



## A Watersoluble Sulfonatomethylated Calix[4]resorcinarene as Artificial Receptor of Metal Complexes

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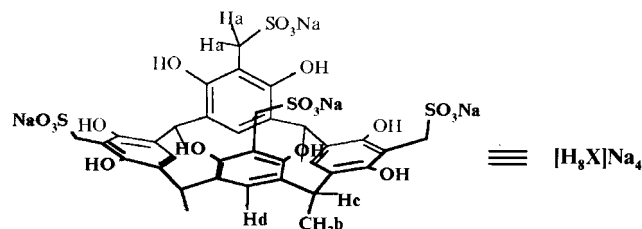
**Key words:** water soluble calix[4]resorcinarene, second sphere complexation.

### Abstract

The binding of different sized and shaped metal complexes [Co(His)<sub>2</sub>]ClO<sub>4</sub> (**1**), [Co(en)<sub>2</sub>C<sub>2</sub>O<sub>4</sub>]Cl (**2**) and [K18-crown-6]SCN (**3**) (en-ethylenediamine, His-L-histidynate-anion) with a new tetrasulfonatomethylcalix[4]resorcinarene ([H<sub>8</sub>X]Na<sub>4</sub>) was investigated in neutral and alkaline aqueous media by NMR and pH-metric titration methods and compared with those of recently studied NMe<sub>4</sub>Br (**4**). The results obtained indicate that the outer-sphere coordination of complexes **1–3** by [H<sub>8</sub>X]<sup>4–</sup> proceeds via the interaction of hydrophobic fragments of the guests with both the negatively charged rim and the hydrophobic cavity as a  $\pi$ -base. The nature of binding does not change for cations **1**, **2** and **4** on going from [H<sub>8</sub>X]<sup>4–</sup> in neutral to [H<sub>4</sub>X]<sup>8–</sup> in alkaline media, while the inclusion of **3** decreases on going from [H<sub>8</sub>X]<sup>4–</sup> to [H<sub>4</sub>X]<sup>8–</sup>.

### Introduction

Water-soluble calixarenes are known to be artificial receptors for organic molecules and ions [1–5]. The investigation of host–guest interactions in aqueous media helps in modeling of recognition and binding processes, taking place *in vivo*. Complexes of transition metal ions are known to play an important role in biological processes, such as transport or antibiotic activity [6]. So, the interaction of metal complexes with natural ionophores, such as antibiotics is also very important [6]. According to X-ray data the outer-sphere complexation of copper and nickel bis-pyridine complexes with tetrasulfonated calix[4]arene is accompanied by the insertion of an inner-sphere coordinated pyridine moiety into the hydrophobic cavity of the host [7]. As a consequence it can be predicted that constants of binding should depend on the complementarity of the ligand environment and the cavity of a host. So, it is rather interesting to recognize how the structure of the ligand environment of metal complexes affects the constants of their complexation with host-anions. As the size of a cavity is complementary with bulky organic substrates [3, 10] ionized calix[4]resorcinarenes are also good hosts for charged complexes of metal ions [8, 9]. Recently we reported a simple, high-yielding method of preparation of the novel water-soluble tetrasulfonatomethylcalix[4]resorcinarenes, which were shown to be selective hosts for amino acids [11] and alkylammonium ions [12].



Both non-substituted and substituted resorcinarenes in alkaline media undergo step-wise deprotonation, forming anions with a bowl-like structure, which in turn can coordinate complex cations, being different from those in neutral media. So, the main goal of this report is the evaluation of binding constants and a <sup>1</sup>H NMR investigation of the binding mode of complexes with different structures of the ligand environment (**1**, **2**, **3**) with tetrasulfonatomethyl calix[4]resorcinarene ([H<sub>8</sub>X]Na<sub>4</sub>) in both neutral and alkaline aqueous media.

### Experimental

The host [H<sub>8</sub>X]Na<sub>4</sub> was synthesized as recently reported [11]. *Trans-i*-[Co(His)<sub>2</sub>]ClO<sub>4</sub>, [Co(en)<sub>2</sub>C<sub>2</sub>O<sub>4</sub>]Cl and [K18-crown-6]SCN were synthesized according to earlier reported procedures [13–15]. The commercial samples of N(CH<sub>3</sub>)<sub>4</sub>Br were purified by recrystallization from methanol. The 250.13-MHz <sup>1</sup>H NMR spectra in unbuffered D<sub>2</sub>O

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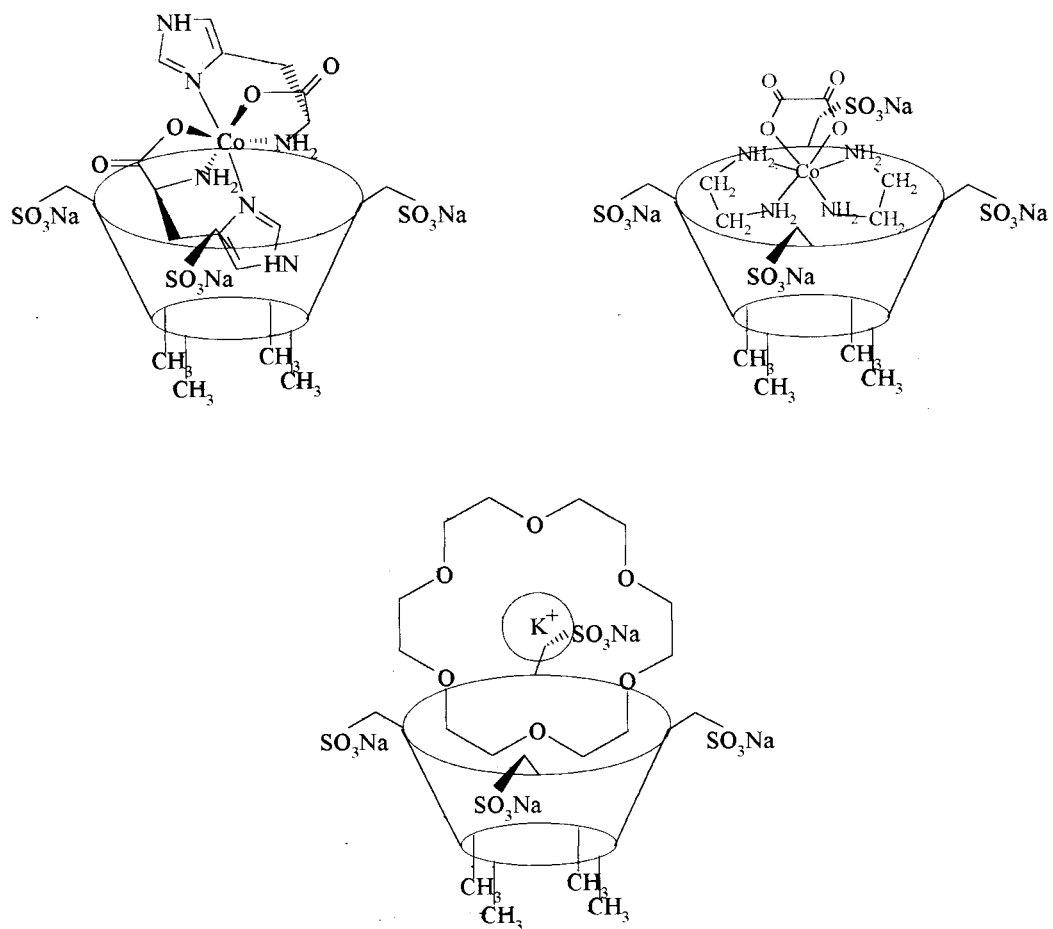


Figure 1. The inclusion modes of guests 1–3 into the  $[H_8X]Na_4$  cavity.

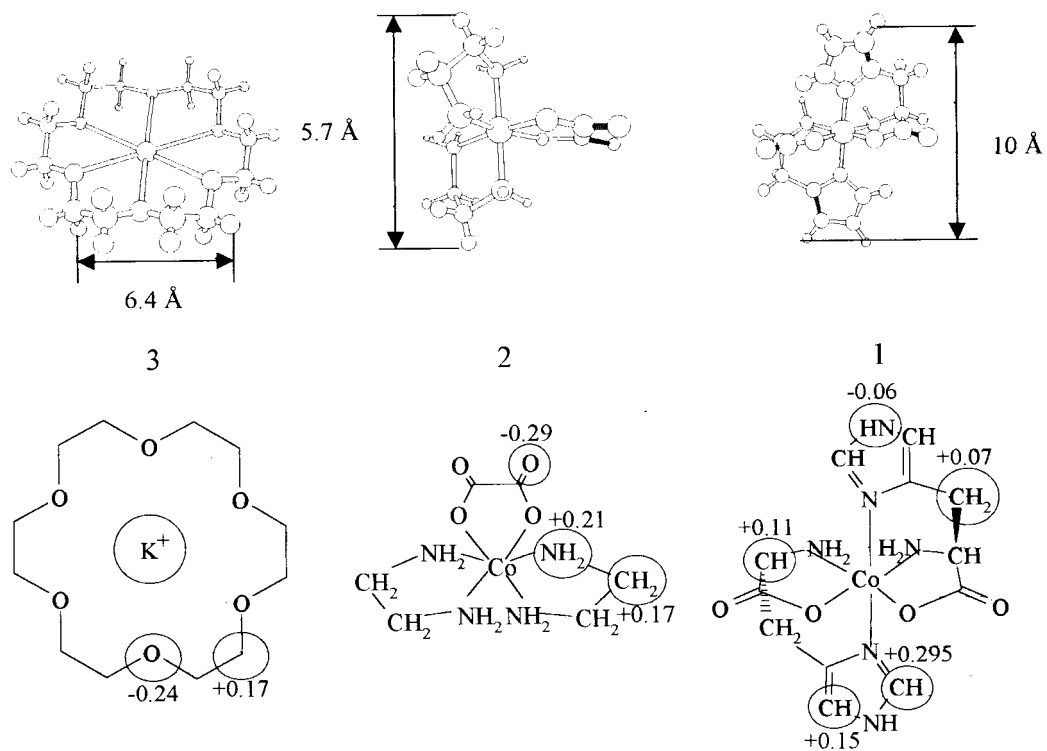


Figure 2. Some geometrical parameters and charge distribution of guests 1–3.

were recorded at 298 K with a Bruker WM-250 spectrometer, using DSS as internal standard. The pH-metric measurements employed for the determination of the binding constants of guests **1–4** with  $[\text{H}_4\text{X}]^{8-}$  were carried out in a thermostated cell at  $298 \pm 0.1$  K on an Ionomer I-130 meter with the error being less than 0.05 pH-units.  $\text{CO}_2$  free NaOH solution ( $c = 2 \times 10^{-2} \text{ mol dm}^{-3}$ ) was used as titrant. The pH-meter was calibrated by a series of buffer solutions. The pH-titration was recorded in the range of pH 6–11 with the  $[\text{H}_8\text{X}]\text{Na}_4$  concentration being  $2 \times 10^{-3} \text{ mol dm}^{-3}$  and a [host]:[guest] ratio of 1:1. About 30–40 experimental points were mathematically treated to calculate both deprotonation and complexation constants from emf data by means of the CPESP computer programme [16].

The *ab initio* calculations were carried out at the RHF/6-31G level [16]. Milliken charges on atoms of the compounds studied were computed at the STO-3G level with the help of the GAMESS (US) Package [17] at a single point. The geometry of molecules have been taken from Cambridge Structural Database (CSD) System Version 5.20 (November 2000) [18].

## Results and discussion

The sulfonatomethylated derivative ( $[\text{H}_8\text{X}]\text{Na}_4$ ) was found to bind alkylammonium cations even in neutral media without deprotonation of its phenolic rim due to four negatively charged sulfonatomethyl-groups [11]. In both neutral and alkaline ( $\text{pH} \approx 12$ ) media the complexation with sulfonatomethylated resorcinarene leads to complexation induced up-field shifts (CIS) of the alkylammonium cations according to their reciprocal orientation within the host's cavity [3, 4, 10]. The outer-sphere complexation of metal complexes **1–3** with  $[\text{H}_8\text{X}]\text{Na}_4$  also results in  $^1\text{H}$  NMR complexation induced shifts (CIS) (Table 1, negative value indicates an upfield shift) of guests at saturation binding to  $[\text{H}_8\text{X}]\text{Na}_4$ . The CIS-value of **4** is also presented in Table 1 to compare with the corresponding values of **1–3**. According to this comparison the encapsulation of **1–3** into the cavity of  $[\text{H}_8\text{X}]\text{Na}_4$  is less than those of **4**, being close to the CIS-values observed for ion-pairing of Zn(II) porphyrinates with tetrasulfonatocalix[4]arene [19]. The interaction of **2–4** with  $[\text{H}_8\text{X}]\text{Na}_4$  does not result in the non-equivalency of the  $\text{CH}_2$  groups of **2** and **3** and the  $\text{CH}_3$  groups of **4**, which in turn is the result of both rotation of the guest within the host rim and rapid exchange between free and complexed guests. Thus the experimentally observed CIS values of guests **2–4** depend on both the proximity to the calix[4]resorcinarene units and the portion of shielded protons.

Owing to the results of *ab initio* calculations the diameter of the ring of **3** is nearly 11.4 Å, being even more than the diameter of the host rim (the greatest distance between opposite oxygens of the OH-groups of the rim is 9.94 Å). Thus **3** can be proposed to be only partly encapsulated into the host cavity (Figure 1), possibly from one of the  $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$  fragments, as its size is nearly 6.4 Å (Figure 2). Due to the smaller size of the hydrophobic part of **2** compared with **3** the best fit of the latter into the host cavity

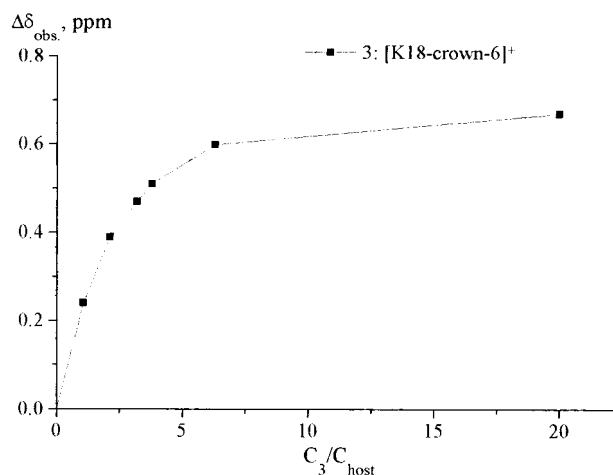


Figure 3. The plots of  $\Delta\delta_{\text{obs}}$  (ppm) of the H proton of  $[\text{H}_8\text{X}]\text{Na}_4$  versus  $C_3/C_{\text{host}}$  with  $C_{\text{host}} = 6 \times 10^{-3} \text{ mol dm}^{-3}$ .

may be proposed (Figure 2). According to the CIS-values the inclusion of **2** may be proposed from both one and two ethylenediamine fragments. But the interaction presented in Figure 1 is more probable, taking into account the electrostatic repulsion between the hydrophilic rim and the oxalate in the inner-sphere of **2**.

According to its size cation **1** (Figure 2) is too large to be included into the rim of  $[\text{H}_8\text{X}]\text{Na}_4$  as a whole. But the up-field shift of the protons of the inner-sphere coordinated histidine moieties being different from each other (Table 1) indicates, that the binding of guest **1** occurs via one of its histidine moieties in the way presented in Figure 1, where the  $\text{CH}^a$  proton of the imidazole ring undergoes the greatest up-field shift, while the  $\text{CH}^d$  proton is shifted least of all (Table 1). So, in the case of cation **1** the up-field shifts of various protons differ from each other, indicating that its movement within the rim of  $[\text{H}_8\text{X}]\text{Na}_4$  is more restricted as compared with **2–4**.

The constants of complexation between  $[\text{H}_8\text{X}]\text{Na}_4$  and guest-cations **1–4** in neutral aqueous media ( $\beta$ ) were evaluated by treating the observed down-field shift of the host ( $\text{H}^d$ ) by the Benesi–Hildebrand analysis [20] under conditions of fixed host and varying guest concentrations. The complexation was found to be in the molar ratio 1:1 with log  $\beta$ -values being in the following order **1 = 4 > 3 > 2**, which does not correlate with the CIS-values, which are in the order **4 > 2 > 3 > 1** (Table 1). For example cobalt bis-histidinate, having CIS-values less than 0.35, is only slightly shielded by calix[4]resorcinarene units, whilst its binding constant is very similar to those for tetramethylammonium. Guests **2** and **3** encapsulate more deeply than **1**, but their binding constants are smaller. So, noticeably the CIS values are substantially smaller for the stronger bound cation **1**. Thus it can be proposed that cation **1** has a binding constant nearly equal to those of **4** due to more effective electrostatic interactions with the rim of  $[\text{H}_8\text{X}]\text{Na}_4$ .

In the framework of this proposal the appearance of additional charge on the phenolic rim due to its deprotonation should result in a different effect on the log  $\beta$  and CIS values for guests, mainly interacting with the rim or

Table 1. The CIS-values of the guest protons in neutral and alkaline media, log  $\beta$ - and  $\Delta \log \beta$ -values

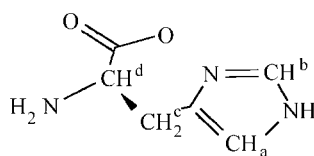
Guest	<b>1</b> [Co(His) <sub>2</sub> ] <sup>+</sup>				<b>2</b> [Co(en) <sub>2</sub> C <sub>2</sub> O <sub>4</sub> ] <sup>4-</sup>	<b>3</b> [K18C6] <sup>+</sup>	<b>4</b> [N(CH <sub>3</sub> ) <sub>4</sub> ] <sup>+</sup>
	H <sup>a</sup>	H <sup>b</sup>	H <sup>c</sup>	H <sup>d</sup>	-CH <sub>2</sub> -	-CH <sub>2</sub> -	CH <sub>3</sub> -
CIS <sub>n</sub>	-0.35	-0.09	-0.13	-0.07	-0.6	-0.49	-1.24
CIS <sub>a</sub>			*		-0.8	-0.44	-1.44
Log $\beta_n \pm \delta_n$			2.4		2.0	2.3	2.4
Log $\beta_a \pm \delta_a$			5.9		5.1	4.0	5.5
$\Delta \log \beta$			3.5		3.1	1.7	3.1

n-neutral media, a-alkaline media,  $\delta$  is standard deviation,  $\delta_n \leq 0.15$ ,  $\delta_a \leq 0.12$ .

The CIS<sub>n</sub>-values of the guests were obtained from the <sup>1</sup>H NMR measurements at selected concentrations, calculated with  $\beta$ -values from the data of the down-field shift of the host under conditions of fixed host and varying guest concentrations.

The CIS<sub>a</sub>-values were obtained from <sup>1</sup>H NMR measurements at pH = 11 for **2**, pH = 12 for **3** and **4** at guest and host concentrations being 0.0025 M<sup>-1</sup> and 0.005 M<sup>-1</sup>, calculated with  $\beta$ -values from pH-metric titration data. The <sup>1</sup>H NMR data in alkaline media do not indicate the hydrolysis of complexes **1** and **2**.

\*The width of <sup>1</sup>H NMR signals prevents the accurate evaluation of the CIS<sub>a</sub>-values.



the cavity of [H<sub>8</sub>X]Na<sub>4</sub>. According to [2] complexation of watersoluble calixarenes with alkylammonium cations results in the decrease of the pK-values of phenolic protons. Thus the pH-metric titration method can be used for the evaluation of binding constants between guest-cations and deprotonated forms of [H<sub>8</sub>X]Na<sub>4</sub>. The log  $\beta$ -values increase on going from [H<sub>8</sub>X]<sup>4-</sup> to [H<sub>4</sub>X]<sup>8-</sup> (Table 1), with the log  $\beta$  increase ( $\Delta \log \beta$  in Table 1) being rather different for cations **1**–**4**. The deprotonation of the host's rim leads to the appearance of the additional charge on the rim and the increase of the  $\pi$ -donating capacity of the cavity, which in turn is the reason for an increase of a CIS-value [4]. The symmetrical charge distribution of **4** is the reason for the increase of the log  $\beta$ -value with the host's deprotonation due to more efficient cation- $\pi$  and cation-negatively charged rim interactions. Thus the significant (by three log-units) increase of the log  $\beta$ -value is accompanied by the increase of its CIS-value (Table 1). The same  $\Delta \log \beta$  value and the increase of the CIS-value from 0.6 to 0.68 ppm were found in the case of guest **2** on going from [H<sub>8</sub>X]<sup>4-</sup> to [H<sub>4</sub>X]<sup>8-</sup>. So, the oxalate anion in the inner-sphere of **2**, being negatively charged (Figure 1), does not affect the  $\Delta \log \beta$  value. Thus the oxalate-anion should be oriented out of the negatively charged host rim to prevent the electrostatic repulsion effect on the  $\Delta \log \beta$ -value. Such an orientation of the oxalate-anion occurs, when the binding of **2** proceeds *via* both having positive charge density (Figure 2) ethylenediamines due to the scheme, presented in Figure 1. Cation **1** also becomes bound more tightly on going from [H<sub>8</sub>X]<sup>4-</sup> to [H<sub>4</sub>X]<sup>8-</sup> with the  $\Delta \log \beta$ -value being the largest for cations **1**–**4**. This in turn indicates that histidinate moieties of guest **1**, having positive charge density (Figure 2), are slightly encapsulated into the cavity, preferably interacting with the negatively charged rim. So, the deprotonation of the rim thus results in the tightest binding of **1**

due to efficient cation-charged rim interactions and the lack of electrostatic repulsion between carboxylic oxygens and the negatively charged rim, which is in accordance with the lack of inclusion of the histidinate moiety. The log  $\beta$ -value of **3** also increases on going from [H<sub>8</sub>X]<sup>4-</sup> to [H<sub>4</sub>X]<sup>8-</sup>, but this increase is the least for cations **1**–**4**, whilst the CIS-value decreases (Table 1). So it is natural to propose that the main reason for the inclusion becoming less deep with the deprotonation from [H<sub>8</sub>X]<sup>4-</sup> to [H<sub>4</sub>X]<sup>8-</sup> is the electrostatic repulsion between negatively charged ether oxygens of **3** (Figure 1) and the deprotonated rim. The  $\Delta \log \beta$ -value being the smallest within **1**–**4** is also in accordance with this proposal.

## Conclusions

The outer-sphere coordination of complexes **1**–**3** by tetra-sulfonated calix[4]resorcinarene in water is driven by the interaction of positively charged hydrophobic fragments of the guests with both the negatively charged rim and the hydrophobic cavity as a  $\pi$ -base. The binding constants decrease in the order: **1** = **4** > **3** > **2**. The mode of inclusion is rather different for complexes **1**–**3**. The observation of a single <sup>1</sup>H NMR resonance for the complexes with guests **2**–**4** suggest that their hydrophobic fragments are rapidly rotating while forming according to Aoyama [4] CH- $\pi$  hydrogen bonds with benzene rings of the host. The <sup>1</sup>H NMR complexation induced shift data of guest **1** suggest that the main driving force of its coordination is the interaction with the charged rim, which in turn results in the lack of inclusion of histidinate moieties into the host cavity. The binding constants increase on going from [H<sub>8</sub>X]<sup>4-</sup> to [H<sub>4</sub>X]<sup>8-</sup>. The increase is the largest for **1**, decreasing in the order: **1** > **2** = **4** > **3**. According to the experimentally observed CIS-

values the mode of binding does not change for cations **1**, **2** and **4** on going from  $[\text{H}_8\text{X}]^{4-}$  to  $[\text{H}_4\text{X}]^{8-}$ . The inclusion of **3** becomes less on going from  $[\text{H}_8\text{X}]^{4-}$  to  $[\text{H}_4\text{X}]^{8-}$  due to the electrostatic repulsion between the ether oxygens and the charged rim of  $[\text{H}_4\text{X}]^{8-}$ .

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