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The Rate of Host-guest Complex Formation of Some Calixarene Derivatives Towards Neutral Aromatic Guests

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In order to determine the factors controlling the response time of the selective chemical sensors, the dissociation dynamics of the complexes of cailx[4]arene with *p*-chloro-trifluoromethyl-benzene was studied with molecular dynamics calculations. The calculated reaction rates show a contradictory temperature dependence in the absence or presence of *tert*-butyl substituent at the upper rim of calixarene host molecules. While the dissociation rate increases with the temperature in the case of calix[4]arene host, it decreases at higher temperature when *t*Bu-calix[4]arene host is applied. The weak interaction energies and the low activation energy of the dissociation process validate that the complex equilibrium is rather thermodynamically controlled. Overall, the formation-decomposition processes of calix[4]arene host with *p*-chloro-trifluoromethyl-benzene guest seems to be a few tens faster then the case when *t*Bu-calix[4]arene host is applied. This observation supports applications of the calix[4]arene rather than *t*Bucalix[4]-arene as host molecules in chemical sensors with short response time. This finding can contribute to the development of high-speed sensitive chemical sensors.

Keywords: Calixarene; Host-guest complexes; Dissociation dynamics

INTRODUCTION

Calixarenes are cyclic oligomers, which have been widely used. It was reported that they are capable of forming stable and selective complexes with ions and neutral molecules [1–3]. Among the several experimental works molecular dynamics method was found to be successful testing ground to study the effect of the guest molecules on the isomerization rates between calixarene conformers [4], the complexation ability towards organic and inorganic cations [5], structure analysis [6], the effect of the solvent on the conformational isomerism of calix[4]-arenes [7].

The complexation behavior and the factors controlling the thermodynamic and kinetic stability or selectivity of some calixarene derivatives towards neutral π-electron deficient aromatics were reported. 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 permittivity [12] on the stability of the host-guest complexes in alcoholic solvents were determined by highly sensitive fluorometric measurements and quantum-chemical calculations. Especially, water-soluble calixarenes have laureate attention since they are hopeful candidates for successful applications in environmental, analytical and separation sciences, and also in pharmaceutical chemistry [13–15]. 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) [16,17] and quantum-chemical methods [18]. This stable and selective complex formation of calixarenes with neutral guests is a fascinating capability of this family of macrocycles.

The reported results are applicable in the development of selective and sensitive chemical sensors for neutral organic aromatics. Accordingly, the signal

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formation and transduction mechanisms of these chemical sensors are known to be affected either by the diffusion in the selective membrane or by the selectivity and strength of interaction with the analyte. The response time of the sensors can be affected by the rate of the complex formation. The selectivity character of calixarene complexes with different species can be modified by changing the cavity shape and by the different functionalisation patterns at the lower and/or upper rims of the calixarene skeleton. However, the response time of the sensors is one of the most important properties of their analytical applications, so it is important to describe the rate of the complex formation and to analyse the selectivity character of calixarene complexes.

Since the *tert*-butyl group is commonly used as upper rim substituent, in our present theoretical work two types of calixarene hosts were studied. The complex formation process of parent calix[4]arene towards neutral aromatic guests was compared to that of the *t*Bu-calix[4]arenes.

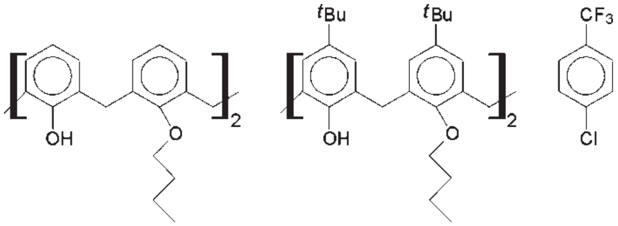
METHODS

Static Equilibrium Conformation of the Host-guest Complex

The equilibrium conformations of calix[4]arene **1a** (MW = 538.31) and *t*Bu-calix[4]arene **1b** (MW = 678.99) with *p*-chloro-trifluoromethyl-benzene **2** (MW = 180.52) were studied with semiempirical AM1 (Austin Model) method, followed by DFT/B3LYP/6-31++G calculations (Fig. 1). The Fletcher-Reeves geometry optimization method was used for the investigation of the conformers. Both the **1a** and **1b** calixarene derivatives were functionalized at 1and 3 positions with o-butyl groups. This functionalization was performed according to our earlier results where increased host-guest interaction was observed when the two opposite rings of the host calixarene are lying parallel each other. This conformation was adjusted by the o-butyl functionalization of the opposite rings at the lower rim of the calixarene skeleton.

Initial Geometry for Molecular Dynamics Simulations

The temperature-dependent molecular dynamic simulations were performed with MM+ forcefield. 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 started. The simulation time step was 0.1 fs.



1a **1b** **2**

FIGURE 1 O-alkylated calix[4]arene **1a** and *tert*-butyl-calix[4]arene **1b** derivatives as hosts and *p*-chloro-trifluoromethyl-benzene **2** as guest.

Temperature Dependence of Dissociation Dynamics

The dissociation dynamics of the host-guest complexes was investigated as a function of the temperature by Langevin molecular dynamic calculations using MM+ forcefield. The molecular dynamic calculations were done at seven different temperatures between 288 K and 348 K in steps of 10 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. To calculate this time, atomic distances between the atoms located at the upper part of the calixarene and atoms of the guest lies deepest in the calixarene cavity (see Fig 2.) were recorded and plotted against the simulation time. Each of this curve shows a minimum and the related simulation time was accepted as reaction time.

Calculation of the Reaction Rate

Reaction rates, k, were determined by fitting k to the calculated fraction of non-reactive trajectories, N/N_0, given by

$$\frac{N}{N_0} = e^{-kt}$$

where t is the reaction time. Accordingly, 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. Static and molecular dynamic calculations were carried out

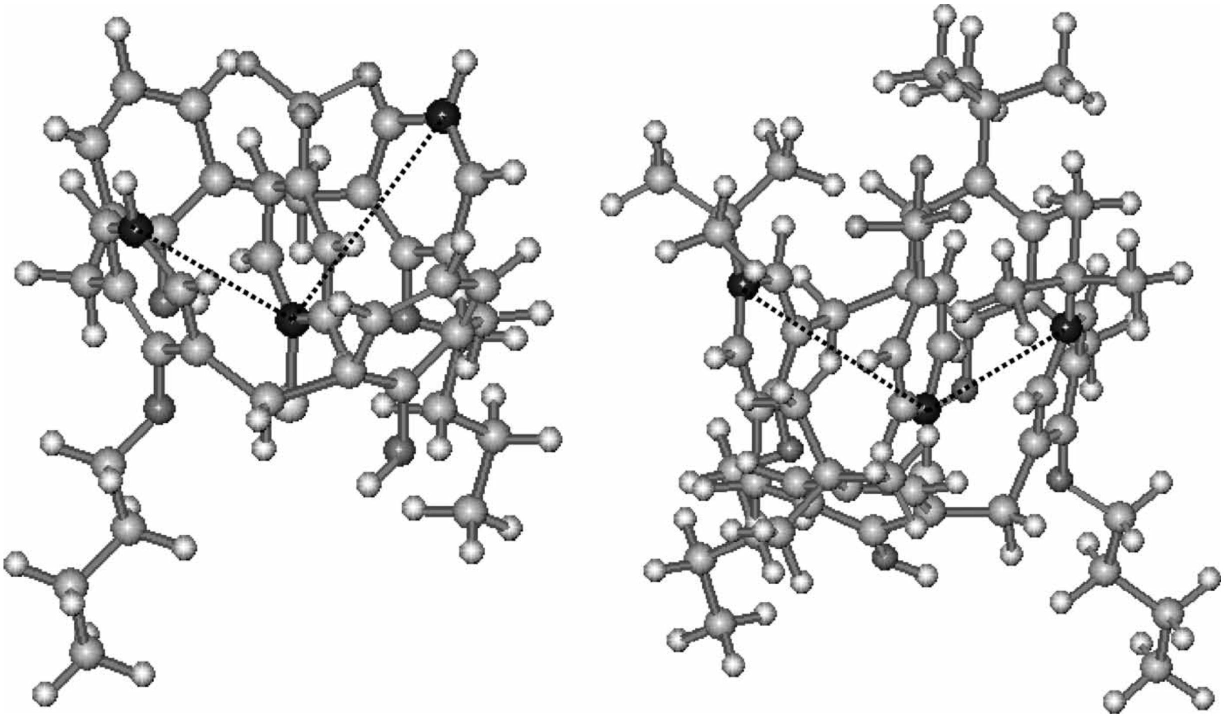


FIGURE 2 Distances of atoms used for the determination of reaction time. Two atoms of the calixarene and one atom of the guest were used for this calculation. They are indicated in black in the figures. Distances of atoms recorded during the dissociation process show a minimum. The simulation time associated to this minimum was accepted as reaction time.

with GAUSSIAN and HyperChem Professional 7 program packages, respectively.

RESULTS

Equilibrium Conformations of the Calix[4]arene and tBu-calix[4]arene Derivatives (1a and 1b, Respectively) with p-Chloro-triflouromethyl-benzene

The equilibrium conformations of complexes of calixarene with neutral phenolic guest molecules are stabilized by π-π type interaction [17]. In the present study, similar to that, the complexes formed during the interactions of the calixarene **1a** or **1b** with *p*-chloro-trifluoromethyl-benzene **2** are preferably stabilized by the π-π interaction between the aromatic π-electron systems of calixarene phenolic units and that of the aromatic guest molecules. Fig. 3 shows that in all cases the two opposite rings of the calixarene are nearly parallel. The average angle between these opposite rings was found to be 45 degree or 56 degree for the **1a** or **1b** derivative, respectively. The guest molecule lies between these rings forming a sandwich-type structure.

Reaction Rates of the Dissociation of Host-guest Complexes

The reaction times of the dissociation calculated above can be used to determine the rate constants of the dissociation at each different simulation temperatures. Fig. 4 shows an example for these calculations. After plotting the $\ln\frac{N}{N_0}$ values against the reaction time, we can describe the rate constant as the slope of the curve fitted to the points. Table I summarizes the calculated rate constants of the two different complexes obtained at seven different simulation temperatures.

Arrhenius Behaviour of the Dissociation Reaction

The calculated rate constants, k, of the dissociation of host-guest complexes (i.e. the *p*-chloro-trifluoro-methyl-benzene leaves the calixarene cavity) were derived from the direct trajectory calculations are shown in the Arrhenius plot in Fig. 4. At each of the seven given temperature levels, the $\ln(k)$ values follow the linear classical Arrhenius equation:

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

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

Figure 5 shows the $\ln(k)$ values plotted against the reciprocal temperatures. The calculated Arrhenius parameters are summarized in Table II.

DISCUSSION

Comparing the rates of the dissociation of the complex (Table I), it can be seen clearly that within

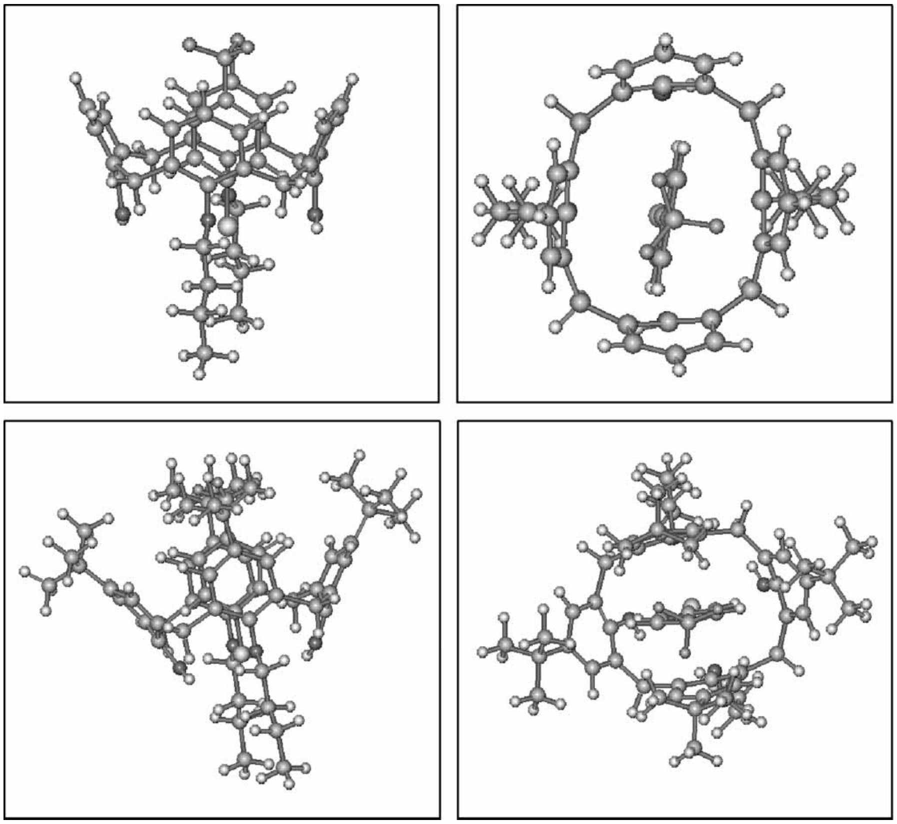


FIGURE 3 Side and top views of the optimized structure of inclusion complex of 1a with 2 (top) and 1b with 2 (bottom). The *p*-chloro-trifluoromethyl-benzene molecule enters into the calixarene cavity and lies between the two opposite aromatic rings of the calixarene.

the temperature range of the examination, the reaction rates in case of **1a**-**2** complexes are higher by nearly one magnitude than in case of the **1b**-**2** complexes. This behavior can be explained by the steric hindering of the *tert*-butyl groups at the upper rim of the **1b** species during the guest **2** enters into the cavity.

The other background of this effect is the force of this process, which becomes from the difference between the energy of the complex and the energy of the separated host and guest. The interaction energy of the **1a**-**2** and **1b**-**2** complexes were determined earlier [10]10] by *ab initio* HF/6-31G calculations and the effect of the solvent chloroform molecules was considered by the TIP3P method. The interaction energy of the **1a**-**2** or **1b**-**2** complexes were found to be 30.2 kJ/mol and 21.7 kJ/mol, respectively. Although the interaction energy between the host and guest, and therefore, the stability of the complex highly depends on the permittivity of the solvent used, the **1a**-**2** complexes shows higher interaction energy and stability in a series of solvents [12] than that of the **1b**-**2** complexes. In a first view, assuming that the complex and the dissociated species are not energetically separated, i.e. the

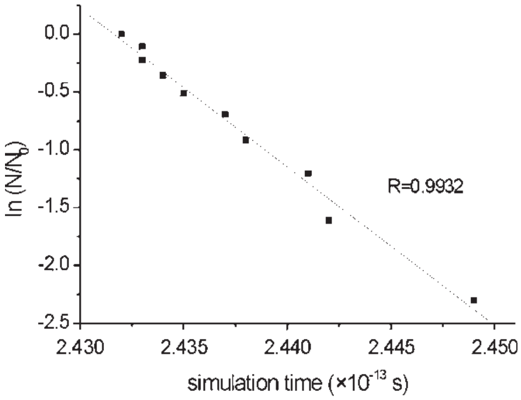


FIGURE 4 A typical plot of the ln(N/N$_0$) values *vs.* simulation time during dissociation of the complex of 1a with 2.Data taken from molecular dynamic simulations at T = 298 K. The observed rate constant determined from the slope of this curve was found to be $1.37 \cdot 10^{15}\ s^{-1}$ at this temperature.

TABLE I The calculated reaction rate constants of calix[4]arene complexes (**1a-2**, left) and of *t* Bu-calix[4]arene complexes (**1b-2**, right) at seven different temperatures between 288 K and 348 K in steps of 10 K.

T [K]	**1a-2** K [s^{-1}]	**1b-2** k[s^{-1}]
288	$1.25064 \cdot 10^{15}$	$1.13620 \cdot 10^{14}$
298	$1.36934 \cdot 10^{15}$	$1.20308 \cdot 10^{14}$
308	$1.47447 \cdot 10^{15}$	$1.14576 \cdot 10^{14}$
318	$1.47903 \cdot 10^{15}$	$1.19163 \cdot 10^{14}$
328	$1.64439 \cdot 10^{15}$	$1.16297 \cdot 10^{14}$
338	$1.70609 \cdot 10^{15}$	$1.12554 \cdot 10^{14}$
348	$1.68067 \cdot 10^{15}$	$1.09012 \cdot 10^{14}$

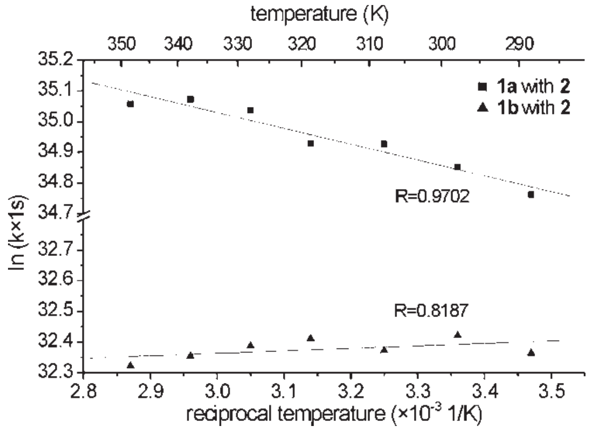


FIGURE 5 Arrhenius plot of the rate constants of the dissociation of host-guest complexes: **1a** with **2** (top) and **1b** with **2** (bottom). Standard deviation of the data points plotted varies between 0.03 and 0.05 ln(k × 1/s).

energy of the transition state related to dissociation process is equal or lower than the interaction energy, the reaction rate preferably determined by the energy difference between the two states of the system. Consequently, in contrast with the rate constants summarized in Table I, higher dissociation rate of **1b**-**2** complexes could be estimated from the interaction energy.

Results summarized on the Fig. 5 show opposite temperature dependence of the rate of dissociation of complexes **1a**-**2** than **1b**-**2** complexes. The dissociation rate of the **1a**-**2** complexes follows the classical Arrhenius equations and show higher rate at higher temperature with activation energy of 4.32 kJ/mol. This value is comparable with the kinetic energy of the particles at the given temperature range, it is 2.48 kJ/mol at room temperature. This means that the dissociation process and the complex formation are thermodynamically controlled in the case of the **1a**-**2** complexes.

However, surprisingly, the dissociation rate of the **1b**-**2** complexes is decreased at higher temperature and an activation energy of -1.38 kJ/mol can be derived from the slope of the line fitted to the ln(k) values. The negative value of the activation energy highlights that the state of the complex and that of the dissociated species are not separated by an energy barrier. Consequently, the complex formation can be described energetically as a two-state system, where one state is the complex and the another state belongs to the separated species. Since the complex formation was found to be exothermic, therefore the complex has lower energy than the separated species. The occupancy of these two energy levels follows the Boltzmann statistics, where the force of the dissociation decreases as the population of the higher energy level is increased at higher temperature. This behavior correlates well to our present results where a decrease of the reaction rate is obtained with increasing temperature. A further explanation for this unexpected temperature dependence of dissociation rate of the **1b**-**2** complexes is based on the increased movements of the tert-butyl groups at higher temperature, therefore this movement inhibits the leaving of the guest molecule from the calixarene cavity. This observation highlights the increased importance of kinetic processes of the dissociation in this particular case.

TABLE II Arrhenius parameters determined for the dissociation process of the 1a-2 and 1b-2 complexes.

	A [s^1]	E_a [kJ?mol^1]
1a-2	$7.75 \cdot 10^{15}$	4.32
1b-2	$6.87 \cdot 10^{13}$	-1.38

CONCLUSION

The response time of the selective chemical sensors can be affected by the reaction rate of the complex formation of the analyte with host molecules applied in the selective membrane layer. Accordingly, the dissociation dynamics of the complexes of calixarene derivatives with *p*-chloro-trifluoromethyl-benzene was studied with molecular dynamics calculations. Results show a contradictory temperature dependence of the reaction rate in the absence or presence of *tert*-butyl substituent at the upper rim of calixarene host molecules. While the dissociation rate increases with the temperature in the case of calix[4]arene host, this rate is reduced at higher temperature when *t*Bu-calix[4]arene host is applied. The low activation energy of dissociation validates that the complex equilibrium is rather thermodynamically controlled. Overall, the formation-decomposition processes of calix[4]arene host with *p*-chloro-trifluoromethyl-benzene guest seems to be a few tens faster then the case when *t*Bu-calix[4]arene host is applied. This finding can contribute to the development of high-speed sensitive chemical sensors.

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