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The Effect of the Electron Density Distribution of Guest on the Entropy Change During Complex Formation of Calix[6]arene Hexasulfonate Host with *ortho*- and *para*-cresols as Guests

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The π–π interaction-based inclusion complexation of calix[6]arene hexasulfonate as host with neutral aromatic guest molecules was studied in aqueous media. To vary the distribution of electron density on the guest's aromatic rings, the phenol parent compound was substituted in the *para*- or *ortho*- positions with CH_3 group. To study the interaction between calixarene and the guests, PL, DSC and quantum-chemical methods were used. The results indicate 1:1 stoichiometry of the formed host-guest complexes. Although the enthalpy change during complex formation of calixarene with *p*- or *o*-cresol are the same, the Gibbs free energy change is significantly higher in the case of calixarene—*o*-cresol complexes. This property is due to the unexpected entropy change during the complex formation. Using molecular dynamic calculations, a guest-induced redistribution of the electron density on the calixarene rings, followed by the restructuring of the solvent molecules was identified as a background of this unexpected entropy change at molecular level.

Keywords: Calixarene; Host-guest complexes; Complexation thermodynamics

INTRODUCTION

One of the most exciting features of supramolecular chemistry is the complex formation of the sterically well-defined structures with neutral organic molecules. Their potential in analytical chemistry as sensors cannot be over-emphasized [1,2].

Calix[n]arenes (n = 4–8), cyclic oligomers of phenolic units linked through the *ortho* positions are widely used macrocycles of well-defined skeleton. They show versatile recognition properties towards metallic or organic ions and neutral molecules [3–5]. Their thermodynamic [6] and redox properties [7], the extent of their metal ion binding character in solutions [8,9], and their wide applications in analytical and separation sciences have recently been reviewed [10–12].

The factors controlling the stability or selectivity of some calixarene derivatives towards neutral π-electron deficient aromatics were reported also in our previous papers [13–16]. 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 aromatic rings of the calixarene host and that of the neutral guest molecule. Among the several calixarene derivatives, water-soluble calixarenes have laureate attention since they are promising candidates for successful applications in environmental, analytical and separation sciences, and also in pharmaceutical chemistry [17]. The inclusion complexation of calix[6]-arene hexasulfonate with different neutral aromatics in aqueous media have been studied recently by PL (Photoluminescence), DSC (Differential Scanning Calorimetry) and quantum-chemical methods

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[18,19]. These results have shown, that the enthalpy change of complex formation predicts strong interaction between the host and the guest. The Gibbs free energy change of the complex formation is small, resulting in a relatively low complex stability [19]. This property is due to the high and negative entropy change during the complex formation. Comparing the thermodynamic parameters observed on the series of the guests, a decrease of the enthalpy change was observed when the electron density on the guest's aromatic ring increased. However, the Gibbs free energy and therefore the stability of the complexes increased when the enthalpy change was lowered. These unexpected results are based on the enthalpy-entropy compensation effect and probably due to the quite different entropy change related to the high and low electron density on the aromatic rings of different guest molecules. Using molecular dynamic calculations, a redistribution of the electron density on the calixarene rings, followed by the reordering of the solvent molecules was identified as a background of this unexpected entropy change at molecular level.

According to the results above, in this paper we examine the complex formation ability of calix[6] arene hexasulfonate towards *para*- or *ortho*-cresol guests in aqueous media. Both of these guest molecules have the same electron releasing (methyl) and the electron withdrawing (OH) group. The aim of this work was to earn some information about the distribution of the same amount of electrons on the guest molecules, and about their effect on complex formation.

EXPERIMENTAL

Calix[6]arene-hexasulfonate salt **1** (MW = 1248.98) was prepared by the direct sulfonation of the parent calix[6]arene with concentrated sulfuric acid [20]. The guests, *p*-cresol **2a** (MW = 108.13) and *o*-cresol **2b** (MW = 108.13) (p.a. grade) were purchased (Merck, Germany) and used without further purification (Fig. 1).

The acid-base equilibria in the solutions of calixarene **1** were studied by potentiometry using a combined pH sensitive glass electrode (Triode pH

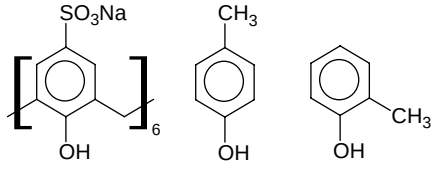

FIGURE 1 Calix[6]arene hexasulfonate salt **1** and *para*-cresol (**2a**) and *ortho*- (**2b**) derivatives were chosen as host and guests, respectively.

electrode, ORION) and Orion 420 Aplus pH meter. The potentiometric measurements were carried out at 298.16 ± 0.1 K. The protonation was studied in aqueous solution of **1** at concentration of 10^{-2} M with ionic strength of 0.1 M tetraethylammonium perchlorate ($[Et_4N][ClO_4]$) background salt. The estimated error of the pH measurements was found to be about 0.02 pH unit. Values of the stepwise protonation constants K_i and the overall protonation constants β_i were computed with the HyperQuad 2000 (Protonic Software) computer program [21–23]. Titrations and calibrations were carried out in a glass cell furnished with a thermostating jacket at a temperature of 298.16 ± 0.1 K. Nitrogen stream was used to remove dissolved O_2 and CO_2. The titrating solutions were added from standard microburet. The glass electrode was calibrated at a constant ionic strength following the procedure described in the literature [24,25]. Slopes were within 3% of the theoretical Nernst value, and square regression coefficients for the Nernst type equation were always better than 0.998.

Both fluorometric and calorimetric experiments were carried out at pH ~ 6.9 using phosphate buffer, 0.025 mol/kg disodium hydrogen phosphate (Merck) +0.025 mol/kg potassium dihydrogen phosphate (Merck); pH 6.96, 6.91, 6.87, 6.84, 6.82, 6.81 at temperatures of 273, 283, 293, 303, 313, 323 K, respectively.

The PL measurements were performed on the Fluorolog τ3 spectrofluorometric system (Jobin-Yvon/SPEX). For data collection a photon counting method with 0.2 s integration time was used. Excitation and emission bandwidths were set to 1 nm. A 1 mm layer thickness of the fluorescent probes with front face detection was used to eliminate the inner filter effect.

Calorimetric measurements were carried out with a highly sensitive nano-II-DSC 6100 (Setaram, France) instrument. The calorimeter is configured with a platinum capillary cell (volume = 0.299 ml). The samples were pressurized to $(3 \pm 0.02) \times 10^5$ Pa during all scans. Using oil rotation pump, standard degassing procedure for 15 min at about 15 Pa was applied before loading the samples into the capillary. The heat flow was scanned between 273 and 323 K. A typical scanning rate of 0.5 K/min was applied. The effect of diffusion and that on the reaction rate were checked for each sample by varying the scanning rate from 0.1 up to 2 K/min. The experimental deviation of the calorimetric results were estimated to be ±5 mJ.

To avoid any interaction other than the interaction related to the host–guest complex formation, the DSC curves of solutions of calixarene in buffer (i), calixarene 1 in water (ii) and buffer by oneself (iii) were recorded against water. No significant differences between the curve of summed (ii) with (iii) and

that of (i) were obtained, which observation reflects that no considerable interaction between the buffer and the host calixarene exists. Similar result was found for the guest cresol isomers.

The equilibrium conformations of calixarene **1** and their complexes with cresol derivatives (**2a, 2b**) were studied with semi-empirical AM1 (Austin Model) method, 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. TIP3P method [26] with extension to the solvent used [27] was applied for considering the solvent effect. The conformation of the complex in water obtained from the above calculations was compared with results derived from the geometry optimization performed at DFT/B3LYP/6-31++G level by using GAUSSIAN 03 package [28]. The PCM (Polarizable Continuum Model) method was used to consider the solvent effect. To obtain the equilibrium conformation, the search was started from the positions where either from inside or outside the cavity the guest was located with different orientation to the host molecule.

The temperature-dependent molecular dynamic simulations were performed with AMBER force-field. The TIP3P method is used to explicitly consider the solvent water molecules. For this calculation a cubic box with 20 Å edge length is used. The box contained 265 water molecules according to the water density at 298K. To find an appropriate initial condition for molecular dynamics a 'heating' algorithm implemented in HyperChem package was used. This procedure heats up the molecular system smoothly from lower temperatures to the temperature T at which molecular dynamics simulation is desired to perform. The starting geometry for this heating phase is a static initial structure. We used the optimized geometry derived from semiempirical AM1 calculations as an initial structure. The temperature step and the time step in the heating phase were set to 2K and 0.1 fs, respectively. After equilibration at the given temperature, the MD simulations were run in 1 ps time intervals with resolution of 0.1 fs. The simulation time step was 0.1 fs. Ten thousand points were calculated in each run. Five water molecules locating closest to the calixarene's phenolic unit was chosen for data analysis. The inclination angles of the C_2 symmetry axis of the water molecules, related to the directions perpendicular to the planes of the appropriate phenolic units of calixarene molecules, were collected during the simulation. The average values of these angles were used to represent the freedom of water molecules around the calixarene rings.

Single point calculations and *ab initio* geometry optimizations were carried out with the GAUSSIAN 03 code [28], while molecular dynamics simulations are performed by the HyperChem Professional 7 program package [29].

RESULTS

Following our earlier procedure [18,19], the stoichiometry and the van't Hoff enthalpy of the complex was determined by spectrofluorometric method. The calorimetric molar enthalpy of the inclusion was determined from the heat flow directly measured by DSC method. The fluorometrically determined van't Hoff enthalpy and the calorimetric enthalpy were compared and used for the examination of the two-state behavior of the formation of such a complex. Quantum-chemical investigations were carried out to examine the entropy effect at molecular level.

PL Measurements

The thermodynamic parameters of the complex formation were determined by a combination of the Job's method and the van't Hoff theory as described earlier [18,19]. In order to determine the stoichiometry of the complexes and thermodynamic parameters of complex formation, 5×10^{-4} M stock solutions of **1** and that of one compound from the cresol derivatives (**2a**, **2b**) were mixed in four different [H]/([G] + [H]) ratio by stepwise addition of n × 300 μl host to (5-n) × 300 μl guest solutions (n = 1, 2, 3, 4) keeping 5×10^{-4} M total concentration ([G] + [H]). The measurements were carried out at four different temperatures and the ratios of the change obtained in the PL peak under the effect of guests and those of the bare calixarene solutions were plotted against the molar fraction of calixarene. In the cases of different guests (**2a** or **2b**), Job's curves showed a mirror symmetry indicating the 1:1 complex stoichiometry. Assuming this 1:1 stoichiometry, the thermodynamic properties of the complexation can be calculated. Details of such evaluation of the Job's curves was described earlier [18,19]. Table I summarizes the results.

DSC Measurements on the Host-guest System

According to our earlier studies [18,19], the determination of the stability of the host-guest complexes is based on the following treatment. Using the expression of the stability constant *K* from the van't Hoff equation, the concentration of a 1:1 host-guest complex can be described as a function of the molar enthalpy, entropy change and the temperature. The amount of the complex being dissociated, while the temperature increases from 273 K to 323 K, can be

TABLE I Thermodynamic parameters of complexation of **1** with **2a** or **2b**

Method	Cresol derivative	ΔG (298 K) (kJ·mol^{-1})	ΔH (kJ·mol^{-1})	ΔS (J·K^{-1}·mol^{-1})
PL	**2a**	−26.27 (6)	−51.3 (4)	−84 (6)
	2b	−37.19 (7)	−50.3 (4)	−44 (5)
DSC	**2a**	−26.78 (8)	−53.3 (3)	−89 (8)
	2b	−38.89 (7)	−52.9 (4)	−47 (6)

expressed as the difference of concentrations of the complex at the two temperatures.

To obtain the enthalpy changes during the dissociation of the complex, the excess heat capacity of the equimolar mixture of **1** with **2a** or **2b** were scanned from the 273 K up to 323 K by the rate of 0.5 K/min. Five different concentrations varying between 1×10^{-3} M and 4.1×10^{-4} M were applied, keeping the host-guest concentration at same value at each individual run.

DISCUSSION

It can be clearly seen from the data in Table I that the Gibbs free energy change, therefore the stability of the host-guest complex is increased when the *o*-cresol guest enters into the calixarene cavity compared to *p*-cresol complexation. Note, that all thermodynamic values reflect to the formation of the complex, i.e. the values in the Table I show the Gibbs free energy of the complex (product) subtracted with the Gibbs free energy of the separated species (reactants). These values are negative. The enthalpy term of the Gibbs free energy shows nearly the same change in both cases. In contrast, the entropy change nearly double in the cases of the **1–2a** complexes. Since the entropy change of the complex formation is also negative, this highlights appearance of a more ordered structure. Consequently, the entropy term of the complexation decreases the complex stability. However, when the negative entropy change decreases this effect increases the Gibbs free energy changes and therefore the stability of the complex.

Overall, the highly exothermic complexation enthalpy, parallel with the significant decrease of the entropy change during complex formation, reflects to the so-called enthalpy-entropy-compensation effect. It is probably due to the increased order of guest molecules relative to the host calixarenes and also due to the increased order of solvent molecules after the complex has been formed.

THE ROLE OF ENTROPY DURING COMPLEX FORMATION

Table I shows that the entropy change is negative during complex formation, which means that the entropy decreases in this process. It is an astonishing behavior in this particular case, especially if we consider the follows arguments. Before the complex formation both calixarene and the guest molecules are solvated, and the solvent molecules around the solutes are ordered. During the complexation, before the guest phenol molecule enters into the calixarene cavity, it has to lose its solvation shell and also, the solvent molecules have to leave the calixarene cavity. The disorder, and therefore the entropy of the system considerably increases during this process. Then, the guest molecules enter into the calixarene cavity forming higher ordered conformation. The entropy during this latest process decreases only to a small extent. Consequently, in contrast to our present results, the entropy of the system would have to be increased after a host-guest formation.

Because of this surprising result, we examined the complex formation at molecular level using quantum chemical calculations, too. The interaction energy between the host and the guest molecules was calculated by the procedure described earlier. All energies were determined in the presence of solvent cage using TIP3P method [26,27], *i.e.* the solvation enthalpies of the interacting species were considered in this way. To obtain the equilibrium conformation, the search was started from the positions where either from inside or outside the cavity the guest was located with different orientation to the host molecule. Only those conformations with the cresol derivatives located inside the calixarene cavity (i.e. cresol interacts with calixarene from the side of the upper rim) were found stable. The orientation of different cresol derivatives inside the calixarene cavity was found to be always the same: the OH group of the cresols is located at the bottom (lower rim) of the calixarene cavity. Same structure was found when the calculations were repeated at DFT/B3LYP/6-31++G level with the PCM (Polarizable Continuum Model) method to consider the solvent effect. The stabilization energy of the complex was evaluated as the absolute value of the interaction energy. The interaction energy was defined as the difference between the total energy of the optimized structure of the complex and that of the separated host plus guest molecules. Fig. 2 shows the top and side view of the optimized structure of the host-guest

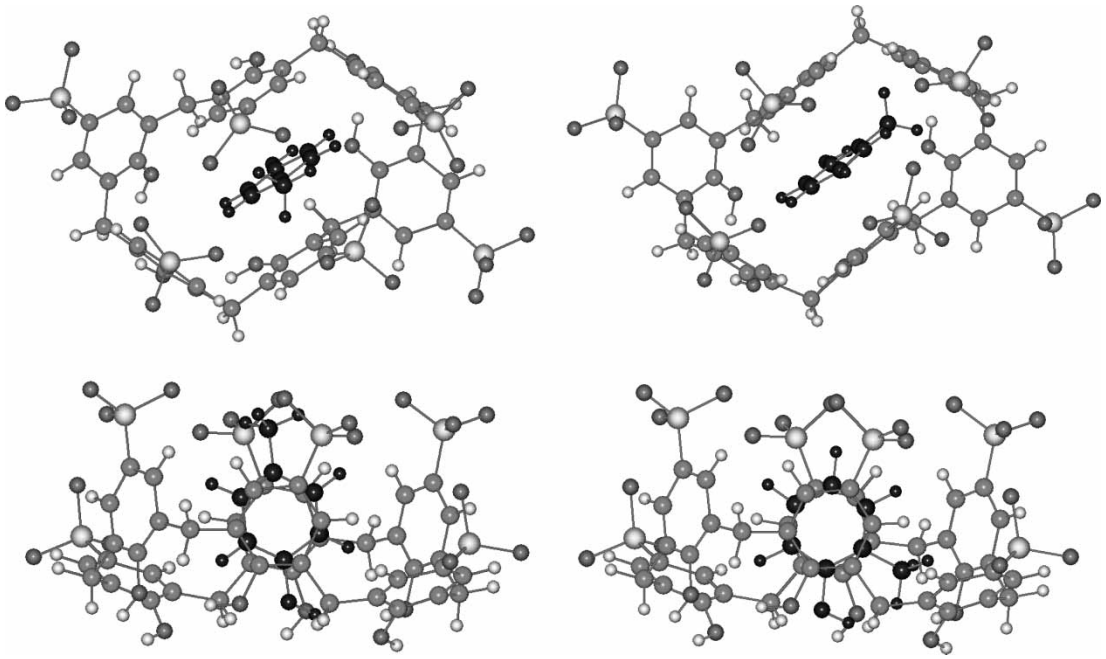

FIGURE 2 Top and side views on the optimized structure of the inclusion complex of **1** with **2a** (left) and **1** with **2b** (right). The cresol molecule (black) enters into the calixarene cavity and lies between the two aromatic rings of the calix[6]arene. The orientation of different cresol derivatives inside the calixarene cavity was found to be always the same: the phenolic OH group is located at bottom. The three parallel aromatic rings form a sandwich-type structure.

complexes. The cresol molecule enters into the calixarene cavity and lies between the two aromatic rings of the calix[6]arene. The three parallel aromatic rings form a sandwich-type structure. Results confirm that this structure might be stabilized either by the $\pi-\pi$ interaction or by hydrogen bonds between the OH groups of the phenolic units of host and the guest, respectively. The related molecular dynamics calculations showed, that the solvent water molecules, which lie in the outer side of the calixarene rings involved into the complex formation, has much higher ordered structure after the guest entered into the cavity (Fig. 3). For quantitative description a similar idea has been used as published for 4-substituted phenols [19]. The angles of the C_2 symmetry axis of the water molecules, relating to the directions perpendicular to the planes of the appropriate phenolic units of calixarene molecules, were collected during the simulation. The deviation from the average values of these angles of five water molecules situated closest to the appropriate phenolic ring of calixarene were used to represent the freedom of water molecules around the calixarene rings. It was found that the average rotation of the water molecules is nearly three times less in the case when the *p*-nitrophenol guest with its charged aromatic ring is entered into the cavity (85°). (The average rotation value for the nearly neutral *p*-methylphenol is 265°.) In spite of the enormous difference in the electronic properties of the substituents, due to the polarization of the aromatic ring, *p*-nitro-phenol and *p*-methyl-phenol (*p*-cresol) shows similar orientation of water molecules.

To obtain a microscopic view about the solvent water molecule, their orientation was examined by

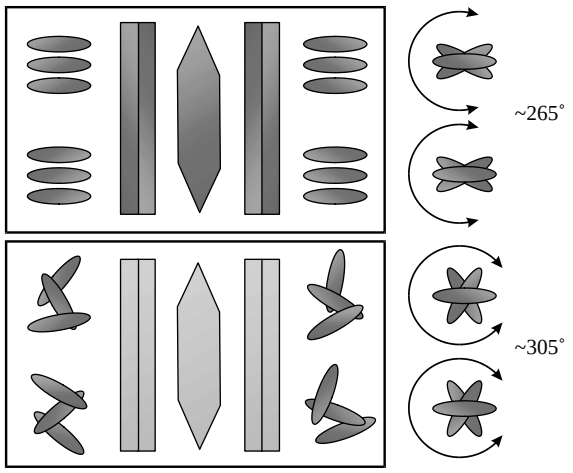

FIGURE 3 Schematic microscopic view of the entropy change during the complexation of cresols by calixarene. Upper figure is about the complexation of *p*-cresol, where the aromatic ring of the guest molecule is polarized by *para* substitution of an electron donating (CH_3) or electron withdrawing (OH) groups. Bottom figure relates to the complexation of *o*-cresol, where the aromatic ring is nearly unpolarized. The change in the distribution of electron density of the calixarene rings results in a higher ordered structure in the former case. The average rotation of the water molecules reduces when the guest having polarized aromatic ring enters into the cavity.

molecular dynamic calculations at that temperature, where the host-guest complex is desired to form. Fig. 3 shows a schematic summary of the results. Accordingly, a recent work showed that the water molecules are coordinated mainly to the OH group of the phenols [30]. However, increasing the coordination number, the coordination becomes more and more close to the other atoms in the aromatic ring [30]. Because of this coordination is stabilized by the OH. . .π bonds, it is obvious that the change in the aromaticity of the phenol molecule will induce changes in the ordering of the water molecules in the molecular environment. However, the electron density of the calixarene rings is modified when a charged guest molecule enters into the cavity. As a result, a more ordered structure was formed when the aromatic ring of the guest molecule was more polarized (Fig. 3). Consequently, the more polarized the aromatic ring of the guest molecule, the higher the entropy change of the complex formation.

CONCLUSION

The π-π interaction-based inclusion complexation of calix[6]arene hexasulfonate as host with neutral aromatic guest molecules was studied by PL, DSC and quantum-chemical methods in aqueous media. To vary the distribution of electron density on the guest's aromatic rings, the phenol parent compound was substituted in the *para*- or *ortho*- position with CH_3 group. The results indicate 1:1 stoichiometry of the formed host-guest complexes. The enthalpy change and also the calculated interaction energy during complex formation of calixarene host with *p*- or *o*-cresol guest are the same, the Gibbs free energy change is significantly higher in the case of calixarene-*o*-cresol complexes. Molecular dynamic calculations highlighted that guest-induced redistribution of the electron density of calixarene rings, followed by the reordering of the solvent molecules describes well the unexpected entropy change at molecular level.

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