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The Inclusion Properties of a New Watersoluble Sulfonated Calix[4]resorcinarene towards Alkylammonium and *N*-Methylpyridinium Cations

ASIYA R. MUSTAFINA*, SVETLANA V. FEDORENKO, NELYA A. MAKAROVA, ELLA KH. KAZAKOVA, ZUL'FIYA G. BAZHANOVA, VLADIMIR E. KATAEV and ALEXANDER I. KONOVALOV

Kasan Scientific Centre of the Russian Academy of Sciences, A. E. Arbuzov Institute of Organic and Physical Chemistry, Arbusov Str. 8, Kasan, 420088, Russia

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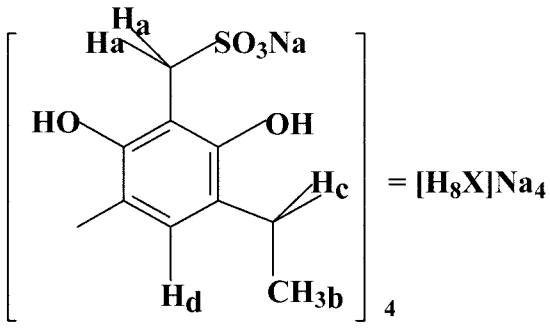
Abstract

The inclusion behaviour of a new water-soluble sulfonated calix[4]resorcinarene towards alkylammonium and *N*-methylpyridinium cations has been investigated on the basis of ^{1}H NMR spectroscopy and pH-potentiometry data. The inclusion of the *N*-methylpyridinium cation has been found to be dependent on pH with the preferable inclusion of the methyl substituent in alkaline and the aromatic ring in neutral aqueous media.

Introduction

The host–guest interactions of calixarenes in water, where most biorelevant processes take place, is a topic of current interest in supramolecular chemistry [1]. The synthesis of sulfonated derivatives of calixarenes or resorcinarenes is a widely used design of water soluble synthetic receptors [2–8].

Recently the synthesis of a new tetrasulfonated derivative of calix[4]resorcinarene ($[H_8X]Na_4$) was reported (Scheme (1)) [9]. This prompted us to investigate the inclusion of organic cations **1**–**4** (Figure 1) by $[H_8X]Na_4$ in neutral and alkaline aqueous solutions. The water soluble resorcinarene synthesized by Aoyama [6] was estimated to prefer guests with hydrophobic moieties. But according to his later article [10] the complexation of water soluble resorcinarene with DMSO and acetone molecules is driven by favorable enthalpy and unfavorable entropy changes as the result of enthalpy-entropy compensation. So, the affinity of the water-soluble resorcinarene to hydrophobic guests is not the result of the so-called hydrophobic effect, but the result of efficient CH-π host–guest interactions. The complexing properties of $[H_8X]Na_4$ having methylensulfonate moieties on the lower rim, might differ from those synthesized by Aoyama, because of the ability of $[H_8X]Na_4$ to interact with guests via both its cavity and methylensulfonate groups. Selectivity in the series of guests having the same charge but various hydrophobicity is one of the necessary conditions for molecular recognition of biorelevant guests. So, the organic cations



Scheme 1.

1–**4** were chosen as the guests for $[H_8X]Na_4$ owing to their similar molecular charge and varying hydrophobicity.

Experimental

The host $[H_8X]Na_4$ was synthesized as reported [9]. The commercial samples of $N(CH_3)_4Br$, $N(C_2H_5)_4I$ and $N(C_4H_9)_4I$ were purified by recrystalization from methanol. $CH_3NC_5H_5I$ was synthesized as reported [11].

The 250.13-MHz ^{1}H NMR spectra in unbuffered D_2O 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 $[H_8X]Na_4$ deprotonation and complexation constants 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. CO_2 free NaOH solution ($C = 2 \times 10^{-2}$ mol dm^{-3}) was used as titrant. The pH-meter was calibrated by

* Author for correspondence: e-mail: Asiya@iopc.knc.ru

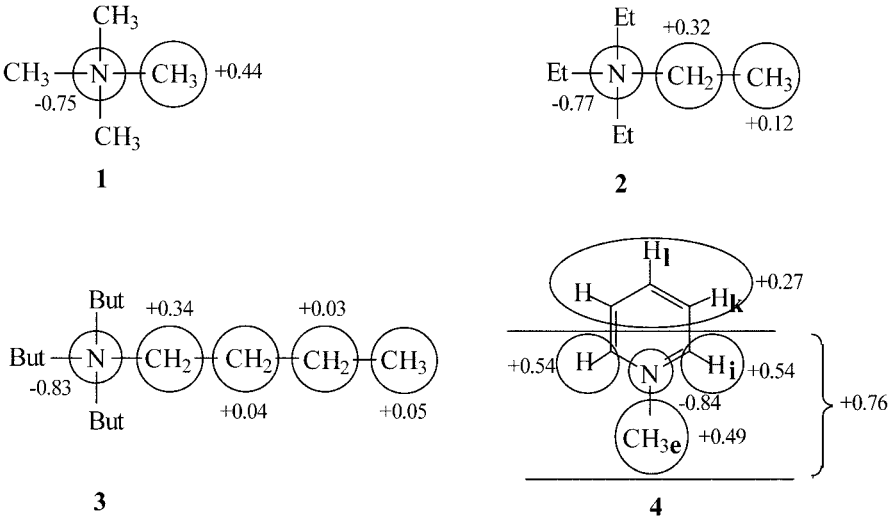


Figure 1. Charge distribution of **1**–**4**.

a series of buffer solutions. The pH-titration was recorded in the range of pH 6-11 with the $[H_8X]Na_4$ concentration being 2×10^{-3} mol dm^{-3} and [host]:[guest] =1:1. The 30–40 experimental points were mathematically treated to calculate both deprotonation and complexation constants from emf data by means of the CPESSP computer programme [12].

The *ab initio* calculations were carried out at the RHF/6-31G level [13].

Results and discussion

The acidity of $[H_8X]Na_4$ in water was investigated by pH-metric titration and subsequent mathematical treatment of the obtained data. According to the pH-metric data $[H_8X]Na_4$ dissociates stepwise up to the octaanion $[H_4X]^{8-}$ with pK-values of 9.0 ± 0.08; 9.3 ± 0.1; 10.8 ± 0.3; 10.6 ± 0.1 in the range of pH 6-11. According to the literature data [13], **1**–**4** should be complexed by $[H_8X]Na_4$ according to equilibrium (1):

$$p[H_{8-n}X]^{(4+n)-} + k[Cat]^+ \leftrightarrow [H_{8-n}X]_p^{(4+n)-}[Cat]_k^+, \quad (1)$$

where p and k are the moles of host and guest and n is the mole of the protons deprotonated, $p = k = 1$ and n can vary from 0 to 4. Later on the complex $[H_{8-n}X]_p^{(4+n)-}[Cat]_k^+$ will be written as $11n$. Due to the presence of sulfonatomethyl groups the binding of **1**–**4** would be expected to take place in neutral media, where deprotonation of $[H_8X]Na_4$ does not occur. In fact the observed shift is upfield for the guest and downfield for the host upon mixing $[H_8X]Na_4$ with **1**, **2**, and **4** in neutral media. The observed downfield shifts of the host (H_d) (Figure 2) under conditions of fixed host and varying guest concentrations were treated by the Benesi–Hildebrand analysis [6] to evaluate the binding constants (Table 1). The relationship of the log β-values in the series of alkylammonium cations obtained was similar with those for binding of **1**–**3** by the tetraanion of nonsubstituted calix[4]resorcinarene ($[H_4L]^{4-}$) in water-dimethylformamide alkaline media [14]. The decrease of binding constants on going from **1** to **2** and **3** is accompanied by the decrease of the complexation-induced shift (CIS, negative value indicates an upfield shift) of proton resonances of guests at saturation binding to $[H_8X]Na_4$ (Table 2). According to the charge distribution of **1**–**3** obtained on the basis of *ab initio* calculations, the increase of the R size in the

Table 1. Binding constants of the complexation of $H_{8-n}X^{(4+n)-}$ (n = 0–4) with **1**–**4**, obtained by NMR ^{1}H spectroscopy (110) and pH-metric titration ($11n$, n = 1–4) methods

Species pkn	Guest	$pK_{11n} \pm \delta$	$\log \beta_{11n} \pm \delta$
110	**1**		2.43 ± 0.05
	2		2.11 ± 0.14
	3		*
	4		2.69 ± 0.10
111	**1**	4.45 ± 0.06	4.55 ± 0.06
	2	4.78 ± 0.08	4.22 ± 0.08
	3	9.00 ± 0.08	*
	4	4.60 ± 0.06	4.40 ± 0.06
112	**1**	4.10 ± 0.05	5.20 ± 0.05
	2	4.59 ± 0.15	4.71 ± 0.15
	3	9.30 ± 0.10	*
	4	4.19 ± 0.09	5.11 ± 0.09
113	**1**	5.85 ± 0.20	4.95 ± 0.20
	2	5.91 ± 0.60	4.89 ± 0.60
	3	10.8 ± 0.30	*
	4	10.8 ± 0.30	*
114	**1**	5.13 ± 0.10	5.47 ± 0.10
	2	5.63 ± 0.13	4.97 ± 0.13
	3	10.6 ± 0.10	*
	4	5.57 ± 0.15	5.03 ± 0.15

*The binding constant is too small for correct evaluation, δ is the standard deviation.

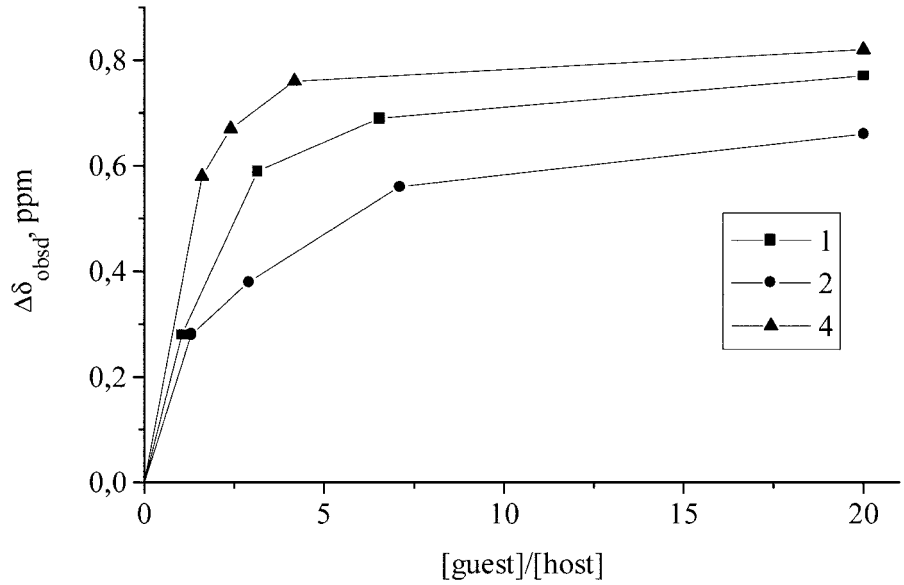


Figure 2. The plots of $\Delta\delta_{obs}$ (ppm) of the H_d proton of $[H_8X]Na_4$ versus [guest]/[host] with [host] = 5×10^{-3} mol dm^{-3}.

Table 2. CIS-values of the guests **1**–**4** in complexes 110 and 114

Guest	**1**	**2**		**3**				**4**			
	CH_3	CH_2	CH_3	CH_2	CH_2	CH_2	CH_3	CH_3	CH	CH	CH
CIS (110)	−1.28	−0.76	−0.90	<0.04	<0.04	<0.04	<0.04	−1.28	−2.18	−2.57	−2.82
CIS (114)	−1.64	−1.14	−1.33	*	*	*	*	−2.27	−2.30	−1.64	−1.67

*CIS-values were not obtained.

series NR_4^+ (R = Me, Et, *n*-Bu) results in the decrease of the positive charge on the terminal CH_3 group, just as the most positively charged CH_2-group is the one next to nitrogen (Figure 1). So, taking into account both the charge distribution and the CIS data, the decrease of binding constants in the series **1** < **2** < **3** could be proposed to be the result of their less efficient electrostatic and hydrophobic (CH-π) interactions with $[H_8X]^{4-}$. The log β-values indicate the most tight binding of **4** (Table 1). The CIS-value (the numeration of the protons of **4** is in Figure 1) is the most for proton *l*, less for *k* and *i* and the least of all for *e* (Table 2), indicating that the inclusion of the aromatic fragment is more preferred in neutral media (structure (I)). According to Aoyama [6] guest **4** behaves as either a σ- or π-acid in the case of methyl or aromatic moiety inclusion, whilst the host behaves as a π-base. The affinity of $[H_8X]Na_4$ to the aromatic fragment of **4** indicates that guest–host π–π interactions are more efficient than CH-π interactions in neutral media, resulting in guest **4** being the most preferred for $[H_8X]Na_4$. According to Arena [8] the preferred inclusion of the aromatic portion of the trimethylanilinium cation (TMA) occurs in the case of the cone structure, whilst there is no selectivity in the case of partial cone tetrasulfonatocalix[4]arene. The change of selectivity on going from cone to partial cone calixarene also can be proposed to indicate the importance of π–π interactions in the preferred inclusion of the aromatic moiety of TMA.

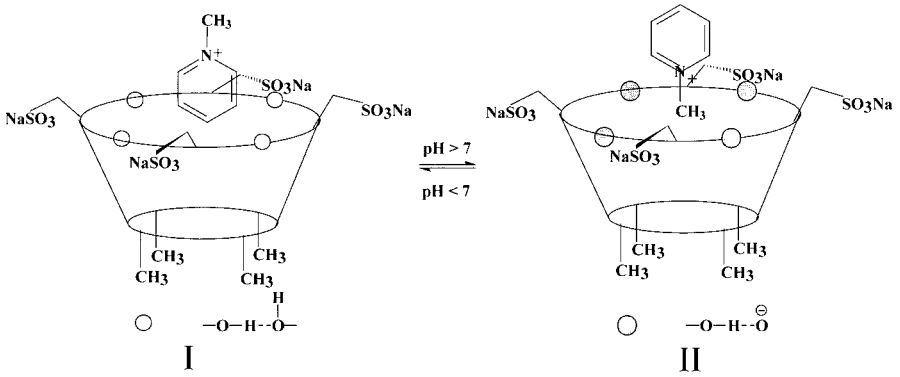
Mathematical treatment of the pH-metric titration data of both $[H_8X]Na_4$ and $[H_8X]Na_4$ in the presence of **1**–**4** was carried out, taking into account the effect of complexes 110 on the equilibrium concentration of $[H_8X]^{4-}$. According to the K_{11n}-values, being the constants of equilibrium (2), it is evident that all guests with the exception of **3** promote the step-wise deprotonation of $[H_8X]Na_4$ due to their complexation with its deprotonated forms (Table 1).

$$[H_{(8-n+1)}X] + [Cat] \leftrightarrow [H_{8-n}X][Cat] + H, \qquad (2)$$

where charges are omitted for clarity. The β-values of equilibrium (1) ($n = 1 - 4$) reported in Table 1 were calculated using Equation (3).

$$\log \beta_{11n} = pK_n - pK_{11n}, \qquad (3)$$

where K_n is the constant of the step-wise deprotonation of $[H_8X]^{4-}$. The deprotonation of the host leads to the increase of the log β-values. The observed increase is nearly two log-units on going from 110 to 111 (Table 1). Upon the deprotonation from 111 to 112 the log β-value increases by 0.6 log-units, while the log β-values of complexes 113 and 114 do not appear to be sufficiently affected by further host deprotonation (Table 1). $[H_7X]^{5-}$ binds **4** with a log β-value being very close to that for **1**, just as $[H_4X]^{8-}$ binds **1** more efficiently than **4** (Table 1). The CIS-values of proton resonances of the guests were obtained in alkaline media, at pH $\approx$ 12, where the host is deprotonated up to $[H_4X]^{8-}$. The increase of the CIS-values of **1** and **2** in alkaline media is the result of the increase of the π-basicity of the host cavity on going from $[H_8X]^{4-}$ to $[H_4X]^{8-}$ (Table 2). But cation **4**



Scheme 2.

is a special case, because its CIS-values are the greatest for protons *e* and *i* and least for *k* and *l*, indicating that the inclusion of the CH_3-moiety of **4** (structure (**II**)) is preferred in alkaline media.

The inclusion of **4** from the CH_3-moiety is in accordance with the charge distribution of **4** (Figure 1). The C_2H_2N–CH_3 fragment being more positively charged than the rest of the molecule may be proposed to ensure more effective electrostatic binding with the negatively charged rim of $[H_4X]^{8-}$. As mentioned above the deprotonation of $[H_8X]^{4-}$ up to $[H_4X]^{8-}$ results in the increase of the log β-values for **1**–**4**, but guest **4** is less preferred than **1** by $[H_4X]^{8-}$ (Table 2). Structures **I** and **II** are very similar to the two binding forms of tetrasulfonated calix[4]arene with the trimethylanilinium cation [2]. The inclusion of the guest from the benzene ring occurs when phenolic groups of the host are not dissociated and from the ammonium moiety when one of the phenolic hydroxy groups is dissociated. The change of binding form is the result of the cation-π interactions becoming more efficient due to the increase of the basicity of the calix[4]arene cavity. In the case of $[H_8X]Na_4$ with sulfonato-groups inserted at the same rim as the phenolic hydroxy-groups the change of the binding form of **4** on deprotonation of the phenolic rim is driven by both the increase of the basicity of the host cavity and the appearance of the additional charge on the rim.

Conclusions

The sulfonatomethylated calix[4]resorcinarene exists in the form of $[H_8X]^{4-}$ in neutral media, undergoing step-wise deprotonation up to $[H_4X]^{8-}$ on going to alkaline media. $[H_8X]Na_4$ is a more efficient host than the non-substituted one being able to bind tetralkylammonium and *N*-methylpyridinium cations even in neutral media. According to the CIS and log β-values the inclusion of symmetrical teralkylammonium cations becomes deeper and the binding tighter on going from $N(nBu)_4^+$ to $N(Et)_4^+$ and $N(Me)_4^+$ both in neutral and alkaline media. The inclusion of the non-symmetrical *N*-methylpyridinium depends on the pH. In neutral media $[H_8X]^{4-}$ binds *N*-methylpyridinium more tightly than alkylammonium cations due to the aromatic moiety of **4** being preferably encapsulated into the host cavity and the π-π being more efficient than CH-π host-guest interactions. The deprotonation of $[H_8X]^{4-}$ up to $[H_4X]^{8-}$ results in guest **1** being bound more tightly than **4** and the inclusion of the most positively charged methyl substituent of **4** becoming more preferred. So, the relationship between hydrophobic and electrostatic contributions should be proposed to determine the pH-dependence of the complexing properties of the sulfonatomethylated calix[4]resorcinarene.

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