Journal of Inclusion Phenomena and Macrocyclic Chemistry (2006) 56: 369–374
DOI 10.1007/s10847-006-9118-x

pH-Driven Variation of the Outer-Sphere Binding Mode of *cis*-[Co(Ad)(en)$_2$Cl]Cl (en-Ethylendiamine, Ad-Adeninate) with *p*-Sulfonatothiacalix[4]arene

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(Received: 03 February 2006; Accepted in final form: 20 April 2006)

Key words: Co (III) bis-ethylendiaminate-adeninate, inclusion complex, NMR ^{1}H spectroscopy, outer-sphere coordination, *p*-Sulfonatothiacalix[4]arene

Abstract

The non-symmetrical cobalt (III) complex *cis*-[Co(Ad)(en)$_2$Cl]Cl (**1Cl**), possessing two flexible ethylendiaminate chelate rings (en) and monodentate N(9)-bound adeninate (Ad$^-$) was chosen as the guest of *p*-sulfonatothiacalix[4]arene (**STCA**) to study the inclusion complex formation at wide range of pH 2–10. It was shown by ^{1}H, NOE NMR methods and pH-metric procedure, that pH-driven variation of the inclusion mode of $\mathbf{1}^+$ into calixarene cavity is the result of the protonation of $\mathbf{1}^+$ via adeninate moiety.

Introduction

The design of various *molecular devices* is a top of current interest during recent decades [1]. Transition metal complexes are of particular importance from this point of view [2–13]. Metal ion complexes are known to underlay the development of molecular scale machines [2–4], logic gates [5, 6], devices for memory storage [7], switches [8], wires [9–12] and sensors [13]. A pH-dependent metal ion coordination [14, 15] or a change of coordination polyhedron as a result of potential change [2–4] are well-known examples of a molecular movement. The development of such systems requires macrocyclic compounds with appropriately preorganized donor groups to provide switchable inner-sphere coordination of metal ion. An outer-sphere coordination of transition metal ions by macrocycles is also known to underlay the design of switchable systems. For example redox driven switching of inclusion complex formation was applied to produce molecular movement [16]. The pH-driven outer-sphere coordination of anionic complex of Fe(III) into polyammonium macrocyclic receptor may be viewed as pH-controlled on/off switch [17]. The inclusion of ferrocene and cobaltocene into *p*-sulfonatocalix[6]arene cavity is also known to result in some redox changes, which can be detected by conventional electrochemistry [18–20]. We have recently found out that some tris-chelates of cobalt (III) form inclusion complexes with *p*-sulfonatothiacalix[4]arene [21, 22]. The inclusion of flexible ethylendiamine chelate rings of cobalt (III) tris-ethylendiaminate and bis-ethylendiaminato-oxalate complexes into the cavity of *p*-sulfonatothiacalix[4]arene results in definite spectral changes of cobalt complexes due to conformational shift of ethylendiaminate ring [21]. Tris-dipyridyl of cobalt (III) was also found to form inclusion type complex with *p*-sulfonatothiacalix[4]arene, which results in detectable changes of redox properties of the former [22]. Thus it seems rather promising to develop inclusion complex formation between *p*-sulfonatothiacalix[4]arene and non-symmetrical cobalt (III) complex, where an inclusion mode of cobalt complex can be changed by a varying of external conditions. The non-symmetrical cobalt (III) complex *cis*-[Co(Ad)(en)$_2$Cl]Cl (**1Cl**), possessing two flexible ethylendiaminate chelate rings (en) and monodentate N(9)-bound adeninate (Ad$^-$) (Figure 1a) with two basic nitrogens (N(7) and N(1)), able to two-step protonation with pK_1 = 6.03 and pK_2 = 2.53 accordingly [23], was chosen as the guest of *p*-sulfonatothiacalix[4]arene (**STCA**) (Figure 1b). The choice of the latter instead of its classical analogue is conditioned by the solubility in aqueous solutions of inclusion complexes with charged cobalt (III) complexes being more for thia-derivative. So, the main goal of the work presented is to study the inclusion complex formation between **1Cl** and **STCA** at the wide range of pH 2–10.

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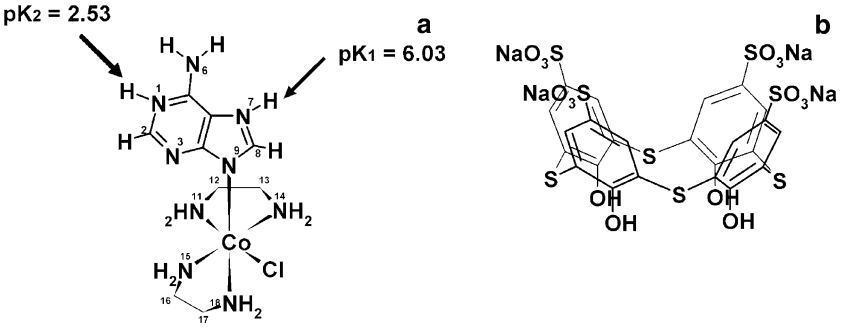

Figure 1. The structures of *cis*-[Co(Ad)(en)$_2$Cl]Cl (a) and *p*-sulfonatothiacalix[4]arene (b).

Experimental

STCA and *cis*-[Co(Ad)(en)$_2$Cl]Cl were synthesized by literature methods [23, 24].

The ^{1}H-NMR spectra were recorded on a Bruker MSL 400 and Bruker Avance 600 spectrometers in buffer solutions at pH = 9.15 ($Na_4B_4O_7$, $c = 2 \times 10^{-2}$ M), at pH 4.8 (KH_2PO_4 $c = 6.6 \times 10^{-2}$ M) in D_2O at 293 °K. The chemical shifts were referred to the signals for the residual protons of the deuterated solvent D_2O ($\delta_H = 4.86$ at 293 °K). To measure NOE's 1D DPFG-NOE [25] method was used with a Hermite-shaped pulses for selective excitation. The ^{1}H-NMR-titration was carried out by the addition of the certain aliquots of **STCA** solutions to solution of **1Cl** with concentration of **1Cl** varying from 3×10^{-3} to 1.5×10^{-3} M and concentrations of **STCA**—from 5×10^{-4} to 1×10^{-2} M. The logβ-values were deduced by means of well-known Benesi–Hildebrandt procedure [26].

The pH-metric measurements were carried out in a thermostatically controlled cell at 25 ± 0.1 °C by use an "I-130 Ionomer" meter with the error being less than 0.05 pH-units. HCl (1×10^{-2} M) solution was used as the titrand. The pH-meter was calibrated by a series of buffer solutions. To evaluate the effect of **STCA** on protonation of $\mathbf{1}^+$ the pH-titration of **1Cl** and **1Cl** in the presence of **STCA** in **1Cl**:**STCA** concentration ratio being 1:1.5 were recorded in the range of pH 2.5–9 with the **1Cl** concentration being 2×10^{-3} M. No extra salts were added in pH-measurements to maintain definite value of ionic strength in order to avoid undesirable association equilibriums. The calculation of the experimentally observed Bierrum function values ($\tilde{n}_{exp}$) from the pH-metric data, (Eq. 1) and their theoretical analogies according to the law of mass action ($\tilde{n}_{calc}$) was performed by CPESSP computer program (short description and examples of computations are presented in [27]). All pH-metric measurements have been performed twice.

$$\tilde{n}_{exp} = 2 - \left[\frac{V_{HCl} \cdot C_{HCl}}{V_0 + V_{HCl}} - 10^{-pH} \Big/ \frac{C_0 \cdot V_0}{V_0 + V_{HCl}} \right] \quad (1)$$

where V_0 and C_0 are initial volume and concentration of the titrate, V_{HCl} and C_{HCl} are the volume and concentration of HCl added.

Results and discussion

According to literature data [23] complex **1Cl** predominantly exists in aqueous solutions in the form of $\mathbf{1}^+$ at pH > 8 (Figure 2). The decrease of pH up to 4.0–4.5 results in the predominance of its monoprotonated form $[\mathbf{1}H]^{2+}$, while at pH < 3 the diprotonated form $[\mathbf{1}(H)_2]^{3+}$ becomes predominant (Figure 2). The ^{1}H-NMR spectrum of **1Cl** in aqueous buffer solution at pH 9.15 possesses two signals of adeninate moiety (C(8)H and C(2)H) and six signals of methylene protons of two ethylenediamine chelate rings, which indicates their non-equivalency (Figure 3a). According to literature data [23] the down-field shift being more pronounced for C(8)H under first step protonation indicates that the first proton added to $\mathbf{1}^+$ resides at N(7), correspondingly the second one—at N(1).

Finally, exact assignment of ethylendiamine protons of **1Cl** at pH 9.15 have been carried out with help of 2D COSY and NOE data[1]. Namely, there are non-trivial NOE's between C2H and some of methylene protons (Figure 3b), which therefore can be assigned to C(12)H$_2$ or C(16)H$_2$.

Taking into account sensitivity of ^{1}H-NMR chemical shifts to host–guest complex formation, this method was chosen to reveal both structural and thermodynamic features of interaction between **1Cl** and **STCA** at a wide pH range in aqueous solutions. According to the distribution presented at Figure 2, pH 9.15 is suitable medium to reveal the probable interaction between $\mathbf{1}^+$ and **STCA**. The ^{1}H-NMR titration data of $\mathbf{1}^+$ by **STCA** reveals that the increase of **STCA** concentration results only in slight up-field shifts of C(8)H and C(2)H (0.08 and 0.05 ppm, respectively), while methylene protons of ethylendiamine ligands demonstrate pronounced high field effects (Table 1). At the same time there are the NOE's between the aromatic protons of **STCA** and C(8)H/C(2)H protons of $\mathbf{1}^+$ in their aqueous solution with the concentration ratio $\mathbf{1}^+$:**STCA** = 1:2 at pH 9.15 (Figure 4). Thus though there are only very few indication on chemical shifts C(8)H and C(2)H of Ad^- protons of their close proximity to aromatic system of **STCA**, the observed NOE's

[1] 2D COSY ^{1}H-NMR spectra of [Co(Ad)(en)$_2$Cl]Cl in D_2O at pH 9.15.

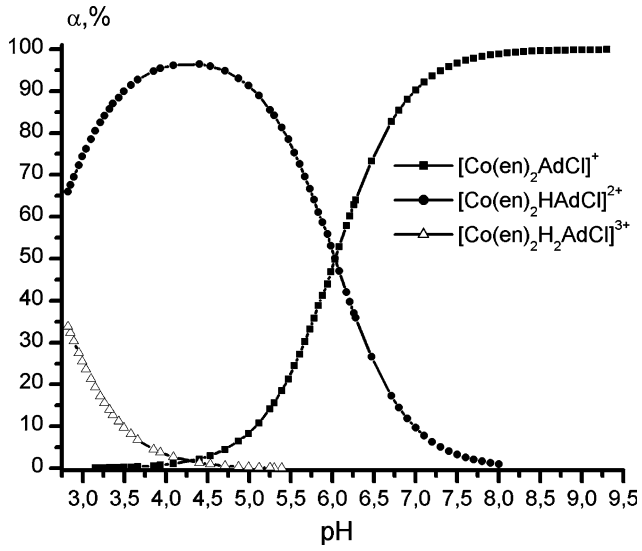

Figure 2. The distribution of $[Co(Ad)(en)_2Cl]^+$, $[Co(Ad)(en)_2Cl(H)]^{2+}$ and $[Co(Ad)(en)_2Cl(H)_2]^{3+}$ vs. pH.

strongly supports such conclusion. The structure shown on Figure 5a illustrates the most possible orientation of adeninate fragment of $\mathbf{1}^+$ over **STCA** cavity, which is in accordance with these NMR observations.

An accurate evaluation of the binding constant for $\mathbf{1}^+$ requires accurate evaluation of complexation induced shift values (CIS-values). Though the CIS-values are most pronounced for methylene protons signals, their overlapping restricts the evaluation of CIS-values for each methylene proton. Thus the accurate CIS-value was obtained only for the signal at 2.14 ppm, which was assigned to $C(12)H_2$ or $C(16)H_2$ methylene proton. The logβ-value (β is stability constant of complex shown in Figure 5a), calculated from the up-field shift of this

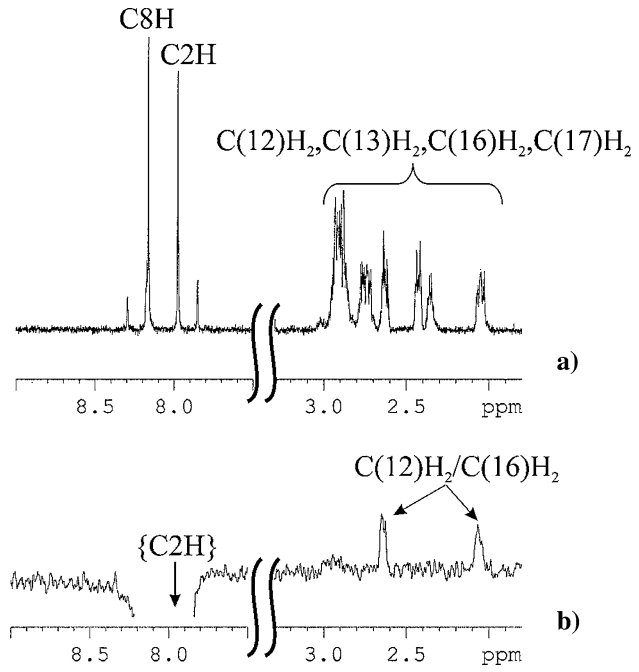

Figure 3. NMR ^{1}H-spectrum of $[Co(Ad)(en)_2Cl]Cl$ at pH = 9.15 (a); 1D NOESY NMR ^{1}H-spectrum $[Co(Ad)(en)_2Cl]Cl$ at pH = 9.15 (b) in D_2O.

Table 1. The values of chemical shifts (δ) of $[Co(Ad)(en)_2Cl]Cl$ protons with *p*-sulfonatothiacalix[4]arene concentration increase and corresponding CIS-values at various pH

PH	$\frac{C_{STCA}}{C_{guest}}$	δC(8)H	δC(2)H	δCH_2
9.15	0	8.29	8.28	2.14
	0.05	8.26	8.23	2.08
	1.04	8.25	8.22	1.98
	1.56	8.25	8.21	1.96
	2.08	8.24	8.2	1.94
	3.13	8.24	8.2	1.93
		CIS		
		0.05	0.08	0.21
4.8	0	8.66	8.41	2.23
	0.05	8.62	8.17	1.44
	1.04	8.59	7.98	1.44
	1.56	8.58	7.92	1.44
		CIS		
		0.07	0.49	0.79
3.26	0	8.85	8.5	
	3	8.64	7.97	
		$\Delta\delta$		
		0.21	0.53	

signal, is 3.6 log units ($\pm$0.2), which is much less than the efficiency of $[Co(en)_3]^{3+}$ binding with **STCA** (logβ > 7), but close to that of $[Co(en)_2ox]^+$ (logβ = 4.0 $\pm$ 0.2) [21]. Comparing the binding constants, one should take into account that binding constants for $[Co(en)_3]^{3+}$ and $[Co(en)_2ox]^+$ were evaluated at pH range 5.5–6.0, where **STCA** exists in the form of penta-anion with four sulfonates on the upper and one deprotonated phenolic group on the lower rim, while **STCA** predominantly occurs in the form of hexa-anion at pH 9.15 (pK_2 = 8.48) [28].

The pH-metric titration of **1Cl** and **1Cl** in the presence of **STCA** reveals (Figure 6) that $\tilde{n}_{exp}$ vs. pH curve lies under $\tilde{n}_{calc}$ vs. pH. The definition of $\tilde{n}_{exp}$ is given in the Experimental section, while $\tilde{n}_{calc}$ is its theoretical analogy calculated from the law of mass action in assumption that protonation of **1Cl** is not affected by **STCA** and vice versa. Though the deviation between $\tilde{n}_{exp}$ and $\tilde{n}_{calc}$ is not pronounced, it indicates some stabilization of the protonated forms $[\mathbf{1}H]^{2+}$ and $[\mathbf{1}(H)_2]^{3+}$ in the presence of **STCA**. The ^{1}H-NMR titration data at pH 4.8, where cobalt complex is $[\mathbf{1}H]^{2+}$ differ sufficiently from those for $\mathbf{1}^+$ at pH 9.15 (Table 1). The increase of **STCA** concentration up to 1.5-fold excess leads to much more pronounced up-field shift of signals of both adeninate C(2)H proton (CIS C(2)H = 0.49) and ethylendiamine protons (CIS = 0.79). The appearance of the additional charge results in more deep inclusion of $[\mathbf{1}H]^{2+}$ than $\mathbf{1}^+$ through its ethylendiamine ring and in the rotation of complex included within the cavity of **STCA**, resulting in the more pronounced inclusion of AdH moiety. The structure shown on Figure 5b illustrates the most possible orientation of **STCA** and $[\mathbf{1}H]^{2+}$. The logβ-value obtained by mathematical treatment of the up-field shifts of C(2)H proton reveals that the binding with **STCA** becomes more efficient

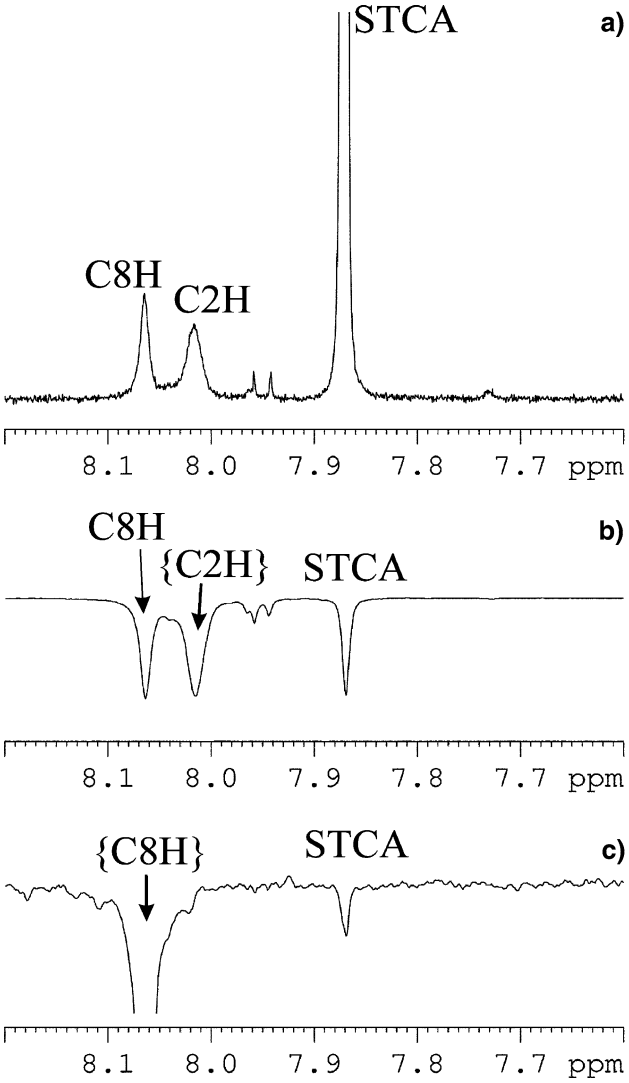

Figure 4. NMR ^{1}H-spectrum of mixture of $[Co(Ad)(en)_2Cl]Cl$ and *p*-sulfonatothiacalix[4]arene (1:2) (a), 1D NOESY NMR ^{1}H-spectra of mixture of $[Co(Ad)(en)_2Cl]Cl$ and *p*-sulfonatothiacalix[4]arene (1:2) (b), (c) at pH 9.15 in D_2O.

on going from $\mathbf{1}^+$ to $[\mathbf{1}H]^{2+}$ (3.6 (0.2 and 4.3 (0.2 correspondingly), which is in accordance with pH-metric data. Comparing those logβ-values, one should take into account that as pH changes from 9.15 to 4.8, penta-anion of **STCA** becomes predominant instead of hexa-anion. That is why the enhancement of the electrostatic interactions efficiency, caused by the increase of the positive charge on going from $\mathbf{1}^+$ to $[\mathbf{1}H]^{2+}$ can be for some extent restricted by the decrease of π-donor capacity of the cavity due to the protonation of the lower rim of **STCA** (Figure 5b).

The precipitation of complex between $[\mathbf{1}(H)_2]^{3+}$ and **STCA** restricts similar NMR ^{1}H titration at pH < 4. That is why only few measurements have been done to evaluate the binding mode at acidic media. In particular NMR ^{1}H data obtained at pH 3.26 indicate that the inclusion via $Ad(H)_2^+$ fragment becomes predominant (Table 1), but the accurate evaluation of CIS-values is not possible. It seams to be very probable that the deviation between $\tilde{n}_{exp}$ and $\tilde{n}_{calc}$ becoming larger at pH < 3 (Figure 6), is caused by an additional stabilization of $[\mathbf{1}(H)_2]^{3+}$ through the complex formation with **STCA**. Taking into account that the experimental error of pH measurements is within 0.05 pH units, the accurate evaluation of the deviation between $\tilde{n}_{exp}$ and $\tilde{n}_{calc}$ at pH < 2.7 requires the use of more concentrated solutions of $[\mathbf{1}(H)_2]^{3+}$ and **STCA** ($c > 10^{-2}$ M). The performance of the accurate pH measurements is also restricted by precipitation of complex between $[\mathbf{1}(H)_2]^{3+}$ and **STCA**.

Summary

According to NMR (^{1}H and NOE) at pH 9.15 there is the outer-sphere association of the $[Co(Ad)(en)_2Cl]^+$ and *p*-sulfonatothiacalix[4]arene hexa-anion (logβ = 3.6), which is not inclusion type with Ad^- fragment of $[Co(Ad)(en)_2Cl]^+$ lying over the rim of *p*-sulfonatothiacalix[4]arene. The pH-driven protonation of $[Co(Ad)(en)_2Cl]^+$ via Ad^- results in more tight outer-sphere association with *p*-sulfonatothiacalix[4]arene penta-anion (logβ = 4.3) with AdH fragment inserted into the

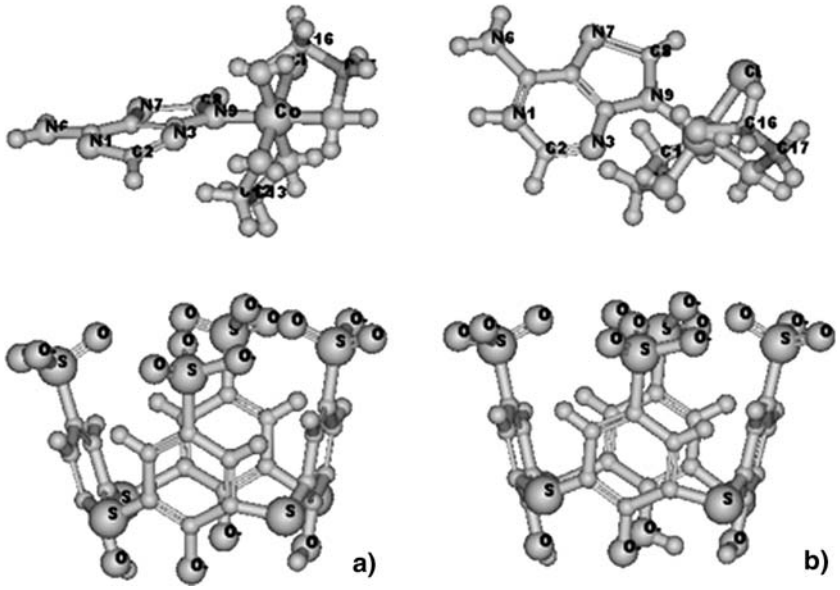

Figure 5. The modes of the outer-sphere association between $[Co(Ad)(en)_2Cl]^{+}$ and *p*-sulfonatothiacalix[4]arene at pH 9.15 (a) and $[Co(Ad)(en)_2Cl(H)]^{2+}$ and *p*-sulfonatothiacalix[4]arene at pH = 4.8 (b).

cavity of *p*-sulfonatothiacalix[4]arene. The further protonation of AdH fragment results in further enhancement of the up-field shift of its protons, but the accurate evaluation of CIS and β values at pH < 4 is restricted by the precipitation of the complex between $[Co(AdH_2)(en)_2Cl]^{3+}$ and *p*-sulfonatothiacalix[4]arene tetra-anion.

Acknowledgements

We thank RFBR (grants N 04-03-32909 and 05-03-32558) and BRHE (grants REC-007 and Y3-C-07-15) for financial support.

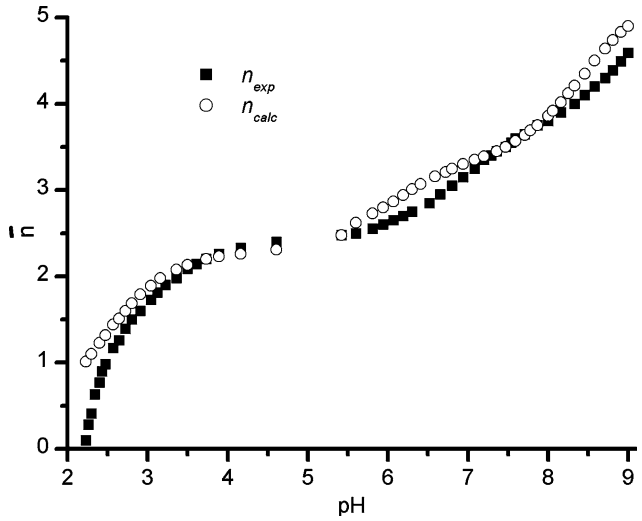

Figure 6. The dependence of experimental ($\tilde{n}_{exp}$) and calculated ($\tilde{n}_{calc}$) values of Bierrum function, derived from pH-metric data for [Co(Ad)$(en)_2$Cl]Cl in the presence of *p*-sulfonatothiacalix[4]arene (1:1.5), vs. pH.

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