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Chemical Sensors for Solvent Vapors: Enthalpic and Entropic Contributions to Host-Guest Interactions

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Abstract Chemical sensors, based on the mass-sensitive quartz micro balance (QMB) or the surface acoustic wave device (SAW), that are coated with thin cyclophane layers allow the detection of harmful organic vapors. The sensor signal of these supramolecular analyte-receptors can be predicted by a method that uses estimated free energies of the host-guest complex formation. From MM3 force field calculations, the reaction enthalpies $\Delta H°$ of host-guest interaction between the macrocycle and the analyte can be calculated, whereas the entropy changes are taken from condensation data. The validity of this condensation model is proven by an excellent linear correlation of the logarithm of the experimental equilibrium constant with the estimated Gibbs energy $\Delta G°$. In this way promising sensor materials can be selected, even before they are synthesized.

Introduction

Meticulously designed chemical sensors [1] open many new application possibilities [2] not only in environmental pollution control but also in medicine and health care as well as in on-line process monitoring.[3] The limiting factor is in most cases the sensitive layer, especially regarding sensitivity, selectivity or stability. A promising solution of these problems can be achieved if the analyte is specifically incorporated by a solid state structure. In this way interstitial sites are occupied and chlathrates for the detection of organic solvent vapors, especially aromatic and halogenated hydrocarbons, are formed. Molecular cavities such as macrocyclic tetraazaparacyclophanes have also proved their ability to form complexes with small organic molecules.[4,5] The enzyme-like recognition observed with these hosts can be used to detect organic solvent vapors, such as harmful halogenated or aromatic hydrocarbons, with chemical sensors.[6] This can be achieved by coating mass-sensitive, microelectronic QMB or SAW devices [7,8]with thin cyclophane films.[9] To cut down time-and-money-consuming synthesis a more detailed understanding of analyte-coating interactions is desirable. Computational chemistry makes it possible to simulate the inclusion process and gives access to a quantitative picture of the host-guest complex in terms of the energy associated with its formation. Therefore we have undertaken to predict sensor effects on the basis of force field calculations [10,11] and estimated changes of

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entropy of complexation for a paracyclophane (Scheme I) as a model for host-guest chemistry.

Experimental

Measurements

The mass-sensitive measurements were performed with an AT-cut quartz-micro-balance (QMB) (gold electrodes with a diameter of 5.5 mm) operating in thickness shear mode with a fundamental frequency of 10 MHz. Frequency measurements were made with a Keithley 775A frequency counter, which gives a resolution of $\pm$ 0.1Hz. After on-line data transfer *via* an IEC bus to a personal computer, the resonance frequencies of a coated and an uncoated device were subtracted digitally to compensate for temperature fluctuations. The analyte mixtures were generated by mixing air saturated with solvent vapors and pure air with Tylan FC-2900 mass-flow-controllers. The gas mixing apparatus and the measuring cell were kept at 20°C. The sensor materials dissolved in chloroform were applied to both sides of gold surfaces of the QMB. The coated devices were tempered for one day in the flow of a solvent/air mixture. A typical thickness of the applied layer was 40 to 50 nm.

Chemicals

The basic structure of compound **1** (Scheme I) is a well known macrocycle. To improve hydrophobic properties, to make the structure more porous and to prevent crystallization, the bridging nitrogen was alkylated with an n-pentyl group. Compound **1** (7,11,21,25-tetra(n-pentyl)-7,11,21,25-tetraaza-2,16-dioxa [5.1.5.1]paracyclophane) was synthesized from the corresponding tosylate, which was obtained by a condensation reaction of 4,4'-bis(4-toluenesulfonylamino)diphenylether and 1,3-dibromopropane. The tosylate is eliminated by concentrated HBr. 0.4 mmol of the resulting cyclic amine (Scheme I, R=H) is dissolved in 184 mmol valeric acid and converted into the desired compound **1** by adding 40 mmol $NaBH_4$ at 60 °C and stirring for 48 hours. The mixture is dissolved in 50 ml CH_2Cl_2 and neutralized by extraction with 5 x 60 ml 2N NaOH and 3 x 50 ml H_2O. The product is isolated from the organic phase and is purified by recrystallization with ethanol/dichloromethane (3:5) (Scheme 1, R= n-pentyl).

m.p.   81°C
1H-NMR (CD_2Cl_2): δ = 6.6 (m, 16 H; H_{ar}), 3.25 (m, 16 H), 1.8 (m, 4 H), 1.55, 1.33 (m, 24 H), 0.9 (t, 12 H)
MS   760 M^+

Force-field calculations

All calculated stabilization or reaction enthalpies of the host-guest complexes were obtained from force field calculations.
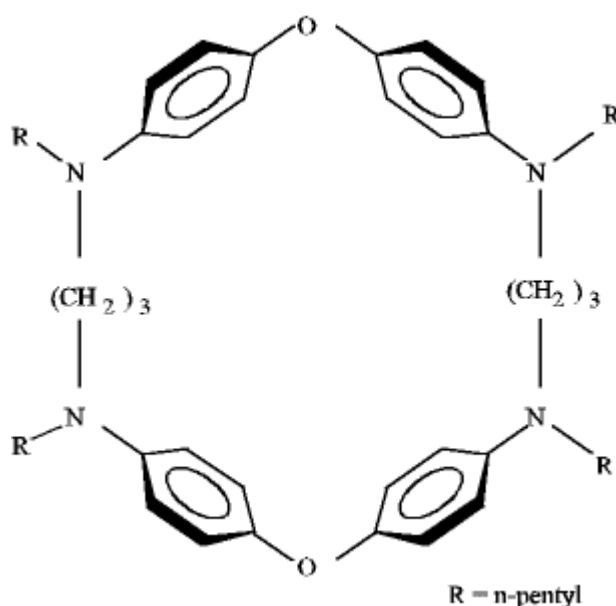
Scheme 1 *7,11,21,25-tetra(n-pentyl)-7,11,21,25-tetraaza-2,16-dioxa[5.1.5.1]paracyclophane = tetraaza- [5.1.5.1]-paracyclophane*

This method does not include electron interactions explicitly but van der Waals and Coulomb interactions are considered implicitly. These calculations are applied here in the field of sensor design to make a screening of the use of different hosts for certain guests and to obtain an idea for promising sensor layers. Since some of the complexes contain more than 100 atoms, the calculation time with semiempirical methods is too long for these applications. To prove the validity of the method used, the calculated data are correlated with experimental data.

All final results were calculated from input coordinates with Allinger's MM3 molecular modeling program [12] on a HP-9000/715/80 workstation. Input generation and geometry optimisation were performed by force-field calculations using the Windows program HyperChem 5.1 on a personal computer . After final calculations, the data were transferred back to the personal computer to display the structures. Force field parameters that are not included in MM3 were calculated at a semiempirical level using the MOPAC V6 program [13] with the PM3 hamiltonian on the workstation.[14] Some of the additionally generated force field parameters are given in Table 1.

Optimizations of the structures of the host and guest were performed separately. Because paracyclophanes are highly flexible molecules, the structure calculations where done by a carefully building up of the compound from single pre-optimized elements. Benzene, the dibenzene ether and the diamine bridge where optimized separately first. When assembling the dibenzene ether and the diamine bridge and afterwards for the addition of the n-pentyl side chains, one part of the structure elements was held constant while the other was optimized and *vice versa*. This was repeated until

Table 1 *Some of additionally generated mm3 force field parameters, using the semi-empirical MOPAC V6 program with the PM3 Hamiltonian*

Torsional Parameters Angle/ Atom Types [a]	one-fold Torsional Constant	two-fold Torsional Constant	three-fold Torsional Constant
2-2-8-1	-1450	3100	0

| **Bending Parameters** Angle / Atom Types [a]	Bending Constant [millidyne A/rad²]	Bending Angle [°]	
2-2-12	550	121.8	
12-2-12	850	119.0	

[a] Atom Types: 1: C, sp3; 2: C, sp2, Alkene; 8: N, sp3; 12: Cl

no changes occurred. For the docking procedure when adding the guest molecule to the host, the same procedure was applied. The guest molecule was held fixed, while the host was optimized in the host-guest complex. Afterwards the host was held fixed and the guest was optimized. This was repeated until no changes occurred.

Results and discussion

Compound **1** can be applied as an excellent sensitive coating for QMB-resonators. As shown in Figure 1 the detection of concentration changes of only 10 ppm tetrachloroethylene is possible with a satisfying signal to noise ratio. Especially the time behavior has to be pointed out since both the response and the recovery time are less than a minute and the sensor also shows a high reversibility. These fast and dynamic reac-

tions are achieved by the pentyl ligands at the nitrogen atom, since the layer obtained in this way is much more porous than in the case of the corresponding amine (Scheme 1, R=H). This excellent dynamic behavior takes advantage of bulk effects by increasing the sensor layer thickness, which leads to an improved sensitivity. Furthermore, the shielding of the polar nitrogens by hydrophobic ligands, in this case the pentyl substituents, leads to a negligible cross sensitivity to water. Figure 2 gives the sensitivities for various analytes. The tetraazaparacyclophanes form inclusion complexes with a large number of analytes. Because of their elongated cavity, these macrocycles are better suited for flat and long analytes. The hydrophobic, electron-rich receptor sites are most suitable for the detection of electron deficient halogenated hydrocarbons or aromatic molecules. That is why the cigar shaped perchloroethylene gives the largest sensor response of all solvent vapors, followed by aromatic and other halogenated solvents. A three-dimensional geometrical fit is nec-
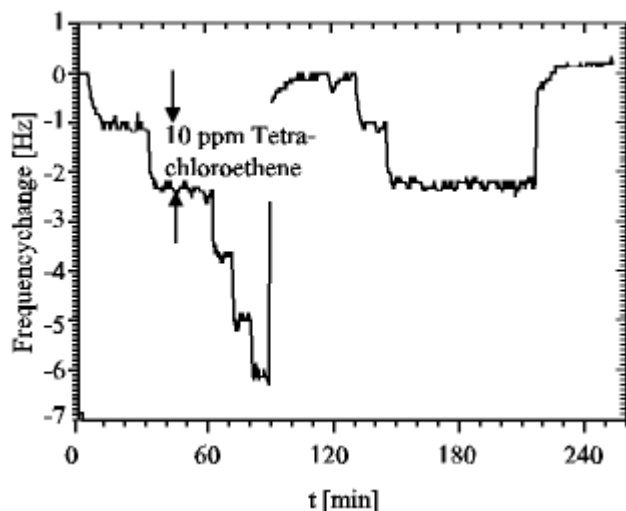
Figure 1 *Sensor response of a QMB-resonator, coated with a 80 nm layer of **1**, to stepwise changes of tetrachloroethylene concentrations. The resonance frequency f_o was 9.995.435 Hz, 20 % relative humidity, 20 °C*
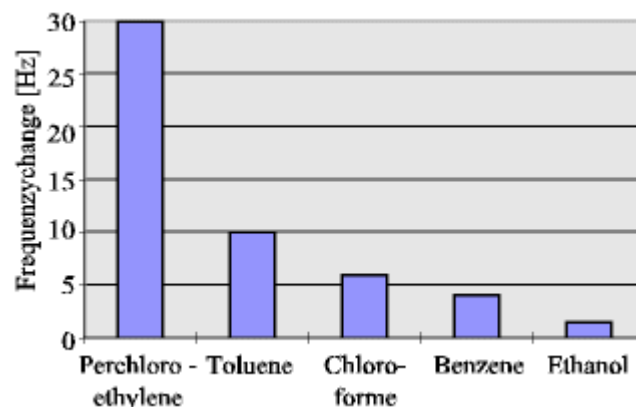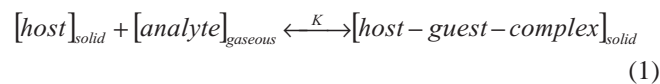

Figure 2 *Sensor response of 10 MHz QMB, coated with ~50 nm paracyclophane (compound **1**) to different solvent-analytes. Solvent vapour concentrations for all analytes are 1000 ppm. All signals were fully reversible*
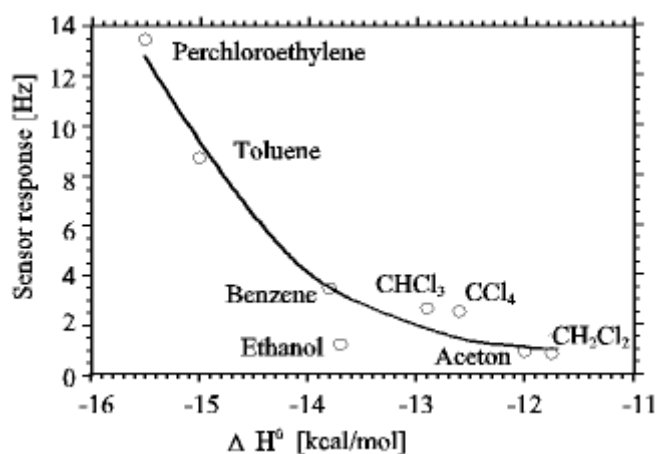
Figure 3a *Correlation of the measured sensor response (arbitrary units, percentage of incorporation) to the calculated stabilization enthalpie of the host-guest complex. Analyte concentration: 1000 ppm, layer thickness: 50 nm, QMB at 10 MHz*

Figure 3b *Equilibrium constant K, eq. (1), due to QMB-data as function of calculated Gibbs energy ΔG^o; in ΔG^o: (●) entropies of condensation (correlation coefficient r, 0.974), (▲) entropies of sublimation (correlation coefficient r, 0.776). Analytes: (a) tetrachloroethylene (b) toluene (c) benzene (d) chloroform (e) tetrachloromethane (f) ethanol (g) acetone (h) dichloromethane. Analyte concentration: 1000 ppm, layer thickness: 50 nm, QMB at 10 MHz*

essary for the inclusion, otherwise repulsion occurs. In addition van der Waals or π-π interactions determine the equilibrium constant of the inclusion process.
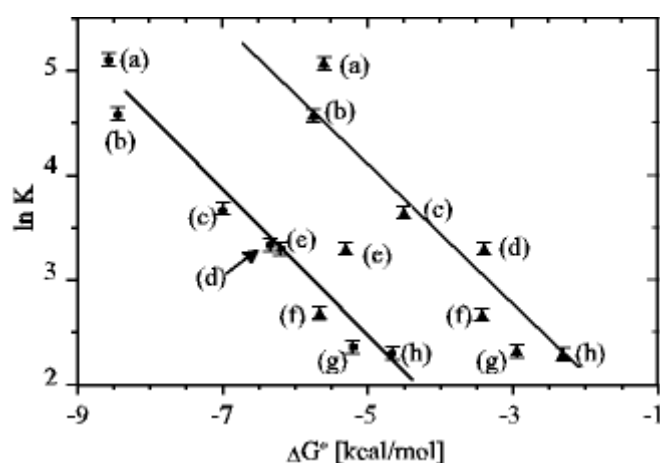
Considering that a pre-selection of promising sensor materials - foregoing time consuming and expensive synthesis - is possible if sensor effects can be predicted, it is our aim to obtain a model fulfilling this requirement. Assuming that the sensor signal is due to the formation of host-guest complexes, the magnitude of the sensor response is determined by the equilibrium constant K of the following reaction:

$$[host]_{solid} + [analyte]_{gaseous} \xleftrightarrow{\quad K \quad} [host-guest-complex]_{solid}$$

$$\tag{1}$$

$$K = p^0 \frac{n[HA]}{n[H]_0 \, p_A} \tag{2}$$

Formula 2 was derived with the assumption that the activity and fugacity coefficients of the compounds are equal to one. In Formula 2 p^0 is the normal pressure, p_A the partial pressure of analyte A, [HA] the concentration of host-analyte complexes and $[H]_0$ the overall concentration of host molecules. Since $n[HA]/n[H]_0$ can be determined by mass-sensitive measurements, it is possible to evaluate K values experimentally.

The equilibrium constant K can be related to the Gibbs energy of complex formation by $\Delta G^0 = -RT \ln K$. For this purpose, the enthalpy ΔH^0 - according to $\Delta G^0 = \Delta H^0 - T\Delta S^0$ - is calculated using MM3 force field calculations (for the calculations the tetra-N-methyl derivative was used as model compound).[15,16] Considering these calculations do not deliver changes of the entropy ΔS^0, we decided to make estimates because the entropy plays an important role in host-guest complexation.[17] The transition of the analyte from

the gas phase to the solid state is dominated by the loss of degrees of translational freedom. Furthermore, it seems reasonable that the larger part of the entropy change is due to a higher order of the guest and not the host, since the host molecules are already constrained to fixed lattice sites. Thus, in terms of entropy changes, the incorporation of the analyte into the sensitive layer is regarded as a condensation or sublimation process of the analyte. Following an idea of Hildebrand [18], the corresponding change of entropy ΔS^0 during condensation is, in the first approximation, mainly caused by the reduction of the average volume v accessible to a single molecule (i.e. the „free volume") according to $\Delta S^0 = R\ln(v^g/v^l)$, where „g" refers to the gas phase and „l" to the liquid phase. In this way it is suggested that host-guest complexation can be expressed as a reduction of the free volume of the analyte to the size of the host cavity. Additionally, degrees of vibrational and rotational freedom may be influenced as a result of analyte inclusion. This is the case if analyte solvents are able to form specific intermolecular bonds in addition to van der Waals interactions. As described by the Pictet-Trouton rule: the entropy of condensation ΔS_v for apolar molecules amounts to 88 J K^{-1} mol^{-1}, whereas higher ΔS_v values are found for polar substances. Therefore, estimating the entropies ΔS^0 using entropies of condensation or entropies of resublimation of the corresponding analytes seems to be reasonable. This assumption indicates that the guest behaves like a molecule in a liquid or in a solid. To obtain stabilization enthalpies for the host-guest inclusion, single point calculations of the final structures of the host and the guest where performed. The stabilization enthalpies are calculated from isolated, gaseous molecules and no lattice en-

ergy is 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-dependant contributions are absent from the energy terms. To obtain a closer picture of how large the difference between the calculated and the real values are, preliminary measurements were performed to determine the temperature-dependency of the equilibrium constant of the host-guest inclusion and hence to obtain experimental values for the stabilization enthalpies of the inclusion process. Measurements were carried out with several analytes like benzene, toluene and chloroform 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 perfectly by the calculations.

In Figure 3a the experimental sensor effect is correlated to the calculated stabilization enthalpy for the host-guest inclusion. Although the agreement is quite good, the data for small and polar analytes show some deviation from the exponential curve. Especially ethanol does not match well. Figure 3b shows the correlation between the experimental ln K values (resulting from mass-sensitive QMB measurements) and the estimated Gibbs energies of complex formation. As can be seen, quite a good correlation is obtained for data based on entropies of condensation. Thus, sensor effects can be predicted according to equation 3, where $\Delta\nu$ is the sensor response [Hz], c(A) the analyte concentration [ppm], $M_m(A)$/$M_m(H)$ the molar mass of the analyte/host [g/mol] and $\Delta\nu(S)$ is the thickness of the sensitive coating [Hz] (40 nm: 1000 Hz):

$$\Delta\nu = 10^{-3}\frac{c(A)\cdot M_m(A)\cdot \Delta\nu(S)}{M_m(H)}e^{-\left(\frac{\Delta H^0 - T\Delta S^0 + 1.6 kcal\cdot mol^{-1}}{1.43 kcal\cdot mol^{-1}}\right)} \qquad (3)$$

The exponential expression is modified by numeric data. The numbers are correction factors for the line in Figure 3b to compensate deviation between theory and experiment. The slope of the straight line should be $-(RT)^{-1} = -1.71$ kcal^{-1}mol
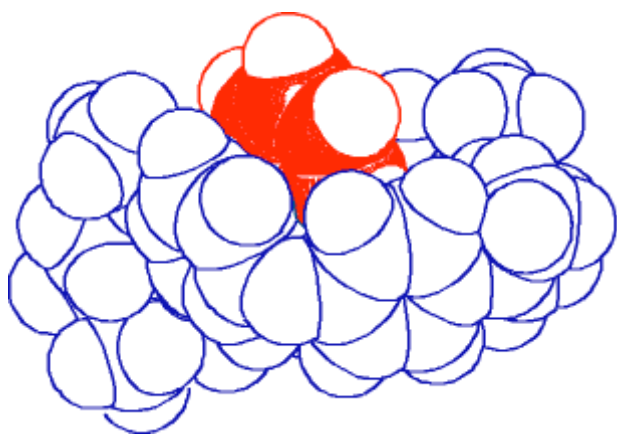
but is -0.7 kcal^{-1}mol, which accounts for the deviation with 1/0.7 = 1.43. ΔG^0 is -1.6 kcal^{-1}mol for ln K = 0 instead of being 0 kcal^{-1}mol, so 1.6 is added to compensate this offset. The difference between experiment and theory is due to different oversimplified assumptions. On the one hand the calculation of the entropy effect from condensation entropies is just an approximation. If the entropy change associated with the inclusion process is greater than those of the condensation reactions the resulting ΔG^0 value is too small. This would be true if the nature of the incorporated analyte lies between that of a liquid and a solid state. On the other hand, if the calculated energies - related to the enthalpies of the compounds - are too large, the complexation enthalpies should have an offset as well.

Host-guest chemistry exhibits behavior analogous to both the crystal packing and the liquid state. Collet et al. found that chloroform in the cavity of cryptophane-A is best described as a pseudo-crystal, whereas methane behaves similarly to a supercritical fluid.[19] In analogy it may be then concluded that analyte molecules complexed by **1** may possess degrees of freedom similar to molecules in the liquid phase. This idea can be confirmed by the fact that the correlation between theory and experiment is much better when using condensation entropies instead of sublimation entropies. The loss of entropy is smaller compared to that which occurs during the corresponding transition into a highly ordered crystalline lattice. In addition, force field calculations of the inclusion are shown in Figure 4. The analyte molecule, in this case toluene, is placed in a pocket of the macrocycle and can rotate in a similar way as in the liquid state. The arrangement of the toluene with the methyl group is directed inside of the macrocycle and shows an *exo* arrangement with nearly the same energy.

Conclusions

In chemical sensor technology the aim is to synthesize „active sites" on the sensor surface that are capable of incorporating analytes with high selectivity. This demands often meticulously designed layers. It could be shown that computational chemistry can help to predict sensor effects in terms of the energy associated with the inclusion process. For the structures presented here the use of force-field methods is sufficient to provide a reliable value for the expected sensor effect for a large variety of analytes in a short time. This suggests that the associated interactions are mainly geometric and van der Waals types and interactions due to directed overlapping from orbitals are less important. A more detailed picture of the nature of the inclusion is obtained, for example that the state of the analyte in the host guest complex is more that of a liquid than that of a solid. This saves money-consuming synthesis time and makes molecular modeling a useful tool for the design of sophisticated chemical sensor layers.

Figure 4 *Modeling picture of toluene incorporated in tetraaza[5.1.5.1]paracyclophane*

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