



Shaping Tetraazaparacyclophanes for Selective Solvent Vapour Detection: Structural Variations in Coating Design*

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Abstract

Paracyclophanes serve well as receptor sites mimicking enzyme analogue recognition. Their application as coatings for the mass-sensitive detection of toxic organic solvent vapours is demonstrated involving synthetic variation of the macrocycle in terms of cavity size, shape and stereoelectronics. In this way it is possible to tailor these hosts towards different analytes such as chloroform or toluene. The computational modelling of the inclusion allows the prediction of both the sensitivities and selectivities of promising coatings before doing time consuming syntheses. Force-field calculations show that the outstanding inclusion behaviour of a xylylene bridged tetraazaparacyclophane towards large aromatic and halogenated analyte molecules is due to the elongated cavity of the host. Temperature-dependent determination of the equilibrium constant *K* of the guest inclusion shows that calculated and measured interaction enthalpies do correlate satisfactorily.

Introduction

The detection of low concentrations of gaseous organic pollutants such as halogenated or aromatic hydrocarbons is still of importance for human beings and the environment alike. There is a need for suitable measurement equipment in widespread applications ranging from work place monitoring [1], environmental protection and process control [2, 3] to leak indication in feed lines of supply systems. Chemical sensing is to be seen as a favourable alternative to conventional analytical methods [4], fulfilling the demand common to all these applications of a fast and sufficiently accurate on-line measurement while avoiding extensive sample preparation. The problem of detecting volatile analytes without a pronounced functionality is successfully overcome by the combination of mass-sensitive quartz microbalance (QMB) oscillators using supramolecular chemistry as the recognition principle. In this context tetraazaparacyclophanes have proven to be highly versatile molecular receptors that function well for sensor applications, providing linearity, short response times, stability and reversibility of signals [5]. The macrocycles are promising candidates for use in analyte group discrimination, because they are easily modified with respect to the size and shape of the cavities [6, 7], which makes it possible to tailor these molecules for different guests [8, 9]. In this paper we present efforts in the design and development of tetraazaparacyclophane-based mass-sensitive sensor systems involving synthetic variation

of the parent structure by varying cavity size, shape and stereoelectronics. The influence of the spacer chain length on both sensitivity and response times and the introduction of aromatic groups to the bridge are particularly discussed. By the introduction of xylylene bridges a rigid, highly pre-organized macrocycle is obtained with an enlarged inner hydrophobic contact surface. This preformed geometry enables especially electron rich aromatic guest molecules to be engulfed [10, 11]. In contrast the use of an alkyl chain bridge reveals a much more flexible host, suitable for the incorporation of various volatile organic solvents. The concept of intracavitative guest complexation is confirmed by computational modelling of complex stabilization enthalpies that are correlated to the mass-normalized sensor-response. Additional experimental values for the stabilization enthalpies of the inclusion process are obtained by temperature dependent measurements.

Materials and methods

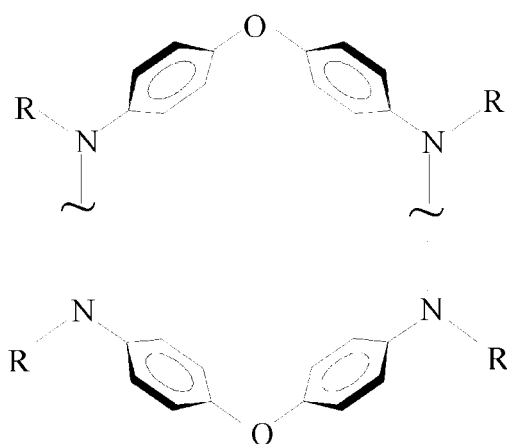
The tetraazaparacyclophanes **1a–1i** (Figure 1a) were synthesized as described elsewhere [12, 13]. Compound **1j** was prepared by using α,α' -*p*-dibromoxylylene as bridging reagent. Compound **1k** (Figure 1b) was prepared by using 1,3,5-tris(bromomethyl)benzene as bridging reagent, resulting in a bicyclic compound.

Measurements were performed using QMBs that work at a resonance frequency of 10 MHz and consist of an AT cut quartz plate covered with gold electrodes of 5.5 mm in diameter. Sensitive layers were deposited on the electrodes by use of a spin-coating process of a chloroform solution of

* Dedicated to Prof Dr. Heinz Hoffmann on the occasion of his 65th birthday.

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a)



b)

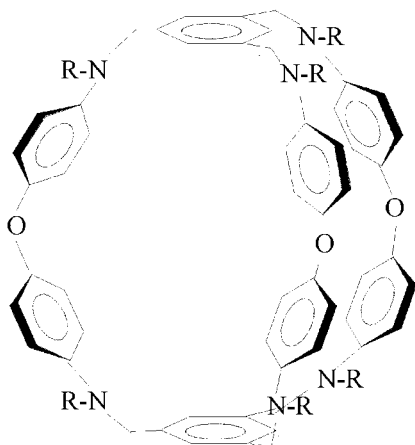


Figure 1. Structural drawing of (a) the tetraazaparacyclophanes **1a–1c**: **R** = ethyl, **a**: $\sim = -(\text{CH}_2)_3-$, **b**: $\sim = -(\text{CH}_2)_4-$, **c**: $\sim = -(\text{CH}_2)_5-$, **1d–1e**: **R** = *n*-pentyl, **d**: $\sim = -(\text{CH}_2)_3-$, **e**: $\sim = -(\text{CH}_2)_4-$, **f**: $\sim = -(\text{CH}_2)_5-$, **1g–1i**: **R** = *n*-decyl, **g**: $\sim = -(\text{CH}_2)_3-$, **h**: $\sim = -(\text{CH}_2)_4-$, **i**: $\sim = -(\text{CH}_2)_5-$, **1j**: **R** = tosyl, $\sim = -(\text{CH}_2)-(\text{C}_6\text{H}_4)-(\text{CH}_2)-$, (b) the bicyclic paracyclophane, **1k**: **R** = tosyl.

the coating material or by dropping and solvent evaporation. The covered device acts as a frequency determining element in an oscillator circuit [14]. Frequency measurements were made with a Keithley 775A frequency counter, which gives a resolution of ± 0.1 Hz and was interfaced to a personal computer via an IEC bus and interface card. To compensate for temperature and pressure fluctuations the difference of the resonance frequencies of a coated and an uncoated reference device was calculated. In these setups the response of the transducers to mass-changes due to analyte ad/absorption is described by the approximated Equation (1), where Δf is the frequency change, f_0 is the initial operating frequency, ρ_q and μ_q are the density and the shear modulus respectively of the quartz, $\Delta m/A$ is the mass change per unit area caused by deposition of the coating and by subsequent interactions of the coating with solvent vapour [15].

$$\Delta f = \frac{-2f_0^2}{A\sqrt{\rho_q/\mu_q}} \Delta m \quad (1)$$

A solvent vapour/air stream of defined analyte concentration was generated by mixing air saturated with solvent vapour and pure air with Tylan FC-2900 mass flow controllers in a thermostated gas mixing apparatus, which was calibrated by MIR-measurements in a multi reflexion gas cell (variable optical path length from 0.25 to 7.5 m, volume 223 ml) with a Perkin Elmer 2000 FT-IR spectrometer. The sensor heads were placed into a thermostated measuring chamber.

Computational calculations were performed with the MM3 force field by Allinger [16]. Preoptimization and input files were created with the HyperChem 5.1 platform (MM+ and forcefield) and transferred afterwards to the MM3-cartesian format by a self-made converting software. Final results were calculated on a HP-9000/715/80 workstation. Output files were transferred back to the personal computer afterwards to display the structure.

Results and discussion

The bulk dissolution of organic solvent vapours was monitored by a quartz microbalance sensor coated with the tetraazaparacyclophanes **1a–1j**. Following our primary interest in the optimization of the cavity size the ethyl substituted compounds **1a–c** were used in order to measure the pure effect of the size parameter without any supporting influence of the spacer groups. A direct relationship between the chain length of the bridge of the moiety and the volume of the analytes was observed in nearly every case, as visualized in Figure 2. As indicated by the degree of mass-loading the small chloroform is more effectively incorporated into the medium host **b**, whereas the bulky analytes carbon tetrachloride and tetrachloroethylene are engulfed by the macrocycle **c** with the largest inner diameter. The same tendency is observed for the large aromatic hydrocarbon toluene and to a certain extent for benzene that again show the most effective incorporation with compound **c**. Thus, it can be concluded that the experimentally measured occupancy is an indicator of analyte size and hence that the analyte is placed inside the cavity.

For the development of sensor coatings with short response times long alkyl chains up to ten – or in other cases twenty – carbon atoms were fixed as spacers to the supramolecular host-cavities of interest. In this context it was found that for the tetraazaparacyclophanes the sensor response was directly dependent on the chain length. The tendency of the host-layer to crystallize decreased with the increase of the length of the side chains. The resulting layer is more porous and diffusion is more easily possible and hence the sensor effect is enhanced. This is visualized in Figure 3 for tetrachloroethylene and toluene which were selected as model analytes for halogenated hydrocarbons and the group of electron rich aromatic solvents. With longer side chains it is easier to gain access to deeper parts of the layer resulting in a greater sensor effect. Response times

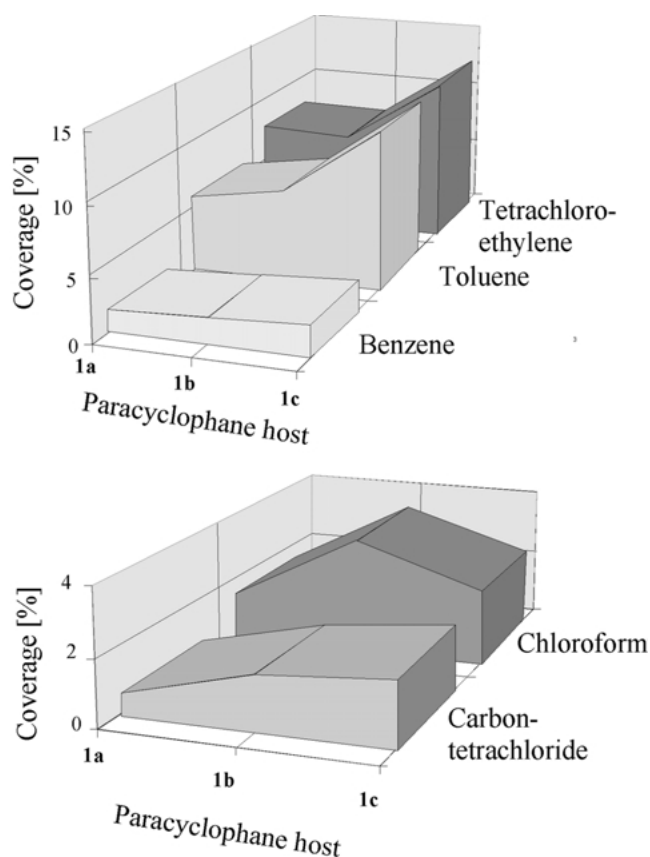


Figure 2. Experimentally measured occupancy of paracyclophanes **1a–1c** at 1000 ppm analyte concentration, layer thickness: 40 nm, $T = 25\text{ }^{\circ}\text{C}$.

are one minute or less which allows the operation of the sensor even with thick layers in a wide concentration range. A second reason for enhanced sensor responses with longer substituents should be the additional complexing properties of the spacer groups that interact closely with the incorporated analyte. In this way additional hydrophobic interactions are generated during complexation which somehow enlarged the size of the cavity. Although by alkylation of the nitrogen atom intramolecular stabilization via hydrogen bonds cannot take place any more, another excellent feature is that the cross sensitivity of the compound to water is reduced to a minimum. Thus, the optimization of cavity size and the introduction of spacers with supporting influence on the complexation shows the direction for tuning the sensitivity of the system.

A further step is to introduce aryl groups as a bridge into the basic macrocycle, yielding compound **1j**. This host molecule is more rigid than the other derivatives so it has an optimum preorganized geometry. According to molecular modelling results no intramolecular self-complexation of the bridging groups nor a blocking of the entrance of the cavity takes place. MM3 calculations reveal that host **1j** is elongated by a factor of approximately 2.5 compared to compound **1a**, which makes this larger cavity well suited to incorporate halogenated or aromatic electron rich guests. This is due to van der Waals interactions with the highly polarizable chlorine atoms or π -cloud overlapping, revealing high sensitivities as demonstrated in Figure 4. Small molecules

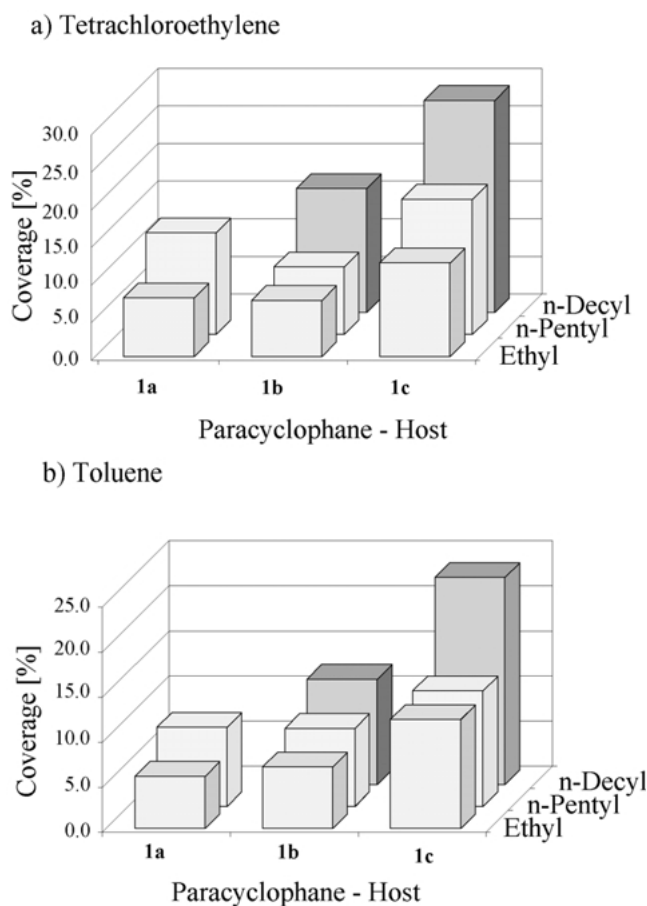


Figure 3. Sensor effect of tetraazaparacyclophanes in dependence on chain length for tetrachloroethylene and toluene at 1000 ppm analyte concentration. Layer thickness is 40 nm, $T = 25\text{ }^{\circ}\text{C}$.

like ethanol or acetone are not incorporated into the cavities. The increased sensitivity to the large guest molecules tetrachloroethylene and toluene is assumed to arise additionally from an extremely good nestling of these large analytes probably due to an induced fit mechanism that appears during complexation. Figure 5 shows the MM3 calculated host-guest geometries for the complexes of the tetraazaparacyclophane **1j** with tetrachloroethylene and toluene. The results indicate a geometrically optimized structure that provides a hydrophobic pocket well adapted to embed the analytes.

Computational modelling was used to calculate host-guest interactions to improve understanding of the mechanism of the selective binding of the analyte. The stabilization enthalpies were calculated from isolated, gaseous molecules and no lattice energy was included. The resulting energies are related to the heat of formation of the structures, although they are not the true enthalpies since thermal motion and temperature-dependent contributions are absent from the energy terms. The overall stabilization enthalpy ΔH^0 was found to be a suitable measure to estimate the sensor signal, as indicated in Figure 6a. ΔH^0 is the difference of the heat of formation enthalpies for the individual host and guest and the heat of formation enthalpy of the host-guest complex. The equilibrium constant K was determined experimentally by mass-loading during vapour exposure at 1000 ppm ana-

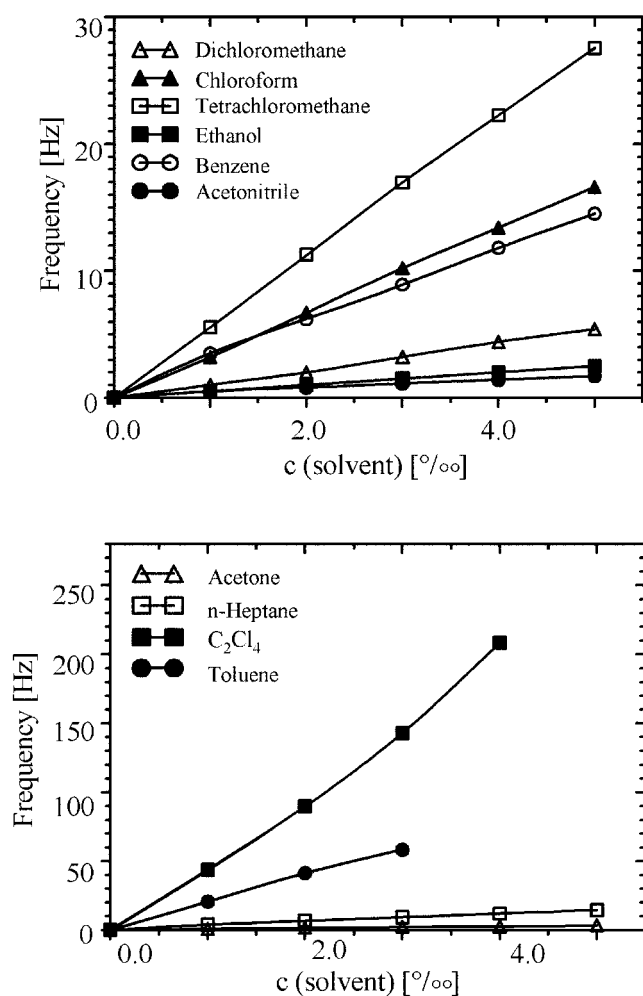


Figure 4. Sensor characteristics of compound **1j** for various solvents. Layer thickness is 40 nm, $T = 25^\circ C$.

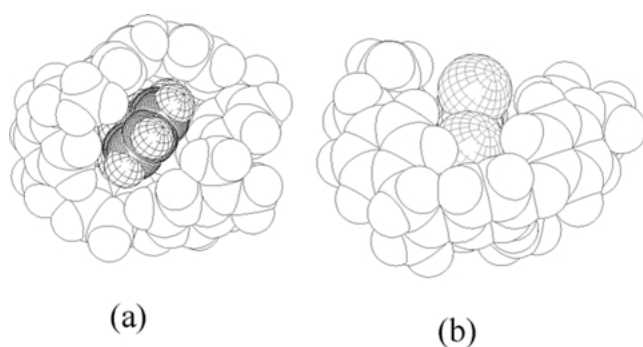


Figure 5. MM3 calculated host-guest geometry of compound **1j** with (a) toluene and (b) tetrachloroethylene.

lyte concentration. Further improvement was achieved by considering the entropic loss during complexation. It can be assumed that the nature of the incorporated analyte is similar to that of a liquid, so the entropic change correlated to the inclusion process can be estimated by the condensation entropy of the solvent. Some improvement of the correlation was obtained when the free enthalpy of complexation ΔG^0 was plotted versus the equilibrium constant of the host-guest inclusion compound (Figure 6b). Only for CCl_4 and $CHCl_3$

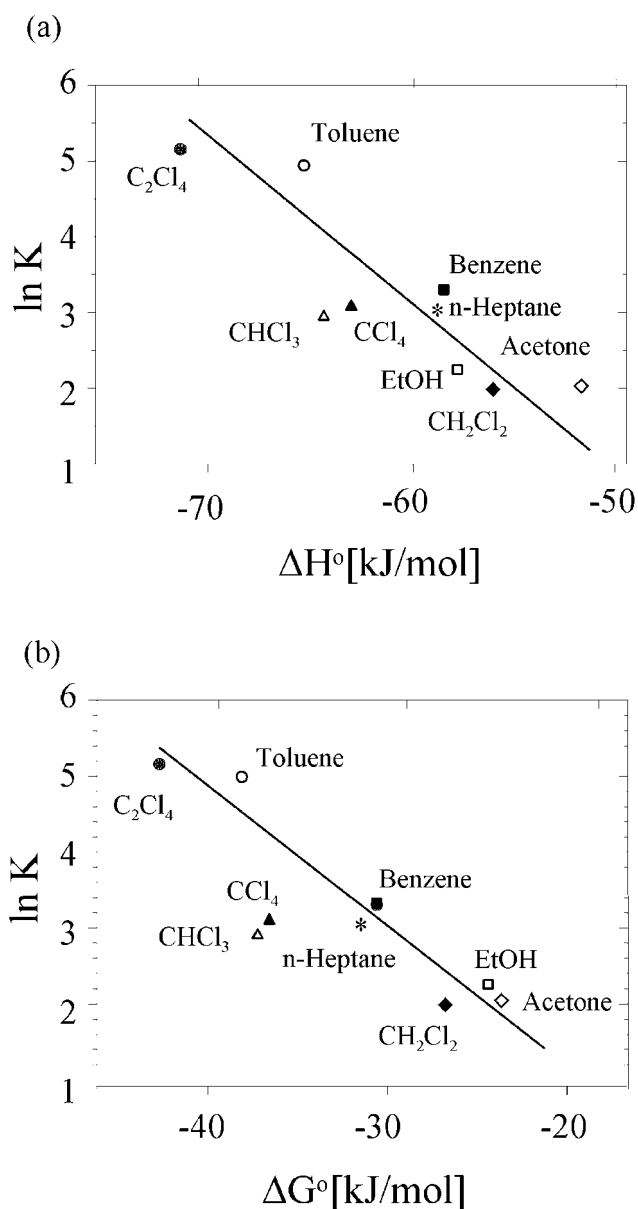


Figure 6. Correlation between the experimentally measured equilibrium constant and the complexation enthalpies for compound **1j**.

were there some deviations from calculated results which could be due to an underestimation of the entropy change.

The observed correlation of the force-field calculations with experimental data is remarkable since they are a strong hint for intracavitative inclusion by the tetraazaparacyclophane receptors and prove the validity of the calculated data and the chosen model when considering the entropic loss. To get a deeper insight into the difference between the calculated and the real values, additional measurements were made in order to determine the temperature dependency of the equilibrium constant of the host-guest inclusion and hence to get experimental values for the stabilization enthalpies of the inclusion process. According to the BET model [17], the mass sensitive sensor responses yield a correlation between the measured effects and the enthalpies ΔH_{Ads} .

Table 1. Experimental and calculated values for the stabilization enthalpies of the host–guest inclusion of benzene, toluene and chloroform in the bicyclic paracyclophane host **1k**. Layer thickness was 60 nm, temperature was varied from 20 °C to 60 °C

Analyte	ΔH_{Ads} [kJ/mol]	ΔH_{MM3} [kJ/mol]
Benzene	−34.3	−48.1
Toluene	−43.5	−48.8
Chloroform	−46.8	−54.4

$$\left(\frac{\partial \ln p}{\partial 1/T}\right)_n = \frac{\Delta H_{\text{ads}}}{R}. \quad (2)$$

The enthalpy ΔH_{Ads} is evaluated by temperature variation of the sensor effects at a constant number of analyte occupied cavities ‘ n ’ measuring the partial pressure p . Measurements were carried out with the bicyclic paracyclophane host **1k** and several analytes like benzene, toluene and chloroform. The layer thickness was about 60 nm and the temperature was varied from 20 °C to 60 °C. Figure 7 gives the result of the temperature dependent inclusion of benzene and it shows that a linear correlation is obtained between $\ln(p)$ and $1/T$. Changes of the resonance frequency f_0 due to temperature dependent quartz properties were compensated for by differential measurements both with a separate QMB and a device consisting of two electrode pairs on the same substrate. The slope of the straight lines yields $\Delta H_{\text{Ad}}/R$. In Table 1 the data for benzene, toluene and chloroform are summarized and the results show reasonable trends to the calculated data. The calculated values are slightly higher by 20–30%, the given tendencies within the experimental data were described well by the calculations. So it can be concluded, that the calculated data describe tendencies in the real system very well and give access to a theoretical approach of explaining sensor effects in a quantitative manner. It is even possible to predict sensor effects with the help of powerful chemical modelling packages. This might help to select promising sensor materials on the computer and to save money consuming synthesis time. In addition to the calculations and mass sensitive measurements FT-IR spectroscopic investigations and application of the BET adsorption analysis were performed. Both clearly showed that the measured sensor responses are due to specific host–guest complexation [17, 18].

Conclusions

The sensor effects of the molecular cavities described depend on the size of the analytes and can be influenced in terms of response time and selectivity by changing the pre-organized geometry of the host, by varying the bridging groups

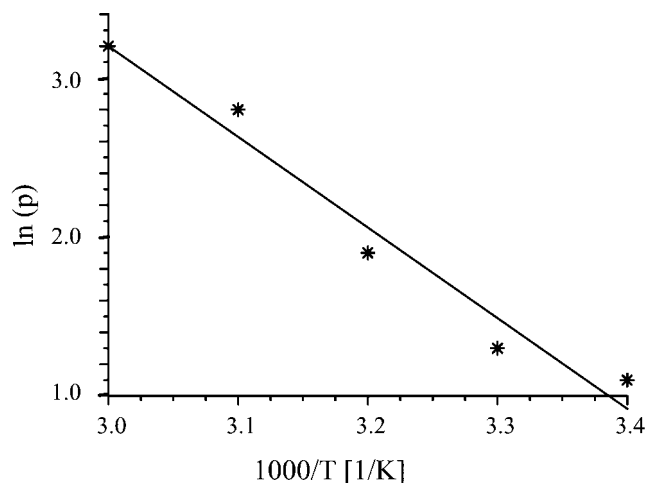


Figure 7. Temperature dependent inclusion of benzene in the bicyclic paracyclophane host **1k**. The layer thickness was about 60 nm and temperature was varied from 20 °C to 60 °C.

and the spacer groups bonded to the nitrogen. Computational chemistry helps to achieve a better understanding of the inclusion process. Therefore, supramolecular materials in combination with mass-sensitive devices show high capabilities for molecular recognition and give the possibility to design sophisticated sensor applications.

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