

Increased Complexation Ability of Water-Soluble Calix[4]resorcinarene Octacarboxylate toward Phenol by the Assistance of Fe(II) Ions

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Complexation ability of water-soluble calix[4]resorcinarene octacarboxylate toward phenol by the assistance of Fe(II) ions was investigated in aqueous solutions by photoluminescence (PL) and quantum-chemical methods. The results show that water-soluble calix[4]resorcinarene octacarboxylate forms stable sandwich-type complexes with phenols by 1:2 stoichiometry. The Fe(II) ions boost slightly the weak interaction between the π -faces of the aromatic host and those of the guest predicted earlier in solvents which have high permittivity.

1. Introduction

Soon after the first syntheses of calixarenes, it was reported that they are capable of forming stable and selective complexes with ions and neutral molecules.^{1–3} Subsequently, efforts were made to study the factors controlling the thermodynamic and kinetic stability or selectivity of the resulting complexes.^{4–7} In our previous papers,^{8,9} the complexation behavior of calix[4]arene and 4-*tert*-butylcalix[6]arene (hosts) with neutral π -electron deficient trifluoromethyl-benzene derivatives (guests) in chloroform and dimethylformamide was reported. The results have shown the importance of π – π interactions between the phenolic rings of the calixarene host and that of the neutral guest molecule. The effects of the cavity shape^{10,11} and of the solvent permittivity¹² on the stability of the host–guest complexes in alcoholic solvents were determined by highly sensitive fluorometric measurements and quantum-chemical calculations. As it has been proved in the latter study, the use of solvents with high permittivity results in less stability of the host–guest complex. Due to the high permittivity of water compared with the alcohols, extremely weak π – π type host–guest interaction between calixarenes and aromatic guest molecules can be predicted in aqueous solvents.

However, the interactions between Fe(II) or Fe(III) ions and aromatic π -faces of biomolecules have been shown to play an important role in physiological processes.¹³ Cation– π interaction linked sandwich complexes of iron are listed among reversible electrochemical mediators used in amperometric biosensors.^{14–18} On the basis of these previous findings, the iron cation-assisted interaction of a resorcinarene derivative with phenol in water was investigated in this work.

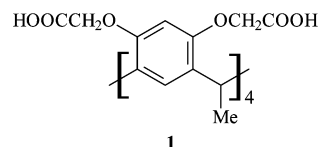


Figure 1. C-methyl-calix[4]resorcinarene octacarboxylate (**1**) investigated in this work.

2. Results and Discussion

2.1. Equilibria of the Interacted Species. Owing to their polarizability, Fe(II) and Fe(III) ions are considered quite different. The ions in lower oxidation state are softer than in higher oxidation state, so Fe(II) can be considered a softer Lewis acid than Fe(III). Octasubstituted C-methyl-calix[4]resorcinarene (**1**, Figure 1) can form both a “hard” and a “soft” ion binding site with its carboxylate arms (“hard” base) and with the aromatic rings (“soft” base), respectively.¹⁹

The acid–base titration showed that, near pH = 7, resorcinarene **1** exists in a double protonated form (ResH₂⁶⁻) and there are no other species in considerable concentration.¹⁹ Under these conditions Fe(II) ions form stable complexes with any of the aromatic rings of the resorcinarenes. Using the thermodynamic parameters, such as the enthalpy, entropy, and Gibbs free energy change of complexation determined earlier,¹⁹ the temperature dependence of the distribution of the different species formed during the complex formation of **1** with Fe(II) ions as a function of $pX = -\log [X]$ ($X = \text{Fe(II)}$) can be calculated. Figure 2 shows that, in a solution containing 10^{−4} M **1** and 10^{−3} M Fe(II) ions, resorcinarene–Fe(II) complexes are formed dominantly with 1:4 stoichiometry. This stoichiometry was only slightly affected by the temperature; more than 98% of **1** forms 1:4 complexes with Fe(II) ions while the temperature ranged from 208 K up to 303 K.

2.2. Effect of Complexation on PL Spectra. Figure 3 shows the PL spectra of resorcinarene taken at 280 nm excitation wavelength, keeping the concentrations of the resorcinarene and of the Fe(II) constant, and adding different amounts of phenol

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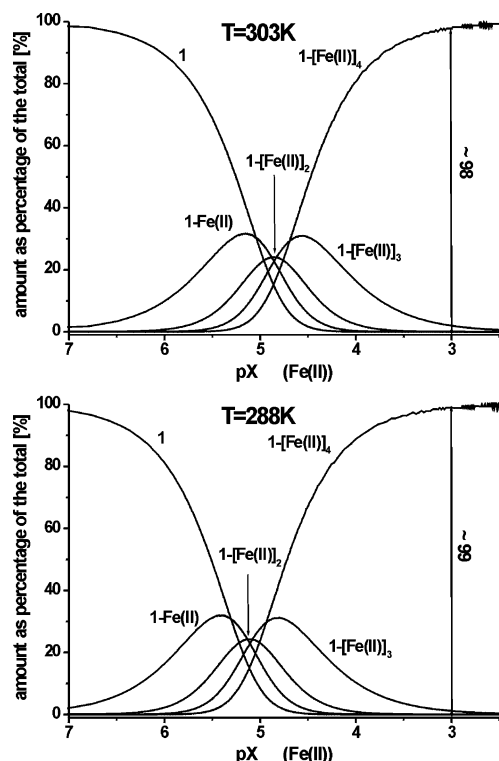


Figure 2. Distribution diagrams of the different species formed during complex formation of C-methyl-calix[4]resorcinarene derivative **1** with Fe(II) ions as a function of $p(\text{Fe(II)})$. Distribution at 303 K (top) and 288 K (bottom).

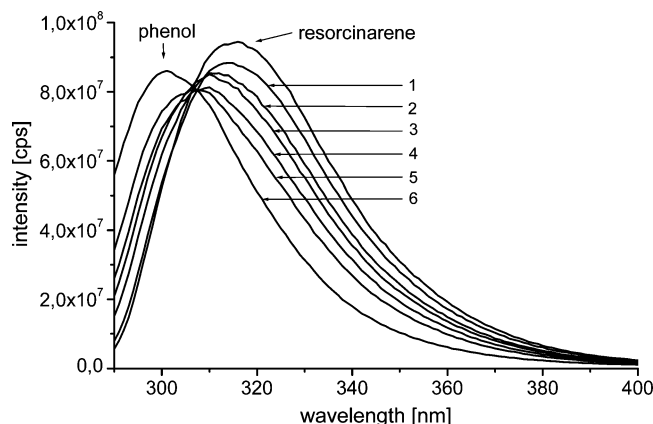


Figure 3. Variation of the PL spectra of C-methyl-calix[4]resorcinarene (**1**)-[Fe(II)]₄ complex in the presence of various amounts of phenol: 2×10^{-4} M (curve 1), 4×10^{-4} M (curve 2), 6×10^{-4} M (curve 3), 8×10^{-4} M (curve 4), 1×10^{-3} M (curve 5) phenol added at 298 K. Curve 6 shows the PL spectra of a 1×10^{-3} M aqueous solution of phenol. ($\lambda_{\text{exc}}=280$ nm).

to the solutions. The concentrations of resorcinarene and Fe(II) were set to 10^{-4} M and 10^{-3} M, respectively, and the phenol concentrations were varied from 10^{-4} to 10^{-3} M. It can be clearly seen that the intensity of resorcinarene emission decreases with the increasing concentration of phenol. A concentration dependent PL peak of the phenol also appears. All measurements were carried out stepwise in the temperature range of 15–35 °C by step size of 5 °C.

2.3. Determination of Thermodynamic Properties. In our earlier studies a combination of Job's method and the van't Hoff theory was found very useful to determine the thermodynamic parameters for inclusion complexes of several calixarenes.^{11,12,19,20} However, in the present work we should avoid the application of Job's method since the variation of the

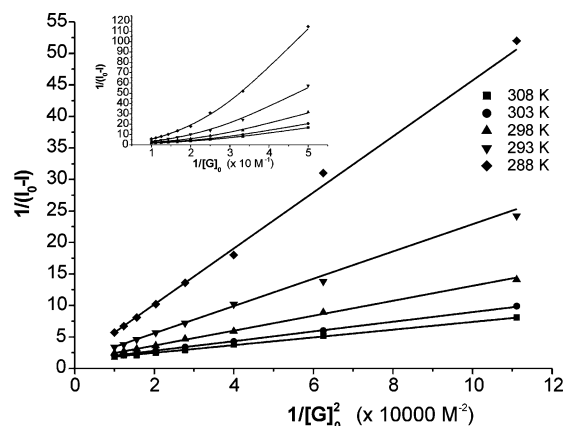


Figure 4. The Benesi–Hildebrand plot of **1**–[Fe(II)]₄:phenol complexes. The inset shows the nonlinearity of the data when a 1:1 complex is assumed.

resorcinarene concentration would result in a change of the 1:4 stoichiometry of the **1**–Fe(II) complexes. However, the stability constant K , assuming the formation of 1:2 **1**–[Fe(II)]₄:phenol complexes, can be calculated on the Benesi–Hildebrand plots^{21,22} using the fluorescence data:

$$\frac{1}{I_0 - I} = \frac{1}{I_0 - I_1} + \frac{1}{K(I_0 - I_1)} \frac{1}{[\text{Ph}]_0^2} \quad (1)$$

where K is the association constant of the 1:2 complex, $[\text{Ph}]_0$ represents the initial analytical concentration of phenol, I_0 and I are the fluorescence intensities in the absence and in the presence of phenol, respectively, and I_1 is the lower limit of the fluorescence intensity, i.e., it is the intensity that could be measured when all resorcinarene molecules would form complexes with phenol. The K values can be obtained from the slope and intercept of the plots. However, it is known that equilibria can depend strongly on the temperature.²³ The thermodynamic parameters for the individual complexes formed in the resorcinarene–phenol system can be determined from the van't Hoff equation:

$$\ln K = -\frac{\Delta G}{RT} = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} \quad (2)$$

and, therefore,

$$K = e^{-\Delta G/RT} = e^{-\Delta H/RT + \Delta S/R} \quad (3)$$

where ΔG is the Gibbs free energy change, ΔS the entropy change, and ΔH the enthalpy change associated with complex formation. Using eq 3, inserting this expression of the formation constants into eq 1, the fluorescence change can be expressed as a function of the ΔH and ΔS values. The thermodynamic parameters associated with the K value were determined from the Benesi–Hildebrand curves by an iterative solution of eq 1 using the expression of K value from eq 3.

The evaluation method discussed above proved the formation of **1**–[Fe(II)]₄:phenol complexes with 1:2 stoichiometry at room temperature. Since the Benesi–Hildebrand plot (Figure 4) shows excellent linear regression ($r > 0.98$), the Gibbs free energy changes related to the first and second complexation steps are nearly the same. ΔG° , ΔH° , and ΔS° values of $-12.1(8)$ kJ·mol⁻¹, $-17.1(5)$ kJ·mol⁻¹, and $-16.1(6)$ J·K⁻¹·mol⁻¹ have been obtained, respectively. However, the above-mentioned temperature dependence of the stoichiometry of the **1**–[Fe(II)]₄ complex slightly decreases the reliability of these values. The

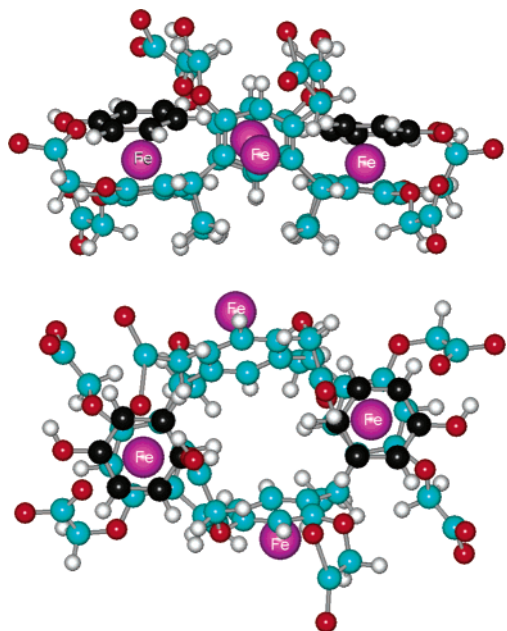


Figure 5. Side and top views of the equilibrium conformation of C-methyl-calix[4]resorcinarene with two phenol molecules by the assistance of Fe(II) cations. (Phenol carbons are indicated in black.)

high similarity of the thermodynamics of the two complexation steps reflects to the independent complexation of the two phenol molecules; i.e., the coordination of the second guest is not influenced by that of the first one. Consequently, the two phenol binding sites do not interact either sterically or electronically.

2.4. Theoretical Structure of the Complex Formed. The structural parameters of the complex with the proposed 1:2 stoichiometry were investigated by quantum-chemical methods. In our earlier study we showed that the geometry optimization of the resorcinarene host shows the CH₃ groups on the methylene bridges located in “all-cis” (rccc) position. The molecule exists in a “boat” (*C*_{2v}) conformation where two opposite rings are nearly parallel, while the other two rings are almost entirely flattened (see Figure 5). At pH = 7, where the experiments were done, **1** exists in a double protonated form. Evaluating the data obtained for the interaction energy of protons with **1**, the protonation of the carboxylate moieties on rings 1 and 3 was found as the most probable way, which just results in the folding of these carboxylate arms through hydrogen bonding. This feature has significant importance with respect to the data evaluation. Although the complexation of a phenol molecule in the cavity of resorcinarene is very weak (especially in aqueous solution), such a complexation still could change the PL signal. However, as an inference of partial protonation of carboxylate groups on the two opposite rings, 1 and 3 of **1**, these carboxylate groups prevent the complexation of phenol in the resorcinarene cavity, i.e., forming a sandwich-type complex with rings 1 and 3 of **1**. This conformational feature clears up the complexation processes since any other than Fe(II)-assisted type complexation of phenol can be excluded. As a further possibility, one can also assume an interaction between Fe(II) ion coordinated to one of the aromatic rings of **1** and the OH group of the phenol molecule. On the basis of our theoretical calculations, however, this type of coordination can be excluded because of the substantially lower interaction energy.

Figure 5 shows the top and side views of the proposed structure which was determined by high-level quantum-chemical calculations. The stability of this structure is 15.6 kJ/mol. Since the phenolic hydroxyl group and one of the carboxylate arms

come to a close proximity upon complexation by the assistance of Fe(II), the structure given in Figure 5 might also be supported by a hydrogen bond. A further stable structure with two phenol guest molecules lying below the resorcinarene rings (out of the cavity) was also found by quantum-chemical calculations. However, the calculated interaction energy of 11.8 kJ/mol predicts very low stability of the complex.

3. Conclusion

Calixarenes are known to form complexes with neutral aromatics predominantly through $\pi(\text{host})-\pi(\text{guest})$ type interaction. The strength of interactions decreases with increasing the solvent permittivity, which feature inhibits the complexation in aqueous solutions. However, as it has been shown recently,¹⁹ Fe(II) ions are coordinated preferably to the aromatic rings instead of the carboxylate arms of resorcinarene. Therefore they are able to boost slightly the interaction between the π -faces of the aromatic host and those of the guest molecules. As a result, water-soluble calix[4]resorcinarene octacarboxylate forms stable sandwich-type complexes with phenol by an assistance of Fe(II) ions.

4. Experimental Section

The host compound was prepared by the hydrolysis of octa-ethoxycarbonyl(methoxy)-C-methyl-calix[4]resorcinarene²⁴ with boiling alcoholic KOH. The obtained octapotassium salt of **1** was precipitated from the reaction mixture in essentially pure form. The product was dried in vacuo at 120 °C (0.1 mmHg/3 h) before use. The ¹³C and ¹H NMR spectra were recorded in D₂O with a Bruker Avance DRX-500 instrument, and the series of signals indicated the presence of single conformer. Selected ¹³C NMR data: δ = 20.10 (CH₃), 30.93 (bridge-CH-), 68.99 (CH₂O), 171.51 (CO) ppm. The ¹H NMR spectrum was not informative due to strong broadening of signals.

Solvents were distilled before use by standard methods. The experiments were carried out at pH = 7.0 using TRIS/tris-(hydroxymethyl)aminomethane/(Merck) buffer. The exact pH value was adjusted by the addition of 0.1 M HCl. Ionic strength was set by using 0.1 M tetraethylammonium perchlorate (Sigma-Aldrich) background salt as recommended in the literature.²⁵ All measurements were carried out under purified nitrogen atmosphere. The potentiometric data were analyzed by the HyperQuad 2000 (Protonic Software) computer program.^{26–28}

The highly sensitive Fluorolog $\tau 3$ spectrofluorometric system (Jobin-Yvon/SPEX) was used to investigate the photoluminescence (PL) spectra of the different solutions. For data collection a photon counting method with 0.2 s integration time was used. Excitation and emission bandwidths were set to 2 nm. A 1 mm layer thickness of the fluorescent probes with front face detection was used to eliminate the inner filter effect. A wavelength of 280 nm was chosen for excitation. A Grant thermostat (Grant LTD6G, Grant Instruments) was used for temperature controlling. The stoichiometry and stability constants of the complexes were determined by the application of the Benesi–Hildebrand method.

The equilibrium conformation of the resorcinarene derivative and its complexes with iron ions was studied with the semi-empirical AM1 (Austin model) method,²⁹ followed by ab initio HF/6-31G* calculations. The Fletcher–Reeves geometry optimization method was used for the investigation of the conformers. The interaction energy of the studied species was described at an ab initio level using HF/6-31G* calculation. The TIP3P method³⁰ with extension to the solvent used³¹ was applied for

considering the solvent effect. All types of calculations were carried out with the HyperChem Professional 5.1 program package.³²

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