioxaoctane in THF to give **6** in 59% yield which was confirmed by the apperance of an imine band at 1643 $cm^{-1}$ in the IR spectra of this compound. It would be a better strategy if the host molecule contains two sites in its structure for the recognition of cations and anions. Thus, compound **6** was converted to its diester derivative with ethylbromoacetate in dry acetone in the presence of potassium carbonate. After 15 h reflux, compound **7** was isolated in 68% yield. The new compounds were characterized by a combination of $^1H$ NMR, IR and elemental analysis. $^1H$ NMR spectroscopy is a versatile tool for the identification of calixarene conformations.[26] The $^1H$ NMR data showed that compound **6** exists in a cone conformation due to the appearence of $ArCH_2Ar$ as a typical AB type proton signal at 3.0 ppm. Compound **7** exists mostly in the 1,3-alternate conformation, which was confirmed from the singlet of $ArCH_2Ar$ splitting pattern at 3.5 ppm. Moreover, the signal for *p-tert*-butyl groups at 1.1 ppm indicates that two ester groups have not been substituted at oxygens (lower rim) *para* to these groups, because the same signal (singlet at 1.1 ppm) has also been observed in the case of compound **6**.

## 2.2. Two-phase solvent extraction

The present work determined the strategic requirements for two-phase extraction measurements. A preliminary evaluation of binding efficiencies of the extractants **4**, **6**–**8** was carried out by solvent extraction of $Na_2Cr_2O_7$ from water into dichloromethane at different pH values. The results are summarized in Tables 1 and 2. From the extraction data given in Table 1 (Fig. 1), it is apparently clear that the starting material **4** has not extracted $Cr_2O_7^{2-}/HCr_2O_7^{-}$ ions significantly. However, the conversion of **4** into a cyclic Schiff-base derivative (**6**) has increased the anion extraction ability of this compound to a remarkable extent. This pronounced increase may be due to more rigid structural features and protonation of imine groups of **6**, which help in transferring anions when compared to **4**.

From the extraction results shown in Table 2, it has been

**Table 1**. Percentage extraction of dichromate by ionophores

Dichromate anion extracted (%)

| Compound | pH | | |
|---|---|---|---|
| | 1.5 | 2.5 | 4.5 |
| **4** | 11.2 | 5.8 | 4.6 |
| **6** | 19.6 | 25.9 | 22.7 |
| **7** | 73.7 | 78.8 | 7.9 |
| **8** | 3.8 | 3.1 | 3.4 |

(1) Aqueous phase, [metal dichromate]=$1\times10^{-4}$ M; organic phase, dichloromethane, [ligand]=$1\times10^{-3}$ M at 25°C, for 1 h. (2) The % extraction *E* is given by [initial aqueous anion]−[final aqueous anion]/[initial aqueous anion]×100.

**Table 2**. Percentage extraction of sodium ions by ionophores

Sodium ion extracted (%)

| Compound | pH | | |
|---|---|---|---|
| | 1.5 | 2.5 | 4.5 |
| **4** | 9.8 | 13.1 | 10.8 |
| **6** | 44.1 | 27.8 | 35.4 |
| **7** | <1.0 | <1.0 | <1.0 |
| **8** | 43.4 | 52.5 | 53.7 |

(1) Aqueous phase, [metal dichromate]=$1\times10^{-4}$ M; organic phase, dichloromethane, [ligand]=$1\times10^{-3}$ M at 25°C, for 1 h. (2) The % extraction *E* is given by [initial aqueous anion]−[final aqueous anion]/[initial aqueous anion]×100.

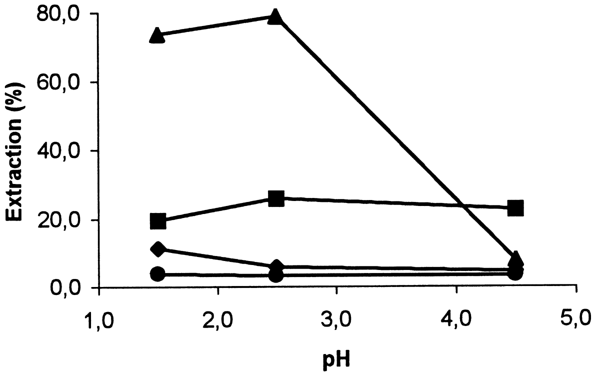
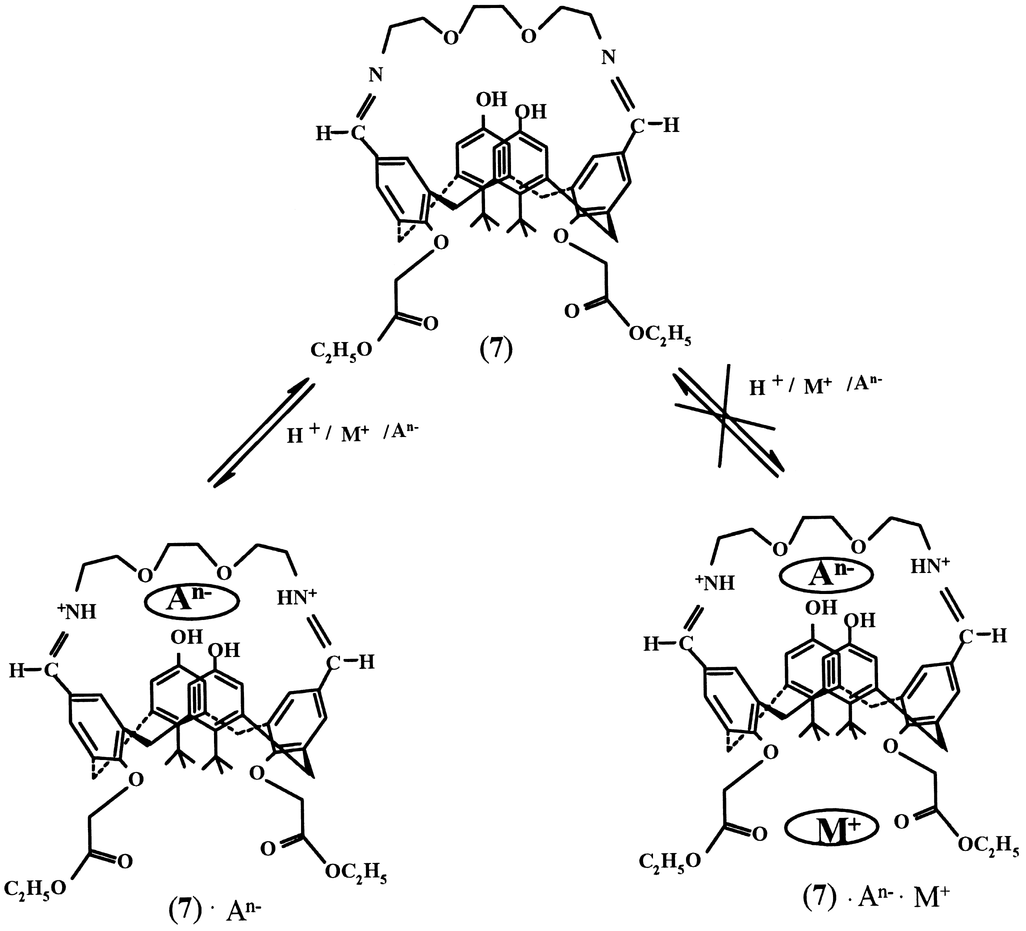


**Figure 1.** Plots of extraction (*E*%) vs pH following the two phase solvent extraction of dichromate with compound **4** (◆), **6** (■), **7** (▲) or **8** (●).



**Scheme 3.**

observed that both compounds (**4** and **6**) exhibit enhanced ion-pair extraction of sodium salt even at low pH. This can be explained by the fact that the hydrophilic nature of OH-groups may affect the extraction ability of these compounds due to their interaction at the water–dichloromethane interface, which may provide a proton exchange process in transferring $Na^+$ ions.

However an interesting result has been observed in the case of **7**. The introduction of two ester groups onto the 1,3-position of lower rim of **6** increases its extraction ability for $Cr_2O_7^{2-}/HCr_2O_7^-$ ions. Due to the presence of bifunctional sites in compound **7**, it was expected that, this compound will extract $Na^+$ by ester groups and $Cr_2O_7^{2-}/HCr_2O_7^-$ ions by imine functionalities. However the results show that compound **7** extracts only $Cr_2O_7^{2-}/HCr_2O_7^-$ ions, no $Na^+$ ions were detected after the extraction experiments (Tables 1 and 2).

From these observations, it has been concluded that, at low pH, compound **7** is protonated and may form a complex with $Cr_2O_7^{2-}$ ions. Moreover, the ester groups are not effective in transferring $Na^+$ ions due to the 1,3-alternate conformation of **7** where *p-tert*-butyl groups may provide steric hindrance and also the allosteric effect of the crown part of the upper rim, which does not allow the ester groups to form complexes with $Na^+$ cooperatively (Scheme 3).

To clarify the phenomena similar experiments were performed on compound **8** (Scheme 4). From the results it has been observed that the diester derivative of *p-tert*-butylcalix[4]arene (**8**), which has a cone conformation, is a good extractant for $Na^+$ ions even at low pH, but a poor extractant for dichromate anions. These observations support the conclusion that in compound **7** the ester groups are not cooperatively supporting each other, probably due to the allosteric effect of the crown part of the upper rim of **7** and steric hindrance of *p-tert*-butyl groups.

The extraction data for **7** was analyzed using the classical slope analysis method. Assuming the extraction of an anion $A^{n-}$ by the anion receptor $LH^{n+}$ according to the following equilibrium:

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

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

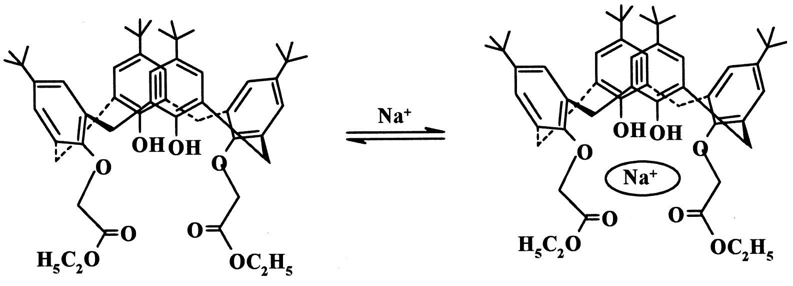
$$K_{ex} = \frac{[((LH^{n+})_n, A^{n-}_n)]_{org}}{[A^{n-}]^n_{aq}[LH^{n+}]^n_{org}} \tag{2}$$

Eq. (2) can be re-written as

$$\log D_A = \log K_{ex} + n \log[LH^{n+}]_{org} \tag{3}$$

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

$$D_A = [A^{n-}]_{org}/[A^{n-}]_{aq}$$



(8) (8)·Na+

Scheme 4.

Consequently a plot of the log $D_A$ vs log[L] may lead to a straight line with the slope $d$ which allows access to the stoichiometry of the extracted species.

Fig. 2 represents the extraction into dichloromethane at different concentrations of the extractant **7** for dichromate anion. A linear relationship between log $D_A$ vs log[L] is observed with a slope of line for the dichromate anion by the ligand **7** which is roughly equal to 1.21 at pH 1.5 suggesting that the ligand **7** forms a 1:1 complex with dichromate anion. This was attributed to the presence of the following equilibrium:

$$HCr_2O_7^- \rightleftharpoons Cr_2O_7^{2-} + H^+ \tag{4}$$

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

$$(LH^+)_{org} + HCr_2O_7^-{}_{aq} \overset{K_{ex}}{\rightleftharpoons} (LH^+, HCr_2O_7^-)_{org} \tag{5}$$

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

According to these assumptions conditional constant was calculated from experimental data with similar $K_{ex}$ and $K'_{ex}$ values with the help of Eq. (3). Calculations of these constant values lead to $\log K_{ex} = \log K'_{ex} = 3.3 \pm 0.2$.

## 3. Conclusions

The current work describes the excellent extraction behavior of **6** and **7** toward $HCr_2O_7^-/Cr_2O_7^{2-}$ anions at low pH. We have presented evidence that the unsubstituted calixarenes at the lower rim can extract metal ions due to their interaction at the water–dichloromethane interface, which may provide a proton exchange process in transferring metal ($Na^+$) ions. The failure of **7** to extract $Na^+$ ions has been attributed to the allosteric effect of the crown part of the upper rim. It is important to note that the conformation of the calix[4]arenes, and the cooperativity and allosteric effects of the functionalities play important roles in two-phase extraction systems. The variety of hydrogen bonding motifs that occur in the studied calix[4]arene derivatives may be of considerable importance for the future design of novel calix[4]arene-based receptors, carriers or supramolecular structures.

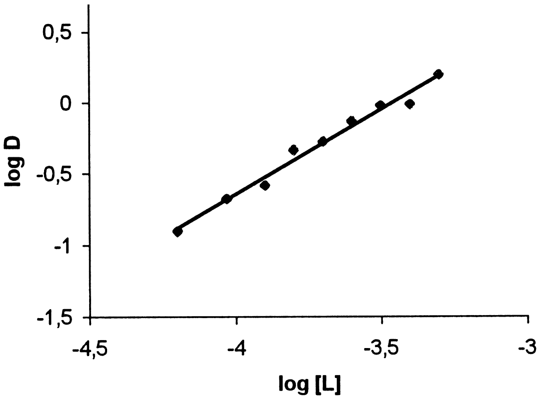


**Figure 2.** Log $D$ vs log[L] for the extraction of dichromate by the ligand **7** from an aqueous phase into dichloromethane at 25°C.

## 4. Experimental

$^1H$ NMR spectra were recorded on a Bruker 250 MHz spectrometer in $CDCl_3$ with TMS as internal standard. IR spectra were recorded on a Perkin–Elmer 1605 FTIR spectrometer as KBr pellets. UV–Vis spectra were obtained on a Shimadzu 160A UV–visible recording spectrophotometer. $Na^+$ metal determinations were made on a JENWAY PFP7 flame photometer. Osmometric molecular weight determinations were carried out on a Kanauer vapor pressure osmometer at concentration of ca. $10^{-3}$ mol/L in $CHCl_3$. Merck $PF_{254}$ silica gel was used for all forms of chromatography. The drying agent employed was anhydrous sodium sulfate. All aqueous solutions were prepared with deionized water that had been passed a Millipore milli-Q Plus water purification system.

### 4.1. Synthesis

Compounds **1–5** and **8** were synthesized according to previously published methods.[24,25,27] The other ligands (**6** and **7** ) were synthesized as follows.

**4.1.1. 5,17-Di-*tert*-butyl-11,23-di-(methyl)-3,5-dioxa-octane-1,8-diimine-25,26,27,28-tetrahydroxycalix[4]arene (6).** A mixture of 5,17-di-*tert*-butyl-11,23-diformylcalix[4]-arene-25,26,27,28-tetrol **5** (5.0 g; 8.4 mmol) pyridine (3.4 mL) and THF (950 mL) was stirred. 1,8-Diamino-3,6-dioxaoctane (1.24 mL; 8.4 mmol) in THF (50 mL) was added dropwise and the resulting mixture was heated under reflux for 4 h. After removal of solvents, the crude mixture was precipitated with methanol and after purification by chromatography (silica-gel) chloroform–methanol system, ionophore **6** was obtained in 59% (3.5 g) yield; Osmometric $M_n$ (CHCl$_3$, 37°C): 710 (calcd: 704); IR (KBr): 3272 (OH), 1643 (C=N) cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 1.1 (s, 18H, Bu$^t$), 2.4 (t, 4H, $J$=6 Hz, CH$_2$–N), 2.6 (t, 4H, $J$=6 Hz, OCH$_2$CH$_2$–N), 3.0 (d, 4H, $J$=13 Hz, Ar–CH$_2$–Ar) 3.4–3.9 (m, 8H, CH$_2$O, Ar–CH$_2$–Ar), 6.8–7.8 (m, 14H, Ar–H, N=CH, ArOH). Anal. Calcd for $C_{44}H_{52}O_6N_2$. C, 74.97; H, 7.44; N, 3.97. Found: C, 75.41; H, 7.25; N, 4.06%.

**4.1.2. 5,17-Di-*tert*-butyl-11,23-di-(methyl)-3,5-dioxa-octane-1,8-diimine-25,27-diethoxyformylmethoxy-26,28-dihydroxycalix[4]arene (7).** A mixture of compound **6** (3.0 g; 4.3 mmol) K$_2$CO$_3$ (3.0 g; 21.5 mmol) and ethyl bromacetate (1 mL; 8.6 mmol) in dry acetone (150 mL) was stirred and heated under reflux for 15 h. Most of the solvent was evaporated, the residue was precipitated with distilled water and neutralized by 0.1 M HCl. The precipitate was filtered and dried (in the oven). The crude mixture was purified by chromatography (silica-gel) chloroform–methanol system, the compound **7** was obtained in 68% yield (2.5 g).

Osmometric $M_n$ (CHCl$_3$, 37°C): 868 (calcd: 876); IR (KBr): 3275 (OH), 1644 (C=N), 1757 (C=O) cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 1.1 (s, 18H, Bu$^t$), 2.32 (t, 6H, $J$=6 Hz, CH$_3$) 2.5 (t, 4H, $J$=4.8 Hz, N–CH$_2$), 2.8–3.3 (brm, 8H, CH$_2$O), 3.5 (s, 8H, Ar–CH$_2$–Ar), 3.9–4.2 (brm, 8H, CH$_2$O), 6.9–7.9 (m, 12H, Ar–H, N=CH, ArOH). Anal. Calcd For $C_{52}H_{64}O_{10}N_2$. C, 71.21; H, 7.35; N, 3.19. Found: C, 71.39; H, 7.65; N, 3.45%.

### 4.2. Analytical procedure

To a vial were pipetted an aqueous solution (10 mL) containing sodium dichromate at a concentration of 1×10$^{-4}$ M, a few drops of 0.01 M KOH/HCl solution in order to obtain the desired pH at equilibrium and maintain the ionic strength and 10 mL of a 1×10$^{-3}$ M solution of calixarene in CH$_2$Cl$_2$. The mixture was shaken 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 dichromate ion remaining in the aqueous phase was determined spectrophotometrically. Blank experiments showed that no dichromate extraction occurred in the absence of calixarene. Each extraction experiment was repeated three times. 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 dichromate before and after the extraction respectively.

## Acknowledgments

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