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The Preorganization Effect of the Calix[4]arene Platform on the Extraction Properties of Acetylhydrazide Groups with Transition Metal Ions

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The binding properties of the cone conformer of *O,O,O,O*-tetrakis[hydrazinocarbonylmethyl]-4-*tert*-butylcalix[4]-arene, the cone and the 1,3-alternate conformers of the corresponding thia analogue have been evaluated by means of liquid–liquid extraction for a large variety of metal ions. The extraction constants and the stoichiometries of the complexes formed have been determined. Comparison of the extraction properties of calix[4]arenes with their acyclic monomeric analogue clearly demonstrated, that the preorganization of acetylhydrazide groups on the calix[4]arene platform is the cause for a significant improvement of its binding properties. The presence of additional "soft" nitrogen binding sites in acetylhydrazide derivatives of calix[4]arenes compared to their amide derivatives leads to a shift from their classical selectivity for alkali and alkaline earth cations to transition metals. The cone conformer of tetrathiacalix[4]-arene shows higher selectivity in a series of d-metal ions compared with its "classical" analogue. The 1,3-alternate conformer exhibits an excellent extraction selectivity for Cu^{2+} and Hg^{2+}.

Keywords: Calixarene; Hydrazide; Alkali metal ions; Transition metal ions; Extraction

INTRODUCTION

When two or more binding sites are combined together within the same architecture, a so-called polytopic system may be constructed [1,2]. These types of receptors open up new perspectives in analytical, coordination and supramolecular chemistry due to the specific properties of polytopic systems in comparison with linear complexons. Despite the fact that each binding subunit has been identified, the ability to multiple recognition and mutual effects of binding sites can lead to a dramatic modification of their properties. In particular, one could expect that a preorganizing effect promotes the extraction efficiency. Calix[*n*]arenes—three-dimensional macrocyclic compounds "with almost unlimited possibilities" [3] are a suitable platform for the construction of such types of molecules. The functionalization of calix[4]phenols by chelate fragments is very promising approach for the building on their basis of supramolecular complexes with "extra-dentate" properties. The chemical reorganization of such systems can be controlled by introduction of additional metal ions, pH changes or addition of low molecular compounds being able to deactivate binding sites in the molecule. As a result, a model for a so-called "activation complex" can be obtained mimicking enzyme functions.

Nowadays many calixarenes, capable to bind different types of cations have been synthesized [4–6]. Introduction of much simpler functional groups such as ethers, esters, amides or ketones has a profound effect on the binding ability of calix[*n*]arenes. These derivatives have notable recognition properties for alkali and alkaline earth metals. Tertiary amides ($R = R' = $ alkyl) extract alkali metal ions better than the related secondary amides ($R = H$; $R' = n$-Bu) [7]. According to the hard-soft acid-base principle better ligands for "soft" transition metal ions could be obtained, by introducing "softer" N and S atoms into the calixarenes. Indeed, some data have been reported

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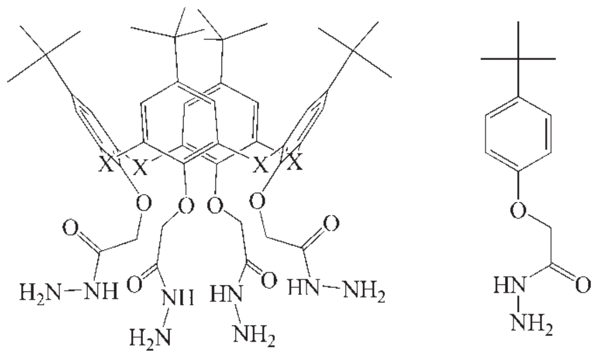
on the complexation of transition metals with amide derivatives of calix[*n*]arene in comparison with numerous data for alkali and earth alkaline ion complexation [8–12].

Recently we have reported the synthesis and characterizations of a new family of nitrogen containing calix[4]arenes, namely calix[4]phenols **1** and **2** (cone conformers), calix[4]resorcinols and calix[4]pyrogallols, functionalized by 4, 8 and 12 acetylhydrazide groups, respectively [13]. Their acyclic monomeric analogue **3** has also been considered therein. These hydrazides have been used in calixarene chemistry as key reagents for the synthesis of other nitrogen containing derivatives [13–17]. The presence of the carbonyl oxygen and additional nitrogen atoms promotes the formation of a chelate binding center in hydrazides in contrast to amide derivatives [18]. Obviously the structure of calix[4]arene would predetermine the relative arrangement of these binding centers. In this context the calix[4]arenes in 1,3-alternate conformation are of great interest due to their structural peculiarities. Two binding sites are located on both sides of the calix[4]arene macrocycle and linked with each other by a π-basic benzene tunnel. This symmetrical arrangement is well-adapted for the formation of 2:1 (M^{z+}:L) as well as 1:1 complexes [19,20]. In this context we have synthesized 1,3-alternate conformer of calix[4]arene **4** containing four hydrazide groups and its structure in solid and liquid phases has been established by NMR and IR spectroscopy (Fig. 1).

The main goal of the present work is to investigate the preorganization effect of the calix[4]arene platform on the extraction properties of acetylhydrazide fragments towards a large variety of metal ions. The extraction efficiency and selectivity, stoichiometry of complexes and extraction constants for transition metals have been established. The influence of cone and 1,3-alternate structure, the size of the lower rim and conformational flexibility of tetrathiacalix[4]arene as compared with "classical" calix[4]arene on the extraction properties will be discussed.



1 X=CH_2 (cone)
2 X=S (cone)
4 X=S (1,3-alt)

3

FIGURE 1 Compounds **1**–**4**.

EXPERIMENTAL

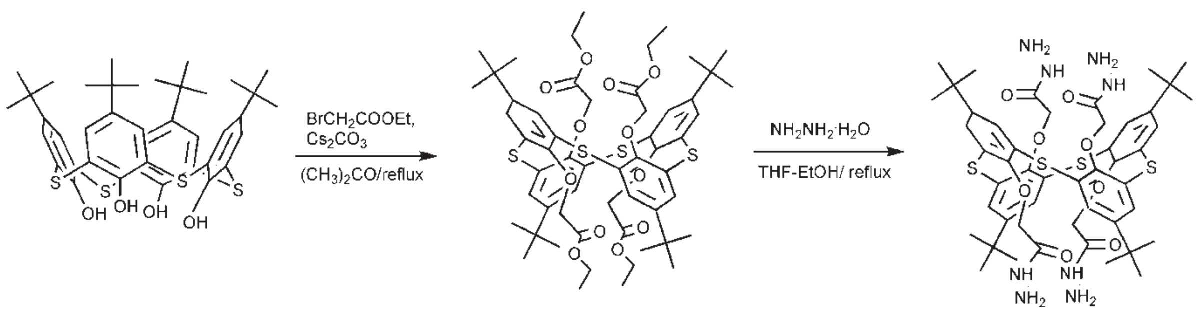
Reagents

All reagents were used as commercially received without further purification. $CHCl_3$ and CCl_4 were distilled over P_2O_5. $CDCl_3$ (99.8% isotopic purity) and DMSO-d_6 (99.5% isotopic purity) from Aldrich were used for NMR spectroscopy. The metal salts for extraction experiments were the following chlorides and nitrates: LiCl, NaCl, NaCl, CsCl, $CaCl_2$, $CoCl_2 \cdot 6H_2O$, $NiCl_2$, $CuCl_2$, $ZnCl_2$, $CdCl_2 \cdot 2.5H_2O$, Hg $(NO_3)_2 \cdot H_2O$, Pb $(NO_3)_2$, $LaCl_3 \cdot 7H_2O$, Gd$\cdot 6H_2O$, $LuCl_3 \cdot 6H_2O$.

The synthesis of **4** is shown in Fig. 2. Parent p-*tert*-butylthiacalix[4]arene [21] and calix[4]arenyloxyacetic acid ethyl esters in 1,3-alternate conformation [22] were prepared according to the literature methods.

5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[hydrazinocarbonylmethyl]-2,8,14,20-tetrathiacalix[4]arene 4

To the 1,3-alternate conformer of tetrathiacalix[4]arenyloxyacetic acid ethyl ester (2.98 g; 2.8 mmol) in the mixture of THF (140 ml) and EtOH (10 ml) under



4

FIGURE 2 Synthesis of **4**.

stirring an excess of $NH_2{-}NH_2{\cdot}H_2O$ (98%, 4.9 ml; 100 mmol) was added. The reaction mixture was refluxed for 24 h. The solvent was removed from the reaction mixture by distillation and the solid remainder was washed by water and recrystallized from EtOH. The product **4** was obtained as a white powder. Yield 90%, mp 276–278°C. ^1H NMR (600.0 MHz, DMSO-D_6, 30°C) δ: 1.23 (s, 36H, Bu^t), 3.23 (br s, 8H, NH_2), 4.36 (s, 8H, $O{-}CH_2$), 7.35 (s, 4H, NH), 7.39 (s, 4 H, Ph); ^{13}C NMR (150.9 MHz, DMSO-D_6, 30°C) δ: 30.78 (CH_3), 33.92 ($C(CH_3)$), 67.38 ($O{-}CH_2$), 147.48 (C(1) in 4-Bu^t-Ph), 127.74 (C(2) in 4-Bu^t-Ph), 126.76 (C(3) in 4-Bu^t-Ph), 154.37 (C(4) in 4-Bu^t-Ph), 165.08 (C=O). ^{15}N NMR (60.81 MHz, DMSO-D_6, 30°C) δ: 52.4 (NH_2), 132.8 (NHC(O)). IR (ν/cm^{-1}, KBr): 3416, 3321 (νNH), 3100–2850 (νCH), 1678 (νC=O), 1622 (δNH_2), 1516 (δNH (*trans*)), 1474, 1451, 1432, (νPh, $\delta_{as}CH_3$), 1381, 1362 ($\delta_s CH_3$), 1267, 1242, 1220 (νCO, νCN, νCC), 1089, 1037 (νCOC, νCCN). Elemental analysis Calc. for $C_{48}H_{64}N_8O_8S_4$: C, 57.12; H, 6.39; N, 11.10; S, 12.71; Found: C, 56.83; H, 6.72; N, 10.83; S, 12.41. Mass spectrum (MALDI-TOF): $m/z = 1011$ $[M + H]^+$; 1033 $[M + Na]^+$; 1049 $[M + K]^+$.

Apparatus

NMR spectra were recorded on a Bruker AVANCE-600 spectrometer (^1H at 600.0 MHz, ^{13}C at 150.864 MHz, ^{15}N MHz at 60.81 MHz) at 303 K. Chemical shifts in ^1H and ^{13}C spectra were referred at the solvent. The ^{15}N NMR spectra referenced to the external urea and converted to the liquid anhydrous ammonia scale ($(NH_2)_2C(O)$ $\delta = 75$ ppm). The pulse programs of the NOESY, HSQC and HMBC experiments were taken from Bruker software library. IR absorption spectra of Nujol emulsions, KBr and CCl_4 solutions (10^{-3}–10^{-5} M) of compounds were recorded on a Vector-22 Bruker FT-IR spectrophotometer with a resolution of 4 cm^{-1}.

Picrate Extraction Experiments

Aqueous metal picrate solution (5 ml) which was buffered at pH = 6.0 with tris(hydroxymethyl) aminomethane-HCl (0.05 M) and the solution of extractant (5 ml, 2.5×10^{-5}–1×10^{-3} M for **1**, **2** and **4** or 4×10^{-3} M for **3**) in $CDCl_3$ were magnetically stirred in a flask. The extraction equilibrium was reached after vigorous stirring for 1.5 h at 20°C. After that, two phases were allowed to settle for 1 h. The absorbances A_1 of the aqueous phase after extraction, and, A_0 of the aqueous phase before extraction, were measured at 355 nm (the wavelength of maximum absorption of the picrate ion, $\lambda_{max} = 355$ nm). The percentage of cation extracted ($E\%$) was calculated as the ratio (1):

$$E\% = 100 \times (A_0 - A_1)/A_0 \tag{1}$$

All data were obtained from two independent experiments. Aqueous metal picrate solutions ([metal salt] = 1×10^{-2} M; [picric acid] = 2.5×10^{-4} M) were prepared by stepwise addition to the calculated amount of metal salt of a 2.5×10^{-4} M aqueous picric acid solution which was buffered at pH = 6.0 and stirred for 1 h.

Extraction Constant Determination

The extraction of metal cations accompanied by z picrate anions and n neutral organic ligands (L) can be described by Eq. (2):

$$M^{z+}_{aq} + z\,Pic^-_{aq} + n\,L_{org} \leftrightarrows [M^{z+}L_nPic^-_z]_{org} \tag{2}$$

Where M^{z+}, Pic^-, L, $[M^{z+}L_nPic^-_z]$ denote the metal ion, picrate anion, ligand, ion-pair metal complex and the subscripts aq and org mean that the species exist in the aqueous or organic phase. Assumptions are made that the partition of the ligand to the aqueous phase is negligible ($[L]_{aq} \sim 0$). The presence of $[M^{z+}Pic^-_z]$org in the organic phase is also negligible. It was confirmed by blank experiments. The extraction percent ($E\%$) and extraction yield (α) can be calculated from Eq. (3):

$$E\% = \alpha \times 100\% = [M^{z+}L_nPic^-_z]_{org}/([Pic^-]_{aq,\,init}/z) \times 100\% \tag{3}$$

$[Pic^-]_{aq,init}$ is the initial concentration of the picrate anion in the aqueous phase. The experimental value $E\%$ was obtained from the ratio Eq. (1). When $M^{z+}L_n$ metal complexes are extracted as an ion-pair with the picrate anion into the organic phase, then the concentration $M^{z+}L_nPic^-_z$ in the organic phase is determined by Eq. (4):

$$[M^{z+}L_nPic^-_z]_{org} = ([Pic^-]_{aq,\,init} - [Pic^-]_{aq})/z = \alpha[Pic^-]_{aq,\,init}/z \tag{4}$$

$[Pic^-]_{aq}$ is the final concentration of the picrate ion in the aqueous phase. The extraction constant (K_{ex}) is evaluated from Eq. (5):

$$K_{ex} = [M^{z+}L_nPic^-_z]_{org}/[M^{z+}]_{aq}[Pic^-]^z_{aq}[L]^n_{org} \tag{5}$$

Substitution of Eq. (4) in Eq. (5) and taking logarithms gives an Eq. (6):

$$\log K_{ex} = \log(\alpha/z(1-\alpha)^z) - (z-1) \times \log[Pic^-]_{aq,\,init} - \log[M^{z+}]_{aq} - n\log[L]_{org} \tag{6}$$

The dependence of the logQ is described as a function of the K_{ex} and the concentrations of the picrate anion and the ligand:

$$\log Q = \log K_{ex} + (z-1)\log[\mathrm{Pic}^-]_{aq,init} + \log[M^{z+}]_{aq} + n\log[L]_{org}, \qquad (7)$$

$$\text{where } Q = \alpha/z(1-\alpha)^z$$

If the extraction is very efficient and $[L]_{org,init}$ is less or comparable with $[M^{z+}]$ and $[\mathrm{Pic}_z^-]_{aq,init}$ then the final concentration of $[L]_{org}$ becomes dramaticaly lower than $[L]_{org,init}$. The concentration of $[L]_{org}$ in such case is determined by Eq. (8):

$$[L]_{org} = [L]_{org,\,init} - n\alpha[\mathrm{Pic}^-]_{aq,init}/z \qquad (8)$$

Under the assumption that $[M^{z+}]_{aq} \approx [M^{z+}]_{aq,init}$ (in our case $[M^{z+}]_{aq,init} > [L]_{org,init}$ and $[\mathrm{Pic}^-]_{aq,init}$), a plot of logQ vs log $[L]_{org}$ should be linear with a slope of n, where n indicates the number of ligands involved per cation in the extracted species. The experimental errors of the extraction yield determination leads to the very large dispersion of the plotted points in the range of rather high or low α. Therefore for the correct building of the graph logQ vs log $[L]_{org}$ we have used only $\alpha = 0.05-0.95$ values. The intercept of the plot with the log Q-axis equals: $\log K_{ex} + (z-1)\log[\mathrm{Pic}^-]_{aq,\,init} + \log[M^{z+}]_{aq}$, which allows one to evaluate the extraction constant.

RESULTS AND DISCUSSION

Synthesis and Characterization of 4-*tert*-Butylthiacalix[4]arene 4

The calix[4]arene **4** functionalizated by acetylhydrazide groups and having 1,3-alternate conformation has been prepared in 90% yield by refluxing calixarenyloxyacetic acid ester with an excess of $NH_2{-}NH_2{\cdot}H_2O$ in THF:EtOH solution for one day (Fig. 2). The formation of tetrahydrazide derivative of calix[4]arene **4** has been confirmed by IR, NMR and mass spectra (MALDI-TOF) data.

The NMR spectra of **4** as well as earlier described spectra of cone conformer **2** [13] correspond to a highly symmetrical structure. The ^{1}H and ^{13}C spectra contain only one signal for each group. The protons of $-OCH_2C(O)-$ moieties in 1,3-alternate conformer are in the shielding field of two adjacent phenyl groups, so they should resonate at a higher field than those of the cone conformer [22]. Indeed the chemical shift of methylene protons as compared with it for **2** (DMSO: 4.86 ppm) is shifted in higher field (DMSO: 4.36 ppm). In addition, the cross-peaks between aromatic and *tert*-butyl protons with methylene protons in 2D NOESY spectrum, also supported that the compound **4** in solution prefers 1,3-alternate conformation. These peaks could not be and really were not observed for a cone conformer **2**.

The signal of the amide protons of **4** is broad and its chemical shift ($\delta(CDCl_3) = 7.36$ ppm, δ(DMSO) = 7.35 ppm) is noticeably less than for cone conformer **2** and even for model compound **3** ($\delta(CDCl_3) = 7.9$ ppm, δ(DMSO) = 8.9 ppm), where the shielding effect of phenyl groups is absent. Thus we can conclude that hydrogen bonds in tetrathiacalix[4]arene **4** are not practically revealed.

The chemical shift values in the NMR spectrum of the compound **4** correspond only to *trans*-amide form of the hydrazide fragment. The assignment to *trans*-rotamer was done on the basis of spin–spin coupling of carbonyl ($\delta(CDCl_3) = 168.3$ ppm; doublet $^2J(C(O),\ NH) = 9.2$ Hz; triplet $^2J(C(O),\ CH_2) = 4.1$ Hz) and methylene ($\delta(CDCl_3) = 67.9$ ppm; $^1J = 148.9$ Hz; $^3J(CH_2,\ NH)$ not observable (<0.5 Hz)) groups according to the ideology described in our previous work [23].

IR-spectrum of **4** in solid state shows a noticeable similarity with spectrum of **2** [13] that is caused by similarity of their structural blocks. As a result, the frequencies of the major characteristic vibrations have almost the same maxima. The considerable differences in the spectral behavior of **4** and **2** arise in the region of the νNH vibrations (above 3100 cm^{-1}). IR spectra of **4** in comparison with **2** have more sharp and high-frequency absorption bands (3412 cm^{-1}, 3321 cm^{-1} for **4** and 3324 cm^{-1}, 3210 cm^{-1} for **2**) in Nujol and (3429 cm^{-1}, 3300 cm^{-1} for **4** and 3348 cm^{-1}, 3207 cm^{-1} for **2**) in CCl_4 solution. At the same time the frequencies νNH for **4** compared to those for model compound **3** (3322 cm^{-1}, 3205 cm^{-1} in Nujol and 3452 cm^{-1}, 3338 cm^{-1} in CCl_4) are only a little bit lower. Obviously, it is a consequence of the disruption of circular intramolecular hydrogen bonds, which occurs when going from cone to 1,3-alternate conformation, and the appearance of weak intramolecular hydrogen bonds between hydrazide groups in compound **4**. Some increase of the $\nu C{=}O$ frequencies from 1678 cm^{-1} to 1685 cm^{-1} in IR spectra of **4** in CCl_4 solutions reflects the effect of medium and intermolecular hydrogen bonds. The presence of amide-II absorption band (δNH) with a maximum at $\sim$1516 cm^{-1} in the IR spectrum in solid state indicates on the trans-conformation of the amide group [13,24] in **4**.

Thus, the spectral characteristics of the calix[4]arene **4** are in agreement with its 1,3-alternate structure.

Extraction

In order to establish the optimum extraction conditions and obtain the comparable data for compounds **1–4** the quantitative extraction experiments with alkali (Li^+, Na^+, K^+ and Cs^+), alkali-earth (Ca^{2+}), and transition (d-: Co^{2+}, Ni^{2+},

Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+} and Pb^{2+} and f-: La^{3+}, Gd^{3+} and Lu^{3+}) metal ions have been carried out in the equal initial conditions. The concentrations of picric acid and metal cations in aqueous phase were identical in all experiments. The stoichiometry and extraction constants for compounds **1**, **2** and **4** have been determined in the same concentration range.

Picrate is known to form preferentially second sphere complexes and the partitioning of the anions from the aqueous to the organic phase will not be extraction limiting due to its lipophilicity [25]. The extraction of HPic into the organic phase can be increased by an increasing of the L concentration, which also causes a decrease in the aqueous Pic^- concentration. This is due to complex formation between L and HPic in the organic phase. The general equilibrium can be formally written as Eq. (9):

$$n\,L_{org} + z\mathrm{HPic}_{aq} \leftrightarrows [L_n(\mathrm{HPic})_z]_{org} \tag{9}$$

This process is pH dependent, what can be illustrated by Fig. 3, where the plot of $\alpha(= ([Pic^-]_{aq,init} - [Pic^-]_{aq})/[Pic^-]_{aq,init})$ vs pH is represented.

It is known, that in aqueous phase HPic acid exists as a completely dissociated form ($K_a = [H^+][Pic^-]/[HPic] = 0.51$) [26]. Thus, under decreasing of pH from 6 to 2 the deprotonated form content remains practically unchanged (from ~100% to 98%). At the same time it is well known that hydrazides as amphoteric compounds are protonated in acidic medium [27]. Therefore, it could be proposed that the most probable reason of such pH dependent phenomenon, when HPic transfers from aqueous to organic phase in the presence of compounds **1–4**, is the protonation of ligands in acidic conditions and the formation of ion-pair complex. Such type of complexes of amide derivative of calix[4]arene with picric acid [28] and mineral acids with carboxylic acid hydrazides [29] has been shown by X-ray data. From this connection the Eq. (9) can be rewritten in Eq. (10):

$$nL_{org} + zH^+ + z\mathrm{Pic}^-_{aq} \leftrightarrows [(L_nH_z^+)\mathrm{Pic}_z^-]_{org} \tag{10}$$

The hydrazide fragments in **4** are shielded by two *tert*-butyl-phenol rings. For this reason the ion-pair complex formation could be hindered, which would be resulted in lower HPic transfer degree than in the case of tetrahydrazides **1**, **2** and their acyclic analogue **3** (Fig. 3).

The increase of pH in aqueous phase would prevent the protonation process and as a result the transfer of HPic to organic phase. To simplify the complex stoichiometry and extraction constant calculation the liquid–liquid extraction experiments were carried out at pH = 6.0 with buffer using. Under such conditions the hydrolysis of metal ions [30] and the transfer of picric acid from aqueous to organic phase ($\alpha < 0.01$ see Fig. 3) are negligible. Thus, in this case the extraction process can be described only by equilibrium (1) without considering of Eq. (10). Moreover, the maintenance of the fixed pH value is necessary for the correct comparison of experimental results and is caused by the effect of pH on extraction efficiency [12,31].

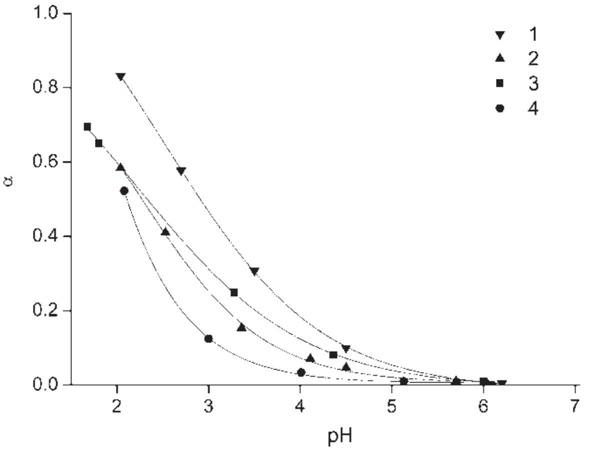


FIGURE 3 Effect of pH on a degree of transfer of HPic in the systems containing extractants **1–4**. [HPic] = 2.5 × 10^{-4} M; [$L_{1,2,4}$] = 1 × 10^{-3} M; [L_3] = 4 × 10^{-3} M).

Metal Extractions

To understand the preorganization effect of the calix[4]arene platform on the metal binding properties of acetylhydrazide groups the behavior of the acyclic monomeric analogue **3** has been studied. It was observed that the metals ions presented in Fig. 4 are not extracted by compound **3** (E < 1%). The arrangement of hydrazide fragments on the calixarene matrix considerably has promoted the extraction efficiency. Indeed, the calix[4]arenes **1**, **2** and **4** have shown a significant complexation with d- and f-elements and a lack of binding with alkali metals (E < 1% as for acyclic analogues **3**). Poor extraction was also observed for alkali-earth metal ion Ca^{2+} (from ~1.7% for **4** to 16.4% for **1**), which is nevertheless higher than for alkali metal ions. It is known that the Ca^{2+} ion is more hydrated than alkali ions [32]. The strong ability of the ligand to desolvate the metal ion can be attributed to the four hydrazide groups preorganized on the lower rim and the hydrophobicity of the molecular cavity.

The profiles of extraction selectivity of **1** and **2** are similar. However the extraction efficiency of **2** towards lanthanide ions is lower. This is probably due to the fact that the S atom is not involved in the metal coordination. But the increased size of the lower rim in thiacalix[4]arenes as compared with "classical" calix[4]arenes leads to an increase of conformational flexibility of **2** which results in a decreasing efficiency of its interaction with some metal ions.

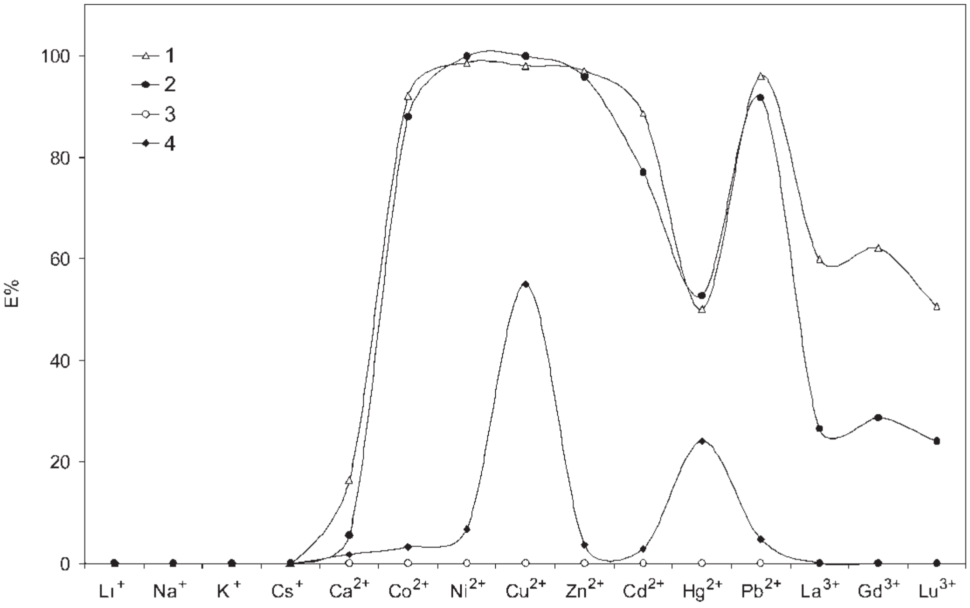


FIGURE 4 Extraction percentages (E%) of metal picrates from water into $CHCl_3$ at 25°C by ligands **1**, **2**, **3** and **4**. [HPic] = 2.5×10^{-4} M, $[M^{z+}] = 1 \times 10^{-2}$ M, $[L_{1,2,4}] = 1 \times 10^{-3}$ M, $[L_3] = 4 \times 10^{-3}$ M); pH = 6.0.

The extraction efficiency of 1,3-alternate conformer **4** is substantially lower than of its cone analogue **2**. However, the selectivity for Cu^{2+} compared with other transitional metal ions has been dramatically increased. Moreover the maximum of extraction for heavy metal ions has been shifted from Pb^{2+} to Hg^{2+}. The extraction of lanthanide metal ions within the experimental inaccuracy was not observed.

The calix[4]arene **4** can bind the metal ion only by means of two hydrazide groups, occupying only four positions in coordination sphere of lanthanide ion, for which coordination number 8–10 in a solution is characteristic [33]. According to the Pearson's classification the lanthanides belong to hard acids [34]. These metal ions are captured on the phenolic oxygen rather than the oxygen of carbonyl group or nitrogen. This is consistent with the SHAB principle, because the carbonyl group and nitrogen atom are much softer basic centers than the phenolic oxygen. Consequently, the lack of "hard" dentate centers in calix[4]arene **4** and as a result the impossibility of coordinatively saturated complex formation with Ln^{3+} ions could be the reason of lack extraction of f-elements by compound **4**.

From the results obtained it may be concluded, that the presence of "soft" binding sites in calix[4]arenes **1**, **2** and **4** could be the reason of high-effective extraction of d-elements over the alkali and alkali-earth metal ions as well as over f-elements what could be used in practice. The sequence ($Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$) of extraction efficiency values for investigated compounds is in accordance with Irving-Williams order for the relative stability of complexes formed by first transition series of metal ions [35].

Stoichiometry and Extraction Constants

The stoichiometry of the extracted complexes and the extraction constants (K_{ex}) have been determined from logQ vs log $[L]_{org}$ plots (see the Experimental section). The extraction dependence on the final concentration of the "free" ligand has been taken into account. The results of extraction experiments for **1**, **2** and **4** compounds with some transition metal ions are represented in Fig. 5 and Table I. In the graphs of extraction dependences for some metal ions two regions can be roughly distinguished: excess of cation and excess of ligand that can be attributed to different stoichiometry of the predominantly extracted species. The analysis suggests that the compound **1** forms 1:1 and 1:2 complexes (M^{z+}/L) with d-elements. In the case of heavy metals only for Hg^{2+} the stoichiometry of 2:1 has been shown. Complexes of the same composition between thiacalix[4]arene **2** and d-elements are formed. It is interesting to note that both compounds **1** and **2** form with Ni^{2+} and Cu^{2+} only 1:2 complexes. The selectivity in the series of Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} ions for 1:2 complexes with compound **2** achieves more than two orders of magnitude ($K_{ex}(Cu^{2+})/K_{ex}(Co^{2+}) = 10^{2.6}$).

The tetrathiacalix[4]arene **2** forms with lanthanide ions (La^{3+}, Gd^{3+} and Lu^{3+}) 2:1 and 1:1 complexes. However, more conformational inflexible calix[4]-arene **1** forms 1:1 and 1:2 complexes. Obviously, the formation of bulky lipophilic complex 1:2 is the reason of more efficient extraction for compound **1**. The extraction constant ($K_{ex} = 10^{15.3}$) is substantially higher than for similar stoichiometry complex

TABLE I Extraction constants and stoichiometry of complexes for calix[4]arenes **1**, **2** and **4**

		Log K_{ex}		
Cation	Metal:ligand stoichiometry	**1**	**2**	**4**
Co^{2+}	1:1	8.6 ± 0.1	9.0 ± 0.3	3.2†
	1:2	13.6 ± 0.1	12.8 ± 0.4	
Ni^{2+}	1:1	–	–	3.6†
	1:2	12.8 ± 0.3	14.7 ± 0.5	
Cu^{2+}	1:1	–	–	8.7 ± 0.3
	1:2	13.0 ± 0.5	15.4 ± 0.4	–
Zn^{2+}	2:1	7.2 ± 0.1	–	
	1:1	9.6 ± 0.1	9.9 ± 0.2	3.3†
	1:2	13.3 ± 0.8	14.4 ± 0.6	
Cd^{2+}	2:3	–	–	
	1:1	8.1 ± 0.3	8.2 ± 0.2	3.2†
	1:2	13.3 ± 0.3	12.5 ± 0.3	
Hg^{2+}	2:1	6.4 ± 0.3	6.4 ± 0.3	
	1:1	9.1 ± 0.3	8.7 ± 0.4	8.1 ± 0.1
Pb^{2+}	1:1	–	–	3.4†
	1:2	13.3 ± 0.5	12.8 ± 0.3	
La^{3+}	2:1	9.9 ± 0.3		
	1:1	12.1 ± 0.3	11.3 ± 0.3	
	1:2	15.3 ± 0.2	–	
Gd^{3+}	2:1	–	9.6 ± 0.3	
	1:1	12.5 ± 0.1	11.5 ± 0.1	
	1:2	15.3 ± 0.4	–	
Lu^{3+}	2:1	–	9.6 ± 0.5	
	1:1	11.8 ± 0.3	12.0 ± 0.1	
	1:2	15.9 ± 0.4	–	

†The extraction constant was evaluated from extraction yield for proposed 1:1 complex stoichiometry.

of calix[4]resorcinarene functionalized by four O,O-dibuthyl-N-phenyl-phenylaminomethylphosphonate groups with La^{3+} ($K_{ex} = 1.6 \times 10^{13}$) [36].

The stoichiometry and the extraction constants for thiacalix[4]arene **4** have been determined from logQ vs log $[L]_{org}$ plots only for Cu^{2+} and Hg^{2+} as for most effectively extractable ions. As mentioned above, the 1,3-alternate structure of calix[4]arene is well-adapted for the formation of 2:1 as well as 1:1 complexes. However, for both metal ions the formation of only mononuclear complexes has been established, what can be caused by negative allosteric effect (an induced conformation change that does not favor binding of the second metal) [37–39].

The determination of stoichiometry and extraction constants from logQ vs log $[L]_{org}$ plots at the low α extraction values is incorrect (see Experimental Section). Therefore, the extraction constants for **4** with the other d-metal ions have been evaluated from α values and the supposed 1:1 complex stoichiometry by using Eq. (6). From the comparison of the extraction constants represented in Table I can be concluded, that the extraction selectivity of calix[4]arene **4** towards Cu^{2+} and Hg^{2+} achieves five orders of magnitude in the series of metal ions Co^{2+}, Ni^{2+}, Zn^{2+} and Pb^{2+}.

CONCLUSION

The solvent extraction data have demonstrated that the presence of additional nitrogen atoms in calixarenes functionalized by hydrazide groups as compared with the amide derivatives leads to the shift of classical selectivity from alkali and alkaline

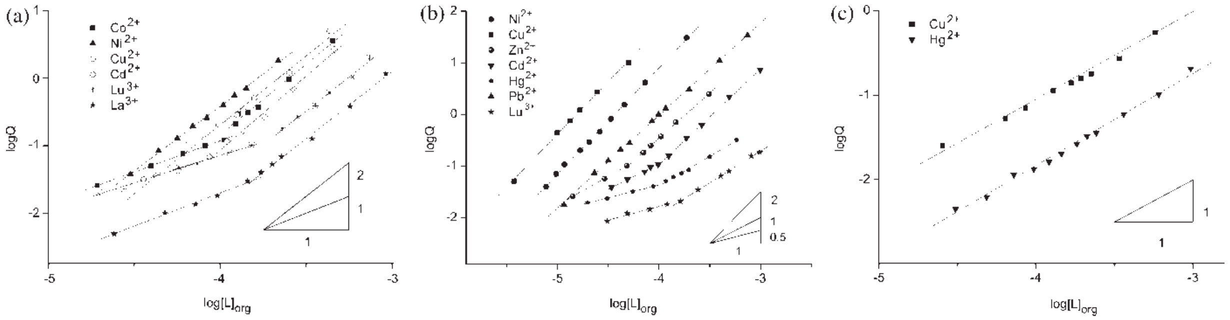


FIGURE 5 LogQ versus log$[L]_{org}$ for some metal ions extracted by **1**(a), **2**(b) and **4**(c) in $CHCl_3$. $[HPic] = 2.5 \times 10^{-4}$ M, $[M^{z+}] = 1 \times 10^{-2}$ M, pH = 6.0.

earth cations to transition metal ions, especially to d-elements. The replacement of CH_2 bridges in the calix[4]arene molecule by sulfur atoms in cone conformer leads also to a better selectivity for d-ions. The extraction selectivity for Cu^{2+} and Hg^{2+} over another transition metals becomes very excellent when we are going from cone to 1,3-alternate conformation of calix[4]arene. The extraction efficiency in the series of metal ions ($Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$) for investigated compounds is in accordance with Irving-Williams order of the relative stability of complexes. From the data obtained it may be concluded, that the cause of high binding ability of investigated calixarenes is the preorganization effect of acetylhydrazide chelate groups on the calix[4]arene platform. These results imply the hydrazide-containing calixarene are a kind of new good receptors and they have potential uses in extraction separation, preconcentrated, phase transfer, recovery of metal and exclusion of the toxic metal ions.

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