

Temperature-dependent solvent effect on the kinetic energy distribution on *p*-cresol molecule as building block of calixarene capsules

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Abstract The solvent effect on the kinetic energy distribution of *p*-cresol molecule was investigated by quantum-chemical (QM) method and molecular dynamics (MD) simulations, then the consequences were checked experimentally by photoluminescence (PL) and differential scanning calorimetry (DSC) methods. Results of QM calculations highlight the coupling of two vibrational normalmodes of *p*-cresol molecule in the presence of ethanol while no similar coupling was observed in methanol. MD simulations show that the normalmode coupling in ethanol is more pronounced at higher temperature and it is preferably based on the molecular friction of the cresol molecule with its environment. The theoretical observations were also proved experimentally. The dissociation rate of calixarene–phenol complexes were measured by DSC method. The decreased dissociation rate of the calixarene–phenol complexes observed in ethanol reflects the increased motion of the methyl groups of cresol units of calixarene in the ethanol solvent, a property which was predicted by the theoretical results. Our findings are applicable to many areas of chemistry where the formation and dissociation rates play important role: e.g., in the development of chemical molecular sensors or developing

molecular containers for drugs towards pharmaceutical applications.

Keywords Molecular recognition · Inclusion complexes · Molecular modeling · Photoluminescence · Calorimetry

Introduction

The weak host–guest interactions are the focus of recent research due to, e.g., their potential applications in reversible chemical sensors [1, 2] and also in the development of molecular containers towards pharmaceutically important drug molecules. Two significant properties are important during the molecular packing and unpacking processes: (i) the kinetic rate of formation and (ii) the thermodynamic stability of the formed host–guest complexes. The competition of these thermodynamic and kinetic processes determines the formation or dissociation of weak molecular complexes at the molecular level. Furthermore, both of these two processes are affected by the temperature, however, on different ways: Following the general van't Hoff theory, the thermodynamic stability decreases at higher temperature while the role of kinetic processes is known as much more complex property. According to the determinant role of the π – π interaction in case of calixarenes [3, 4] sensing aromatic compounds, the dissociation dynamics of calix[4]arenes and *p*-chloro-trifluoromethyl-benzene complexes was studied in our previous works [5]. Molecular dynamics calculations were shown to be efficient means for these investigations and the results were validated experimentally by differential scanning calorimetry (DSC). In those studies the calix[4]-arene, 4-methylcalix[4]arene and 4-*tert*-butylcalix[4]arene were chosen as host model-compounds according to their

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binding selectivity toward aromatic guests. Surprisingly, results show significantly different temperature dependence of the reaction rate on various substituents (H, Me, *t*Bu) at the upper rim of the calixarene skeleton. Since the 4-methylcalix[4]arene skeleton is built by *p*-cresol molecules linked through methylene-bridges, we focus on the dynamic motions of these units. Especially, in this work the results of theoretical simulations are presented to clarify how the kinetic processes can be affected by the solvent in solution phase. Furthermore, the ring-vibration of *p*-cresol skeleton transformed to the kinetic energy of the methyl group will be presented.

Methods

Theoretical calculations

The geometry optimizations of the *p*-cresol molecule (Fig. 1, **1**) and the calculation of its IR spectra were performed by DFT/6-31++G(p,d) quantum-chemical calculations and the solvent effect was considered with the Polarizable Continuum Method (PCM). These methods are implemented in the Gaussian 03 packages [6]. To examine the effect of temperature on the kinetic energy distribution on the molecular skeleton of *p*-cresol molecular dynamics (MD) simulations were used within two different approximations by the HyperChem Professional 5.1 code [7]. Either the solvent molecules were considered explicitly by the TIP3P method using an appropriate extensions by Bender [8] or, in another approximation, the solvent effect was considered by the Langevin method [9, 10] using the frictional parameter γ obtained from the Einstein relation. The frictional coefficients of methanol and ethanol were estimated using the experimental diffusion data of these solvents [11]. During the molecular dynamics calculations the AM1 Hamiltonian [12] was used. To find an appropriate initial condition for Langevin dynamics a ‘heating’ algorithm implemented in HyperChem was used. This procedure heats up the molecular system smoothly from

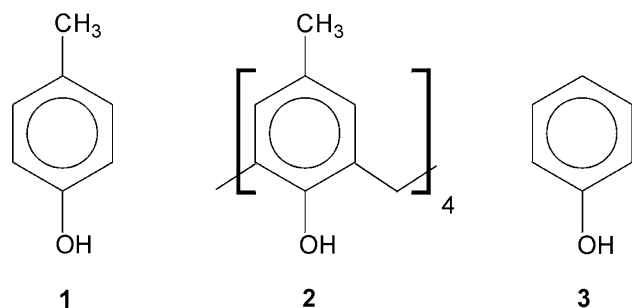


Fig. 1 *p*-Cresol (**1**), the 4-Me-calix[4]arene (**2**) and the phenol (**3**) molecules were investigated in this work

lower temperatures to the temperature T at which it is desired to perform the molecular dynamics simulation. The starting geometry for this heating phase is a static initial structure. The optimized AM1 geometry of vinyl bromide was taken as the initial structure, and the temperature step and the time step in the heating phase were set to 2 K and 0.1 fs, respectively [13, 14].

Materials and experimental methods

4-Methylcalix[4]arene **2** was prepared as described in the literature [15]. The guest phenol compound **3** was purchased from Aldrich and used without further purification. Dry methanol and ethanol (HPLC grade, water content <0.05%) were purchased from Panreac (Spain) and used as received.

Photoluminescence measurements

A highly sensitive Fluorolog τ 3 spectrofluorometric system (Jobin-Yvon/SPEX) was used to determine the complex stability by PL method following our methodology described earlier [16–21]. For data collection a photon counting method with 0.2 s integration time was used. Excitation and emission bandwidths were set to 1 nm. 1 mm layer thickness of the fluorescent probes with front face detection was used to eliminate the inner filter effect.

In order to investigate the interaction of **2** with **3** guests, 10^{-4} M stock solutions were prepared in methanol or ethanol solvents. According to the Job's method, samples were prepared as mixture of the appropriate stock solutions of **2** and **3** with 1:9, ...9:1 molar ratios. The PL spectra were recorded in 16 different temperatures within the range from 283 K to 313 K with 2 K steps.

Kinetic measurements

Calorimetric measurements were carried out with a highly sensitive nano-II-DSC 6100 (Setaram, France) instrument. The calorimeter is configured with platinum capillary cell, both the sample and reference compartments are built with volume of 0.299 mL. The samples were pressurized to $(3 \pm 0.02) \times 10^5$ Pa during all scans. The measurements were performed in methanol and ethanol solvents. Due to the high volatility of the alcohols, samples are pressurized above 3×10^5 Pa in a closed calorimetric cell. Exploiting the reversible character of the ‘host–guest’-type complex formation, cyclic scans were performed within the 273–343 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. However, each scans were separated with

15 min idle time due to the slow diffusion-controlled formation of host–guest complexes. Accordingly, during our measurements, the heat flow was scanned between 273 and 343 K with the scanning rate of 0.5, 1, 1.5, and 2 K/min forward and backward and the second heating curve was applied for the data evaluation. In order to investigate the interaction of calixarene with phenol, 10^{-3} M solutions were prepared in methanol or ethanol solvents. The excess heat capacity was calculated by subtracting the baseline using the own software of the calorimeter (CpCalc/SETARAM, 2003). The reaction rate was calculated by the Kissinger's method [22], where a plot of a function of heating rate and $\ln\left(\frac{H_r}{RT_{\max}^2}\right)$ versus $1/T_{\max}$ gives E/R from the slope and A/E from the intercept:

$$\ln\left(\frac{H_r}{RT_{\max}^2}\right) = -\frac{E}{RT_{\max}} + \ln\left(\frac{A}{E}\right)$$

Results and discussion

Calculated IR spectra

Figure 2 shows the calculated IR spectra of *p*-cresol dissolved in methanol or ethanol solvents. Calculations were performed at ab initio level considering the presence of solvent by the PCM method. Although the result shows that the spectra are only slightly modified by changing the solvent from methanol to ethanol, significant changes were observed on a few particular molecular vibrations (Fig. 3). Two peaks associated to the two low-frequency vibrations of the aromatic rings were analyzed in detail accordingly. In methanol, the mentioned two peaks are observed at 420.5 and 431.5 cm^{-1} . These two peaks are shifted towards higher frequencies (to 425.2 cm^{-1} and 436.7 cm^{-1} , respectively) when methanol was changed to ethanol. This shift is

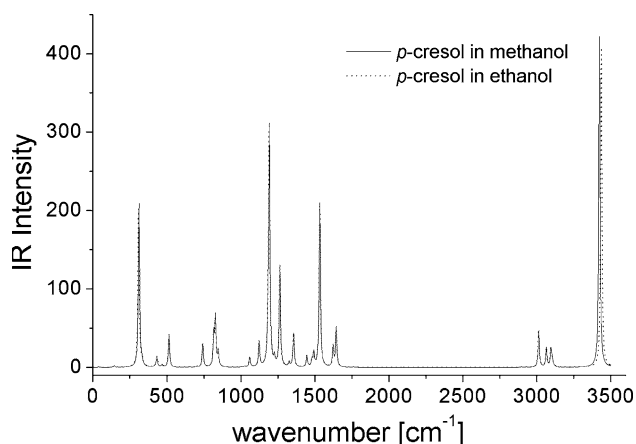


Fig. 2 IR spectra of *p*-cresol calculated in methanol or ethanol solutions by DFT/6-31++G(p,d)/PCM method

probably due to the increased atomic forces in ethanol having lower permittivity ($\epsilon_{r,T=293\text{K}} = 25.3$) compared to the permittivity of methanol ($\epsilon_{r,T=293\text{K}} = 32.6$).

Figure 4 shows the atomic displacements associated to the two IR peaks discussed above and observed in methanol (Fig. 4, top) or in ethanol (Fig. 4, bottom). As it can be seen clearly, the peak observed in methanol at the 420.5 cm^{-1} is associated to the in-plane, while the peak at 431.5 cm^{-1} is associated to the out-of-plane vibrations of the *p*-cresol molecule.

Furthermore, in contrast to the methanol solutions, the in-plane and out-of-plane vibrational modes are coupled in ethanol (Fig. 4, bottom), therefore both the in-plane and out-of-plane atomic motions are involved in each of the two examined normal mode vibrations in ethanol. In addition, after the solvent changed from methanol to ethanol, the intensity of the lower frequency peak is increased from

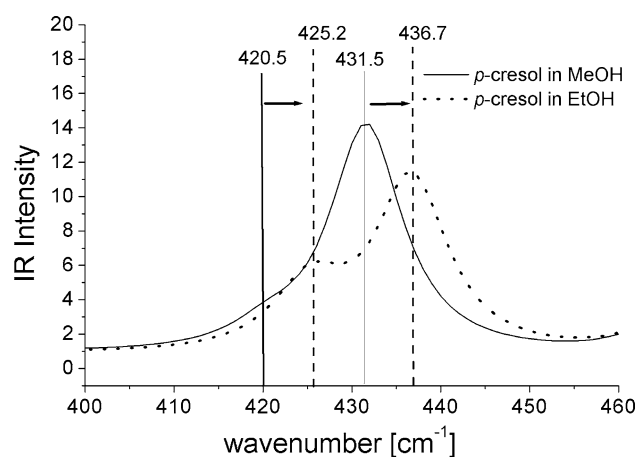


Fig. 3 Spectral changes observed in the IR spectra of *p*-cresol when the solvent changed from methanol to ethanol

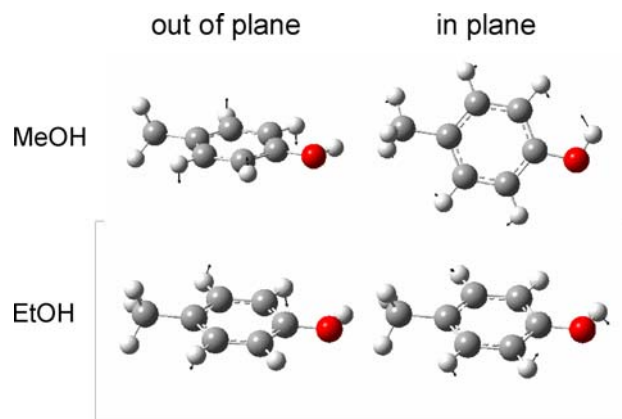


Fig. 4 Atomic motions of *p*-cresol molecule calculated in methanol (top: 420.5 cm^{-1} (left) and 431.5 cm^{-1} (right)) and in ethanol (bottom: 425.2 cm^{-1} (left) and 436.7 cm^{-1} (right)) solvents

1.12 a.u. to 3.91 a.u. while the higher frequency peak slightly decreased from 13.5 a.u. to 10.3 a.u.

Molecular dynamic simulations

Two types of MD simulations were performed to examine the temperature effect on the energy distribution of kinetic energy on the molecular skeleton of *p*-cresols. In both MD simulations the Hamiltonian was represented at semi-empirical AM1 level, however, the molecular environment is considered either by the Langevin method or by the TIP3P method, where the solvent molecules are explicitly considered. Results highlighted that the coupling of the molecular vibrations has significant effect on the temperature dependence of kinetic energy distribution. Considering the kinetic energy raises from bond vibrations and from the rotation of the Me group of cresol in ethanol as 100%, Fig. 5 shows the percentage change of this kinetic energy calculated by the TIP3P or Langevin methods in methanol or ethanol solvents. Accordingly, the kinetic energy located on the methyl group increases or decreases with the temperature in the ethanol or methanol solvent, respectively (Fig. 5). The TIP3P method, where the solvent molecules are explicitly considered, shows lower temperature dependence of the curves compared to the results derived with the Langevin method. This observation offers fine tuning of kinetic energy distribution by choosing appropriate solvent.

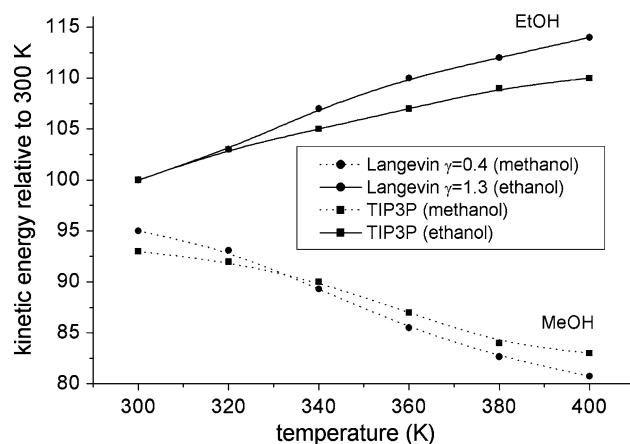


Fig. 5 Changes of the kinetic energy located on the methyl group of *p*-cresol molecule as a function of the temperature. The solvent effect is represented by the molecular friction γ between the solute and solvent molecules

Experimental evidence according to the theoretical results

Unfortunately, it is hard to obtain direct experimental evidence for the theoretical observation above due to the enhanced molecular motions at the given frequency range and also because in the solution phase the peaks were broadened. We decided therefore to examine a model on which the consequences of the theoretical findings can be studied. Accordingly, we performed experiments on the dissociation kinetics of 4-Me-calix[4]arene (**2**)–phenol (**3**) complexes (see Fig. 1). The calixarene **2** molecule is built by cresol segments linked through methylene bridges. This compound is known to form complexes with single aromatics (e.g., references [19–21]). The stability of the calixarene **2** with the phenol molecule **3** was determined first by PL measurements.

The formation thermodynamics observed by PL studies

Table 1 summarizes the thermodynamic parameters of complex formation of calixarene **2** with the guest **3** phenol molecules observed by PL measurements. The results show nearly same stability of the complexes in methanol and ethanol solvents which property relates to the well known enthalpy–entropy compensation. That is, although the π – π interaction is known to be stronger in a solvent having lower permittivity, however, as a parallel effect, higher entropy decreasing can be obtained during formation of **2**–**3** complexes in ethanol due to the increased order of the system under the effect of the stronger molecular interactions.

Reaction rate studies by DSC measurements

To investigate the dissociation rate of the complexes of **2** with **3**, the DSC curves were recorded with five different concentrations within the temperature range from 283.16 K to 313.16 K. The concentrations are chosen below 10^{-2} M to avoid considerable dimerization of the phenol molecules. Further details are described in the experimental section. Initial concentration of the complexes in the calorimeter's capillary is determined as described in ref. [23]. Following the Kissinger's method [22], the observed kinetic Arrhenius parameters about the dissociation of calixarene–phenol complexes in methanol or ethanol are collected in Table 2.

Table 1 Thermodynamic parameters observed during the complex formation of **2** with **3**

Solvent	ΔH enthalpy kJ/mol	ΔS entropy J/Kmol	ΔG free enthalpy kJ/mol	Log K (298.16 K)
Methanol	–35.1 (3)	–24.9 (4)	–27.7 (3)	4.86
Ethanol	–37.2 (3)	–33.4 (3)	–27.2 (3)	4.77

Table 2 Arrhenius parameters related to the decomposition kinetics of 2–3 complex

Solvent	E kJ/mol	A 1/s
Methanol	29	−1.30
Ethanol	67	−1.27

Results show much faster dissociation in methanol than in ethanol.

The dissociation observed in methanol shows much lower activation energy compared to that observed in ethanol. Probably this is the main reason why faster dissociation was observed in methanol, especially, if we consider that the frequency factors are nearly the same in both solvents. The increased activation energy can be associated to the increased motions of the methyl group [5]. This is because during formation or dissociation of an inclusion complex, a minimum cross section of the entrance channel required. The cross section of the channel is determined by the just entering or leaving guest molecule. If this channel is too narrow, e.g., due to the large substituents at the upper rim of the calixarene, the channel have to be broadened prior the guest molecule enters into the cavity. An upper rim located small group with high motion can reduce the cross section of the reaction channel showing intensive motion at higher temperature. Broadening the channel assumes also the torsion of the whole calixarene skeleton which costs additional energy. As a result, the activation energy of reactions associated to the dissociation of the complexes is also increased.

Conclusion

The temperature-dependence of the solvent effect on the kinetic energy distribution on the *p*-cresol molecule was investigated by both theoretical and experimental methods. The kinetic energy of the vibrations of the aromatic ring shifted towards the methyl substituent in ethanol at an elevated temperature. In contrast, in methanol a decreased kinetic energy was observed on the methyl group when the temperature increased. QM and MD analysis highlighted that the significantly different temperature dependence could be originated from the interference of two normal mode vibrations (in-plane and out-of-plane) of the aromatic ring in ethanol. A consequence of these properties has been observed by DSC method on the dissociation rate of calixarene–phenol complexes. Statements are applicable in wide scale of chemistry where the formation–dissociation rate plays important role: in development of chemical molecular sensors or developing molecular containers for drugs in pharmaceutical applications.

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