

# Competitive thermodynamic and kinetic processes during dissociation of some host-guest complexes of calix[4]arene derivatives

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**Abstract** The formation-dissociation dynamics of the calixarenes' host-guest complexes is one of the key features both in sensor applications and in use as molecular containers. The thermodynamic and kinetic description of the formation-dissociation processes could help in developing procedures to design new molecular capsules. In this work the dissociation dynamics of calix[4]arenes and *p*-chloro-trifluoromethylbenzene complexes was studied with molecular dynamics calculations. According to their binding selectivity, calix[4]arene, 4-methylcalix[4]arene and 4-*tert*-butylcalix[4]arene were chosen as host model-compounds. Results show significantly different temperature dependence of the reaction rate on various groups (H, Me, *t*Bu) substituted at the upper rim of calixarene skeleton. This property reflects the competitive thermodynamic and kinetic processes during the complex dissociation. Our related experimental results obtained by DSC method seem to validate the theoretical results.

**Keywords** Complex formation · Molecular capsules · Rate of dissociation · Molecular dynamics

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## Introduction

The importance of calixarenes, that was highlighted already as they had been discovered, is due to their ability to form host-guest complexes with several types of guests ranging from ions to different kind of neutral molecules [1, 2]. Nowadays, these materials are of great importance in designing molecular containers [3, 4], but still a plenty of results are published about new calixarene derivatives [5, 6] and their complexation ability towards ionic and neutral species [7, 8].

Molecular dynamics (MDs) calculations are fruitful testing techniques to analyze the dynamic processes at molecular level. Accordingly, several MDs studies about the complexes of calixarenes can be found in the literature. The isomerization of calixarenes by using the continuum model to describe the solvent effects has been described [9]. The structural properties of the calixarene complexes with organic and inorganic cations have been calculated [10], and modelling of the interaction between calixarenes and alcohols in water has been carried out [11]. There are several further studies about the extraction of ions by calixcrowns in ionic liquids [12] or by calixarenes at the water-oil interface [13].

To optimize the practical performance of calixarenes as molecular containers or sensor materials, detailed knowledge about their complex formation—dissociation processes is required, in particular at molecular level. In this study we investigated the complex formation and dissociation of calixarenes with neutral aromatic guests by MDs calculations. In our previous papers [14, 15] the importance of  $\pi$ - $\pi$  interactions between the phenolic rings of the calixarene host and that of the neutral guest molecule was reported. The effects of the cavity shape [16, 17] and of the solvent permittivity [18] on the stability of the host-guest

complexes in alcoholic solvents were determined by highly sensitive fluorometric measurements and quantum-chemical calculations. The stability of the complexes in water can be increased by the assistance of “soft” Fe(II) ions [19]. The inclusion complexation of calix[6]arene hexasulfonate with neutral aromatic guests in aqueous media have been studied recently by photoluminescence, differential scanning calorimetry (DSC) and quantum-chemical methods [20, 21]. Furthermore, calixarene derivatives were successfully tested as container molecules for improving solubility of C<sub>60</sub> fullerenes [22].

Our previous theoretical study [23] on the dissociation dynamics of the complexes formed by calixarene hosts with *p*-chloro-trifluoromethylbenzene guest suggests that different type of processes participate in the molecular dissociation. Accordingly, in the present paper the formation—dissociation processes of a series of the upper-rim-substituted calixarene complexes formed with a benzotrifluoride guest are theoretically examined in usual temperature range with higher resolution. In addition, DSC experiments were performed to validate the theoretical results.

## Materials and methods

### Experimental

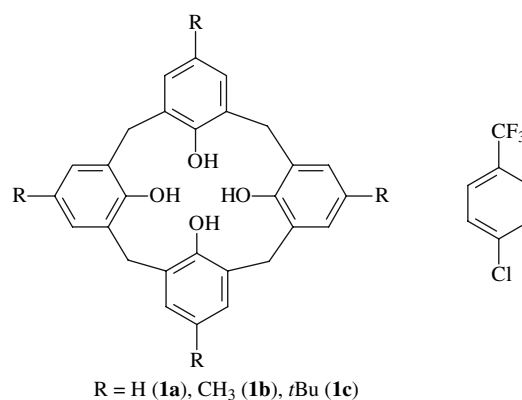
Calix[4]arene **1a**, [24] 4-Me-calix[4]arene **1b** [25] and 4-*t*Bu-calix[4]arene **1c** [26] were prepared as described in the literature. The guest, *p*-chloro-trifluoromethylbenzene **2** was purchased from Aldrich.

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. The measurements were performed in chloroform solvent, because our earlier results showed higher stability of the host-guest complexes in low permittivity solvents [18]. Chloroform (Fluka) was purified according to the known procedure: washed with water, dehydrated on CaCl<sub>2</sub>, distilled and stored under argon prior to use. Due to the high volatility of chloroform, to perform measurements above the 313 K wouldn't be possible because bubbles appear in the solutions at higher temperature. However, in a closed calorimetric cell, which is built for measuring the molar heat capacity, samples are pressurized above  $3 \cdot 10^5$  Pa. Exploiting the reversible character of the ‘host-guest’-type complex formation, cyclic scans were performed within the 273–313 K temperature range. Results show that all the undesirable bubbles leave the solutions after the first cycle, therefore the second cycle can be successfully used for the

data evaluation. Accordingly, during our measurements, the heat flow was scanned between 273 and 313 K with the scanning rate of 2 K/min and 1 K/min forward and backward and the second heating curve was applied for the data evaluation. In order to investigate the interaction of **1a-c** with **2**, 10<sup>-3</sup> M solutions were prepared in chloroform solvent. The DSC curves of solutions of calixarenes' host-guest complexes in chloroform were recorded against chloroform. The excess heat capacity was calculated by subtraction of the baseline using the software of the calorimeter (CpCalc/SETARAM, 2003). The reaction rate could be characterized qualitatively by the centre of gravity of the curves: that reaction is the faster one whose DSC curve has its centre of gravity at lower temperature.

### Model

The complexation selectivity of calixarenes can be modified by functionalization at the lower and/or upper rims of the parent compound. We have chosen three calix[4]arene derivatives as host model compounds (see Fig. 1): calix[4]arene, 4-methylcalix[4]arene and 4-*tert*-butylcalix[4]arene. Since the upper rim of the calixarene skeleton is localized as entrance and exit site for a guest molecule, unlike our previous work, the calix[4]arene derivatives applied here do not possess 1,3-*O*-alkyl substituents at the lower rim. In this way the motion of these alkyl groups is eliminated, furthermore, the cyclic hydrogen bonds existing at the lower rim participate in the stabilization of the conic molecular shape. *p*-Chloro-trifluoromethylbenzene was chosen as guest molecule, which was tested in our related earlier work as well [23]. The earlier results showed good complex formation ability of this molecule with calixarenes [14, 15].



**Fig. 1** Calix[4]arene (**1a**), 4-Me-calix[4]arene (**1b**) and 4-*t*Bu-calix[4]arene (**1c**) applied as host molecules and *p*-chloro-trifluoromethylbenzene (**2**) applied as guest molecule

## Theoretical calculations

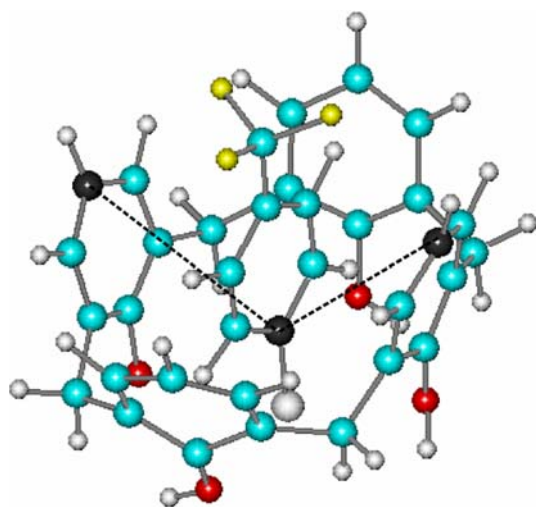
The static equilibrium conformations of calix[4]arene **1a**, 4-Me-calix[4]arene **1b** and 4-*t*Bu-calix[4]arene **1c** with *p*-chloro-trifluoromethylbenzene **2** were studied with semi-empirical AM1 (Austin Model) method, followed by DFT/B3LYP/6-31++G calculations. The Fletcher-Reeves geometry optimization method was used for the investigation of the conformers.

The dissociation dynamics of the host-guest complexes was investigated as a function of the temperature by Langevin MDs calculations. The simulation time step was 0.1 fs. The MDs calculations were done at ten different temperatures between 273 and 318 K in steps of 5 K. Ensembles of  $N_0 = 10$  trajectories with a time resolution of 0.1 fs were calculated at each given temperature, for a period of 0.8 ps.

Reaction time was described as the simulation time measured until the aromatic guest leaves the calixarene cavity (see Fig 2.). Reaction rates,  $k$ , were determined by the relation of

$$\frac{N}{N_0} = e^{-kt} \quad (1)$$

where  $t$  is the reaction time,  $N_0$  is the total number of trajectories and  $N$  is the trajectories which didn't react until the time  $t$ . Trajectories, which do not end with a reaction within the maximum allowed time (0.8 ps), contribute to the determination of the rate constant by their involvement to  $N_0$ . The rate constant could be described as the slope of the curve fitted to the points of the  $\ln(N/N_0)$  values plotted



**Fig. 2** The atomic distances between the carbon atoms located at the upper part of the calix[4]arene (cone conformer) and carbon atom of the guest lying deepest in the calixarene cavity are recorded. (All three atoms are highlighted in black)

against the reaction time. The calculated rate constants,  $k$ , of the host-guest complex formation derived from the direct trajectory calculations are shown in the Arrhenius plot in Fig. 3. When the dimension of  $k$  is given in 1/s, the results could be analyzed using the linear classical Arrhenius equation in the following form:

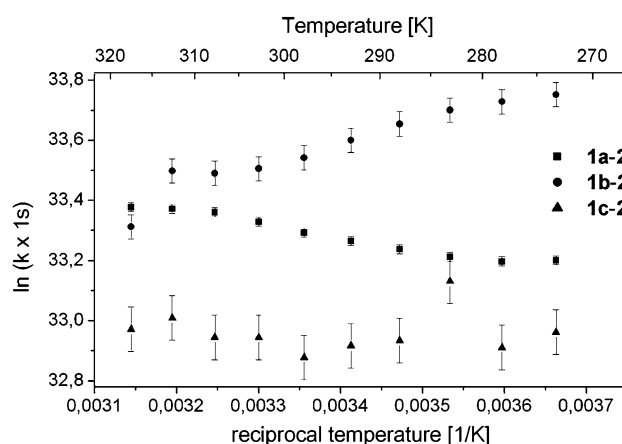
$$\ln(k) = \ln A - \frac{E_a}{k_B T} \quad (2)$$

where  $A$  is the preexponential (frequency) factor,  $E_a$  is the activation energy,  $k_B$  the Boltzmann constant and  $T$  is the temperature.

The calculation procedures of the rate constant have been described more detailed in our previous paper [23]. The static calculations were carried out with GAUSSIAN 03 program package [27] and the MDs investigations with HyperChem Professional 7 program package [28].

## Results and discussion

Our earlier results [e.g. 21] show that the equilibrium conformations of the complexes of calixarene with neutral aromatic guest molecules are stabilized by  $\pi$ - $\pi$  interactions between the aromatic  $\pi$ -electron systems of calixarene phenolic units and that of the aromatic guest molecules. The role of interaction between OH groups and the guest's Cl atom in the stabilization of the complex was investigated by analyzing the total energy when the guest molecule reaches the calixarene from the lower-outer side with its Cl atom. The interaction energy between the host's OH groups and the Cl atom of the guest was found to be below the kinetic energy of particles around the room-temperature ( $\sim 3.8$  kJ/mol) as it can be derived from the equipartition theorem. This property is probably due to the fact, that the



**Fig. 3** The rate constants' Arrhenius plot of the host-guest complexes' dissociation

attractive forces raised from the possible OH–Cl bonds are compensated by the repulsive Coulomb-type O–Cl forces. In this way, the complexes formed during the interactions of the calixarene **1a**, **1b** or **1c** with *p*-chloro-trifluoromethyl-benzene **2** are preferably stabilized by the  $\pi$ – $\pi$  interaction. In all cases the two opposite rings of the calixarene are nearly parallel and the guest molecule lies between these rings forming a sandwich-type structure. Since the phenolic units of calixarenes are linked in *ortho* position, the upper part of the molecules is more flexible. This property supports the upper part as entering and leaving channel for the guest molecules during their complex formation. Any substitution of hydrogen atoms at the upper rim by larger substituents would narrow the complexation channel mentioned above. During complex formation or dissociation reaction, the minimum cross section of the channel required is determined by the just entering or leaving guest molecule. If the channel is too narrow, e.g. due to the large substituents at the upper rim, broadening of the channel prior the complexation or dissociation process follows the torsion of the whole calixarene skeleton. This conformational change of the calixarene costs energy increasing the saddle point of the energy surface associated to dissociation channel. As a result, the activation energy of reactions associated to the complex formation is also increased. Accordingly, two significantly different processes can be associated to the driving forces of these complexation reactions: one of them is the interaction energy, which is the difference between the energy of the complex in thermal equilibrium and the energy of the separated host and guest. This energy difference is about 70 kJ/mole and doesn't vary significantly with the temperature. The other process is the effect of the upper-rim substituents, which affect the energy surface of the reaction channel across narrowing the cross section of the association–dissociation channel. When these substituents show intensive motion at higher temperature, the cross section of the channel can drastically be reduced. However, ones cannot simply say that the cross section of the reaction channel decreases with the size of the upper-size substituent. According to the equipartition theorem, the motion of the larger group at a given temperature is slower compared to that of a smaller substituent. Therefore, a small group with high motion can reduce the cross section of the reaction channel to higher extent, i.e. to inhibit the reaction, than a larger group with its slow moving. According to the latest effect, due to the necessity of broadening the channel during a formation–dissociation process, the activation energy varies from zero up to 80 kJ/mole depending on the size and the actual motion of the upper-rim substituents. Although the rate of former process is known to be increased by the temperature, the latest process can decrease the reaction rate due to the increased activation energy when the motion of the

upper-rim substituents was increased at higher temperature. Consequently, two competitive processes exist in same time, one is supported, while the other one is inhibited at higher temperature.

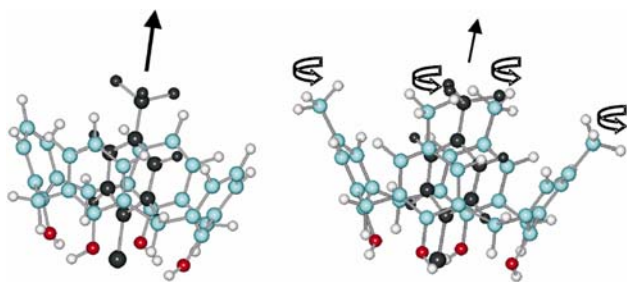
In Table 1 the calculated reaction rate constants of the three different complexes at ten different simulation temperatures are summarized. The values are varied between  $1.15274$ – $4.55060 \times 10^{14}$  1/s, that means  $1.92123$ – $7.5843 \times 10^{-10}$  mol/s. The rate constant determined experimentally ( $2.58979 \times 10^{-11}$  mol/s) falls in the above range of calculated rate constants. The difference obtained by the quantitative comparison of the experimental and theoretical values can stem from the neglected solvent effect during theoretical calculations. When we compare the dissociation of the three complexes, it can be clearly seen, that in the analyzed temperature range the calculated reaction rate constants are the highest in the cases of **1b-2** complexes and the lowest in case of **1c-2** complexes.

Figure 3 shows the  $\ln(k)$  values plotted against the reciprocal temperatures. At each of the ten given temperatures, the  $\ln(k)$  values follow the linear Arrhenius equation (see Eq. 2). The dissociation rate of the **1a-2** complex follows the linear classical Arrhenius equation, therefore it is higher at higher temperature. The activation energy of this reaction is 48.13 kJ/mol reflecting the thermodynamic control of the formation and dissociation processes of the **1a-2** complex.

Surprisingly, the dissociation rate of the **1b-2** complex decreases at higher temperature. Therefore, the activation energy has a negative value of  $-89.09$  kJ/mol. In this case, from the viewpoint of the energy, the formation of the host-guest complexes could be described as a two-state-system, where one state is assigned to the complex and the other state to the separated molecules. As the complex formation is exothermic, the complex has lower energy than the separated molecules. Let us suppose that the two energy level follows the Boltzmann distribution, then the decrease of the dissociation with increasing temperature could result in the increase of the population on the higher energy level. The unexpected dissociation rate of the **1b-2** complex can be attributed to the increasing rotation of the methyl groups at higher temperature, thereby this 'temperature-increased bulkiness' can prevent the guest molecule from leaving the calixarene cavity (Fig. 4). Therefore, the kinetic control on the dissociation process of the **1b-2** complex is more pronounced than in the case of other complexes. The dissociation rate obtained for the **1c-2** complex was found to be nearly independent on the temperature. This is probably due to the competitive kinetic and thermodynamic processes, where the increase of the thermodynamic processes at higher temperatures is compensated by the increased motion of the *tert*-butyl groups.

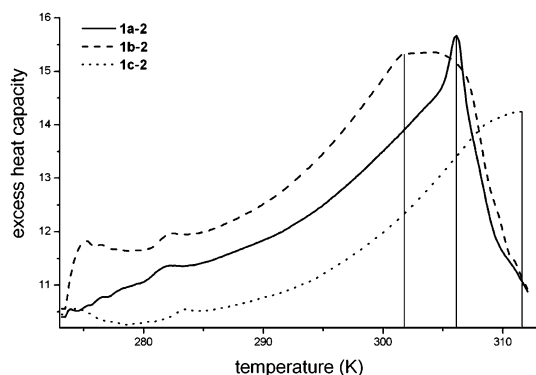
**Table 1** Calculated reaction rate constants of calix[4]arene complexes (**1a-2**, **1b-2**, and **1c-2**) at ten different simulation temperatures between 278 and 318 K in steps of 5 K

T [K]	<b>1a-2</b> k [ $\times 10^{14}$ 1/s]	<b>1b-2</b> k [ $\times 10^{14}$ 1/s]	<b>1c-2</b> k [ $\times 10^{14}$ 1/s]
273	2.62241	4.5506	2.06618
278	2.6139	4.44632	1.96371
283	2.65375	4.32123	2.44769
288	2.72235	4.12739	2.00948
293	2.79589	3.91035	1.97507
298	2.87261	3.68779	1.15274
303	2.98066	3.55744	1.23113
308	3.07582	3.50324	1.23202
313	3.11092	3.53043	1.3144
318	3.12904	2.93065	1.26504

**Fig. 4** A schematic view how the kinetic processes can inhibit the dissociation rate

The competitive thermodynamic and kinetic processes could result in different controls on the complex stability. While at lower temperature the guest is locked into the calixarene cavity by the dominating thermodynamic processes, the kinetically controlled processes are responsible for the same phenomenon at higher temperature.

To provide experimental support for our theoretical calculations, calorimetric measurements were performed. Figure 5 shows typical DSC curves of the mixture of equimolar solutions of **1a** and **2**, **1b** and **2**, as well as **1c** and

**Fig. 5** DSC curves of the complexes **1a-2**, **1b-2** and **1c-2**

**2**, recorded against chloroform with a scanning rate of 2 K/min. The vertical lines show the appropriate centre of gravity of the curves. The results indicate that the dissociation of **1b-2** complex is the fastest, followed by the dissociation of the **1a-2** complex and the dissociation of the **1c-2** complex is the slowest. These results are in a good agreement with the theoretical calculations described above.

## Conclusion

Dissociation dynamics of the complexes of host calixarene derivatives with *p*-chloro-trifluoromethylbenzene guest was studied by MDs calculations and DSC method. The selectivity character of calixarene was modified by functionalisation at the upper rim of the parent compound. The results obtained with calix[4]arene and 4-methylcalix[4]arene hosts show opposite temperature dependence of the reaction rate, while the 4-*tert*-butylcalix[4]arene shows almost temperature independent dissociation dynamics. Competitive thermodynamic and kinetic processes of different proportions are concluded to be responsible for these unexpected complex dissociation phenomena. This property is very probably due to the increased motion, especially the fast spinning of the Me and *t*Bu groups at the upper rim. Theoretical calculations seem to be proved by experimental results obtained by DSC method. Our results can contribute to the development of selective and sensitive chemical sensors and to design effective molecular containers for small aromatic compounds.

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