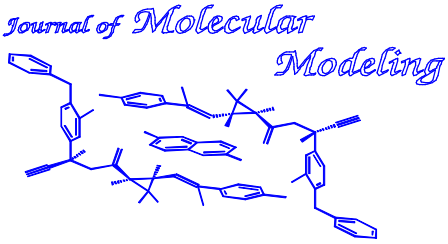
J. Mol. Model. **1996**, *2*, 410 – 416



Molecular Modeling of Host-Guest Inclusion Compounds: Calculations and Practical Application to Chemical Sensors

Franz L. Dickert*, Hubert Reif and Helen Stathopulos

Institute of Analytical Chemistry, University of Vienna, Währinger Straße 38, A-1090 Wien, Austria
(fdickert@olivin.anc.univie.ac.at)

Received: 17 May 1996 / Accepted: 19 September 1996 / Published: 31 October 1996

Abstract

Molecular modeling by force-field methods is a straightforward highly convenient tool for the calculation of host-guest systems comprising a large number of atoms. [1, 2, 3] As a practical application we use the calculated data to interpret and predict the potential of mass-sensitive chemical sensors that utilize coating materials on the basis of supramolecular host compounds. Inclusion complexes of modified β-cyclodextrins and tetraazaparacyclophanes with fluorochlorinated anesthetics were calculated and compared to experimental data.

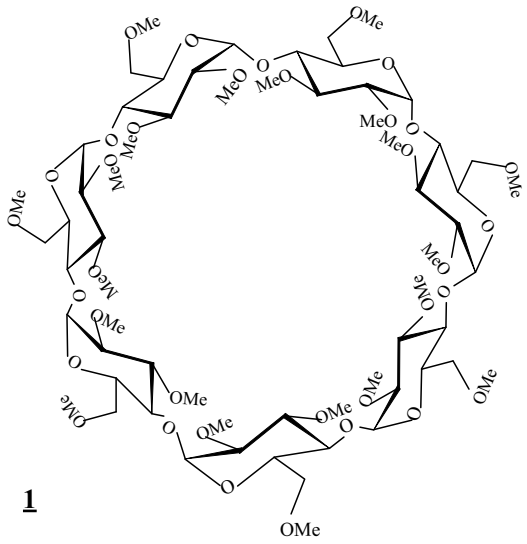
Keywords: MM3 force field, host-guest-chemistry, β-cyclodextrin, paracyclophanes, fluorochlorinated hydrocarbons, mass-sensitive detection, prediction of sensor effects.

Introduction

Supramolecular host molecules are innovative synthetic materials that engulf analyte molecules by enzyme-analogue molecular recognition mechanisms,[4] both in the liquid[5] and the gas phase [6]. When they are used as coatings on mass-sensitive devices, such as the quartz microbalance (QMB) or the surface acoustic wave (SAW) resonator, the detection of halogenated or aromatic solvents in the vapour phase is possible down to a few ppm.[7,8] If such a transducer is integrated as the frequency determining element into an oscillator circuit, every change of mass due to analyte incorporation is measured as a frequency shift Δf.[9, 10] Both methylated β-cyclodextrin **1** and the series of tetraazaparacyclophanes **2a - 2d** (Figure 1) are highly capable of incorporating solvent molecules without distinct geometry or functionality by a host-guest mechanism.[11, 12, 13] Consequently such coated QMB- or SAW-oscillators offer a favorable method for the detection of anesthetics belonging to the group of halogenated hydrocarbons in concentrations relevant to medical applications. Molecular modeling by the MM3 force-field enables an efficient analyte incorporation to be predicted.[14, 15] The theoretical determination of the stabilization enthalpies of the complexes formed helps the selection of a promising coating material. To promote knowledge on the inclusion mechanism, the geometries of the complexes were examined.

In this paper we present the MM3-calculations of host-guest interactions between methylated β-cyclodextrin **1** or tetraazaparacyclophanes **2a - 2d** as host compounds and gaseous anesthetics, such as the halogenated hydrocarbons halothane, enfluran, isoflurane, and sevoflurane and we demonstrate the practical significance of those theoretical data for the development of mass-sensitive chemical sensors.

* *To whom correspondence should be addressed*



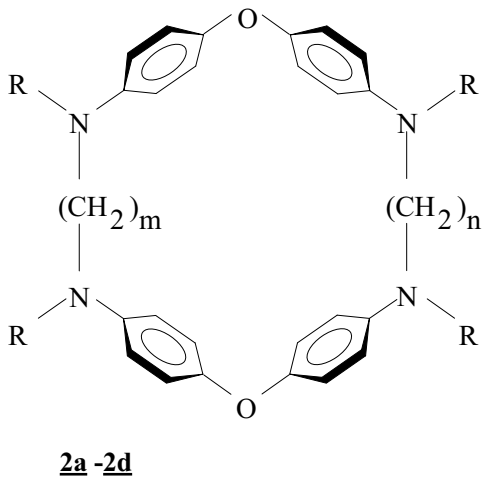


Figure 1. *Structure of the established host-compounds;* ***1****: TMBCD,* ***2****: R = -CH*$_3$*,* ***[m,n]*** *:* ***2a****: m = 3, n = 4,* ***2b****: m = 4, n = 4,* ***2c****: m = 4, n = 5,* ***2d****: m = 5, n = 5.*

Computational Procedure

Molecular Modeling

The host-guest stabilization enthalpy ΔH_f(host/guest) is given as the difference between the heat of formation of the host-guest complex ΔH_f (complex) and the sum of the heats of formation of the isolated host ΔH_f (host) and the free guest ΔH_f (guest) (Equation 1).

$$\Delta H_f \text{ (host / guest)} = \Delta H_f \text{ (complex)} - [\Delta H_f \text{ (host)} + \Delta H_f \text{ (guest)}] \quad (1)$$

These data were computed by Allingers MM3 program.[16, 17, 18, 19] The input files were created with the HyperChem4.0 MM+ force field and transformed to the MM3 format with the help of a self-made converting software. After optimization by the MM3 force-field the output data were used for calculating the energy contributions (Equation 1) and with the back-converted files the optimized host-guest geometries were visualized. Since the MM3 force field lacks of some parameters for the calculation of fluorinated hydrocarbons these were generated by a parametrization procedure demonstrated in the following for the dihedral angle F-C(sp^3)-O-C(sp^3) of the MM3-type atoms 11-1-6-1. Accord-

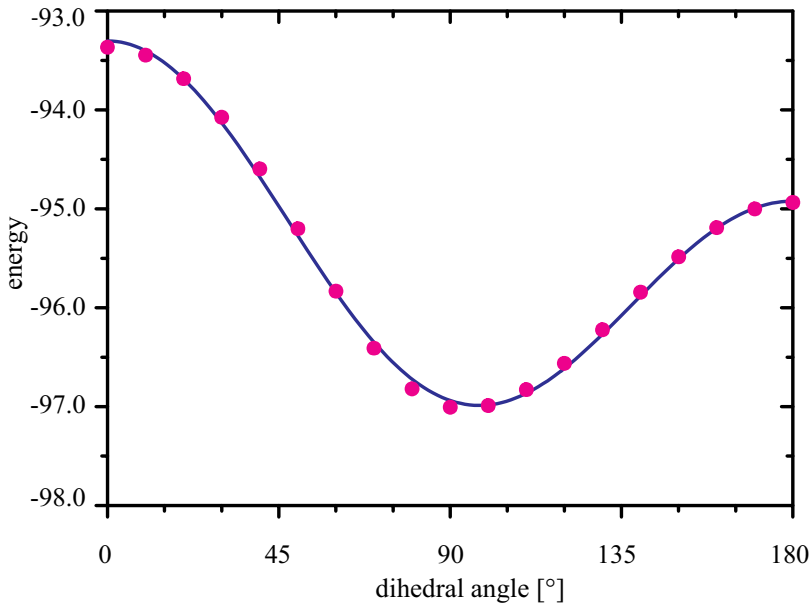
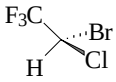
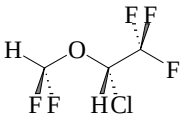
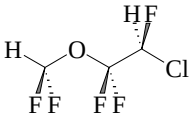
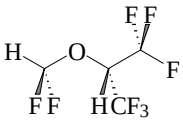


Figure 2. *Fit function of the dihedral angle with the calculated parameters (blue line) and semi-empirically calculated energies (dots).*

Table 1. *Dipole-dipole interactions of anesthetics and TMBCD (μ_{TMBCD} = 1.90)*

anesthetic		$\mu_{anesthetic}$	$angle_{\mu(host/guest)}$	dipole-dipole-stabilization [kcal/mol]
halothane **3a**		1.64	69°	-0.24
isoflurane **3b**		2.17	54°	-0.82
enfluran **3c**		2.34	104°	-1.58
sevoflurane **3d**		3.31	131°	-4.05

ing to Equation 2 which gives the energy of torsion at a dihedral angle ω in a Fourier series expansion in cosine the parameters V_1, V_2 and V_3 are needed in the MM3-program.

$$E_T = \frac{V_1}{2}(1 + \cos\omega) + \frac{V_2}{2}(1 - \cos 2\omega) + \frac{V_3}{2}(1 + \cos 3\omega) \quad (2)$$

The complete energy is the sum of all torsional energies that contribute to this rotation. The parameters V_1, V_2 and V_3 are determined *via* a complete rotational profile of monofluorodimethylether as model substance that was semiempirically calculated by MOPAC. The complete rotational energy E(rot) was corrected for the torsion energies of the remaining participating groups. The resulting calculated profile of the torsion energy was used for estimating the parameters of the F-C(sp^3)-O-C(sp^3) torsional angle with the help of PLS. In Figure 2 the semiempirically calculated energies and the fit function of the dihedral angle making use of the determined parameters V_1 = 1.589, V_2 = -2.826 and V_3 = 0.031 for the F-C(sp^3)-O-C(sp^3)-type angle are shown.

Experimental

Measurements

For the mass-sensitive measurements, QMB devices consisting of an AT-cut quartz with gold electrodes of 5.5 mm in diameter were covered with sensitive layers in a thickness up to one hundred nanometers. The QMBs work at a resonance frequency of 10 MHz and were measured with a Keithley 775A frequency counter at a resolution of ± 0.1 Hz. All data were computer-aided on-line interpreted. To eliminate ambient parameters such as varying temperature or humidity that lead to signal drifting, the measurements were performed under thermostated conditions in a differential quartz setup with an uncoated quartz as internal reference.

Chemicals

The synthesis of the tetraazaparacyclophanes has been described previously.[20, 21, 22]The methylated β-cyclodextrin TMBCD can be prepared according to literature.[23] A methylated and polymeric linked β-cyclodextrin was synthesized by the reaction with epichlorohydrin[24] which was followed by methylation.

interaction type [a]	halothane	enfluran	isoflurane	sevoflurane
compression	-0.18	-0.05	-0.11	-0.24
bending	-0.33	-0.31	+0.10	-0.94
bend-bend	-0.02	+0.10	+0.03	+0.04
vdW 1,4	+0.25	-0.18	-0.17	-0.19
vdW other	-14.19	-12.27	-11.61	-11.40
torsional	-0.31	+1.66	+0.01	+2.52
dipole-dipole	-0.24	-1.58	-0.82	-4.05
overall stabilization H_f [b]	-17.67	-14.96	-14.90	-16.53

Table 2. *[a] Energetic contributions of host-guest interactions [kcal/mol] and [b]overall stabilization enthalpies ΔH_f(host/guest) [kcal/mol] for TMBCD*

Results and Discussion

We pre-calculated the inclusion of the mixed halogenated anesthetics halothane **3a**, isoflurane **3b** and enfluran **3c** and the fluorinated hydrocarbon sevoflurane **3d** (Table 1) by compounds **1** and **2a - d**. The analytes show an increasing dipole moment in the order mentioned and host-guest inclusion should be mainly on the basis of electrostatic and dispersive interaction forces.

Methylated β-cyclodextrin (TMBCD) **1** is an already synthetically optimized cone-shaped host compound with a hydrophobic inner surface and all three hydroxyls methylated. Thus, even with varying humidity the sensor material shows no distinct interaction with water molecules, while all established anesthetics are completely incorporated due to shape and stereoelectronic recognition. In Figure 3 the side-cut view of the incorporation complex of sevoflurane reveals how the analyte joins closely to the lipophilic inner walls of the cavity. This excellent nestling is the reason why all four host-guest-complexes show high stabilization enthalpies ΔH_f in the range of -14.9 kcal/mol up to about -17.7 kcal/mol. The energetic contributions of several host-guest complexes and the overall energetic stabilizations which represent the heats of complex stabilization ΔH_f are listed in Table 2. The major part of the complex stabilization are van der Waals (vdW) forces. Contributions of this nature are split into intramolecular 1-4-interactions and the sum of all other van der Waals increments. Compared to the latter, the 1-4 van der Waals contributions are extraordinarily small for the ether compounds and destabilizing for halothane, indicating that the close neighbourhood of the atoms does not change them electronically both in the host and the guest compound. Therefore the inclusion mechanism seems to be similar to a key lock principle without distinct conformational adaption.

The second stabilization type worth mentioning is of electrostatic nature. In Table 1 the calculated data for dipole-

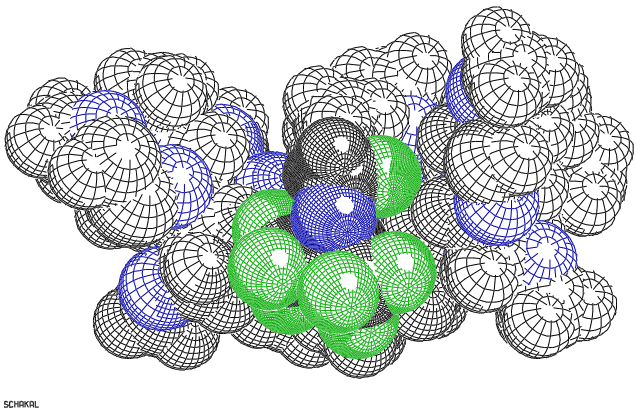


Figure 3. *Host-guest complex of TMBCD **1** and sevoflurane; wide grids: host, narrow grids: guest; blue: oxygen, black: carbon, green: fluorine.*

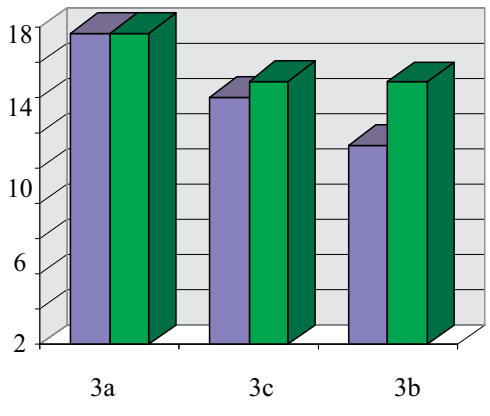


Figure 4. *Predicted values $-\Delta H_f$ (host/guest) [kcal/mol]* ■ *and experimentally measured normalized logarithmic sensor effect at 1000 ppm analyte concentration* ■.

Table 3. *Stabilization enthalpies of monocyclic tetraazacyclophanes and anesthetics*

anesthetic	tetraazaparacyclophane [m,n] **2**			
	[3,4] **2a**	[4,4] **2b**	[4,5] **2c**	[5,5] **2d**
halothane	-15.20	-13.45	-13.54	-13.04
enfluran	-14.61	-14.77	-13.36	-13.85
isoflurane	-15.53	-13.56	-14.31	-14.68
sevoflurane	-16.03	-17.79	-14.53	-15.45

dipole interactions are presented. The amounts of these stabilizing forces depend on the sum of the dipole moments of the isolated compounds as well as on their orientation. The highest electrostatic stabilization enthalpy is calculated for the inclusion of sevoflurane with -4.05 kcal/mol, since this anesthetic has the highest dipole moment of μ = 3.31 D in the series and the angle of interaction of 131° is nearest to the optimum 180° value. At the other end of the series for the TMBCD/halothane complex the lowest dipole-dipole stabilization results with a value of -0.24 kcal/mol because of the small dipole moment of the free halothane molecule and the quite disadvantageous angle of 69° between host and guest. In conclusion, the strongly polar sevoflurane molecule shows the highest electrostatic stabilization while the overall host-guest stabilization enthalpy of the TMBCD/halothane complex is calculated to be the most stable. According to these results the sensor behavior of a methylated β-cyclodextrin polymer, which was linked by epichlorohydrin, to the series of anesthetics was tested. The experimentally measured sensor effects at 1000 ppm analyte concentration were compared to the theoretical prediction. Since the sensor signal is determined by intracavitative incorporation, the stabilization enthalpy was found to correlate to the sensor effect. As demonstrated in Figure 4 the procedure established is a preferential method for the investigation of sensor behavior in the forefield of synthetic or experimental work.

Subsequently azaparacyclophanes of the [m,n]-type **2** in Figure 1 that differ in their inner diameter were theoretically examined according to their analyte engulfing abilities. Their tendency to form host-guest complexes can be compared to that of the β-cyclodextrin, although these host molecules have aromatic biphenylether moieties, but due to the chemical nature of the system no other interactions than electrostatic or van der Waals bonding play an important role. In Table 3 the stabilization enthalpies for the series of **2a** - **2d** are listed. The energetic contributions for the halothane or sevoflurane incorporation into tetraazaparacyclophanes [m,n] with a successively increasing number of bridging carbon atoms in the compounds **2a** - **2d** are presented in Table 4. The inner contact surface is the limiting factor for the development of an effective incorporation geometry and therefore for a strong

Table 4. *Energetic contributions of several host-guest interactions [kcal/mol]*
[a] halothane
[b] sevoflurane

interaction type [a]	[3,4] **2a**	[4,4] **2b**	[4,5] **2c**	[5,5] **2d**
compression	-0.22	-0.16	-0.20	-0.21
bending	-0.67	+0.74	-1.02	-0.40
bend-bend	0.00	-0.01	-0.06	-0.02
vdW 1,4	-0.10	+0.11	+0.08	+0.01
vdW other	-11.88	-11.25	-10.87	-9.63
torsional	+1.07	-0.22	+1.03	-0.12
dipole-dipole	-1.62	-0.73	-0.56	-0.90

interaction type [b]	[3,4] **2a**	[4,4] **2b**	[5,5] **2d**
compression	-0.44	-0.31	-0.20
bending	-2.17	-0.59	-1.02
bend-bend	-0.07	-0.04	-0.06
vdW 1,4	-0.59	+0.53	+0.08
vdW other	-11.54	-11.76	-10.87
torsional	+2.54	-0.31	+1.03
dipole-dipole	-2.34	-2.73	-0.56

stabilization. Again in this systems mainly van der Waals and dipole-dipole forces are responsible for the host-guest inclusion. The small halothane molecule is intimately adapted to the [3,4]-paracyclophane with the smallest cavity size. With increasing diameter of the host the intermolecular van der Waals stabilization decreases from -11.88 kcal/mol to -9.63 kcal/mol for the largest [5,5]-compound **2d** and the same is observed in overall host-guest stabilization enthalpies. In a similar way the inclusion of sevoflurane can be interpreted. Here the spacy analyte is optimally incorporated into the [4,4]-host **2b** with a medium diameter. For this sevoflurane/[4,4]-complex the van der Waals stabilization has a maximum with -11,76 kcal/mol which is reduced by 1,89 kcal/mol up to the largest [5,5] complex.

As demonstrated, the driving force for host-guest inclusion of the halogenated anesthetics by cyclodextrins or tetraazaparacyclophanes are mainly shape recognition and an optimum fit to the inner surface of the host-structure is important. For the prediction of sensor effects of the tetraazaparacyclophanes we calculated the inclusion complexes with aromatic and chlorinated solvents, too. Here chloroform, benzene and the bulky analyte toluene show the best fit with the [5,5] host **2d**, while due to their diameters the complete incorporation in smaller cavities is hindered and because the larger more flexible hosts adopt an unfavorable

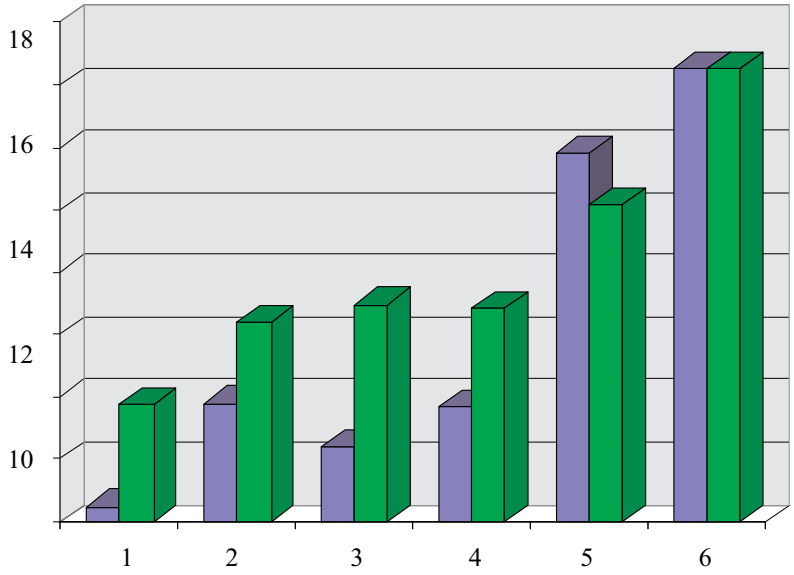


Figure 5. *Predicted values $-\Delta H_f$ (host/guest) [kcal/mol]* ■ *and experimentally determined lnK* ■ *for complexation formation of* ***2*** *(R = $-C_5H_{11}$, [5,5]) and various analytes; 1) methylene-chloride, 2) chloroform, 3) carbontetrachloride 4) benzene, 5) toluene, 6) tetrachloroethylene.*

conformation during complexation.[14] The stabilization enthalpies ΔH_f (host/guest) for some aromatic analytes as well as halogenated hydrocarbons and the [5,5] compound are set against the logarithm of the experimentally obtained equilibrium constant K of the host-guest formation in Figure 5. Equation 3 gives the relationship between mass-normalized sensor effect, equilibrium constant K and stabilization enthalpy ΔH_f. For a first consideration the entropic terms are assumed to be constant since the condensation entropies of the solvents should follow the rule of Pictet and Trouton.

$$\ln \textit{(sensor effect)} \sim lnK = -\frac{\Delta H_f}{RT} + \frac{\Delta S_f}{R} \qquad (3)$$

Altogether, for the widespread range of chemically different analytes and sensor materials with force-field methods host-guest interactions can be modeled involving van der Waals, dipole-dipole or even π-bondings with sufficient accuracy.[25, 26, 27, 28, 29]

Conclusion

Molecular modeling is a favorable tool for the interpretation of host-guest inclusion phenomena for systems with up to one thousand atoms. A promising application is the adaption of theoretical data for the prediction of sensor responses of mass-sensitive devices that make use of host-guest-chemistry as the detection principle. In this way computational chemistry helps the sophisticated design of sensitive chemical coatings.

Acknowledgement We gratefully thank Dr. Castor, SIEMENS ELEMA, Sweden, for the supply of the anesthetics halothane, enfluran and isoflurane.

References

1. Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M.; Ferguson, D. M. Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179-5197.
2. Immel, S.; Brickmann, J.; Lichtenthaler, F. W. *Liebigs Analen* **1995**, *6*, 929-942.
3. Klein, C. T.; Kohler, G.; Mayer, B.; Mraz, K.; Reiter, S.; Viernstein, H.; Wolschann, P. *J. Inclusion Phenom. Mol. Recogn.* **1995**, *22*, 15-32.
4. Vögtle, F.; Sieger, H.; Müller, W. M. In *Topics in Current Chemistry 98*; Boschke, F. L. Ed.; Springer Verlag: Berlin, 1981; pp 107-161.
5. Saenger, W. *Angew. Chem.* **1980**, *92*, 343-361.
6. Schierbaum, K. D.; Gerlach, A.; Göpel, W.; Müller, W. M.; Vögtle, F.; Dominik, A.; Roth, H. J. *Fres. J. Anal. Chem.* **1994**, *349*, 372-379.
7. Cammann, K.; Lemke, U.; Rohen, A.; Sander, J.; Wilken, H.; Winter, *B. Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 516-538.
8. Dickert, F. L.; Haunschild, A. *Adv. Mater.* **1993**, *5*, 887-895.
9. Hauptmann, P. *Sens. Actuators A* **1991**, *25-27*, 371-377.
10. Sauerbrey, G. *Z. Phys.* **1959**, *155*, 206-222.
11. Lucklum, R.; Henning, P.; Hauptmann, P.; Schierbaum, K. D.; Vaihinger, S.; Göpel, W. *Sens. Actuators A* **1991**, *25-27*, 705-710.
12. Dickert, F. L.; Bauer, P. *Adv. Mater.* **1991**, *3*, 436-438.
13. Dickert, F. L.; Haunschild, A.; Kuschow, V.; Stathopulos, H. *Anal. Chem.* **1996**, *68*, 1058-1061.
14. Dickert, F. L.; Reif, M.; Reif, H. *Fresenius J Anal Chem* **1995**, *352*, 620-624.
15. Dickert, F. L.; Haunschild, A.; Maune, V. *Sens. Actuators B* **1993**, *12*, 169-173.

16. Allinger, N. L.; Yuh, Y. H.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551-8566.
17. Allinger, N. L.; Schmitz, L. R.; Motoc, I.; Bender, C.; Labanowski, J. K. *J. Am. Chem. Soc.* **1992**, *114*, 2880-2883.
18. Allinger, N. L.; Rahman, M.; Lii, J. H. *J. Am. Chem. Soc.* **1990**, *112*, 8293-8307.
19. Allinger, N. L.; Schmitz, L. R. *J. Am. Chem. Soc.* **1990**, *112*, 8307-8315.
20. Soga, T.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 4351-4354.
21. Snyder, H. R.; Heckert, H. *J. Am. Chem. Soc.* **1952**, *74*, 2006-2009.
22. Stetter, H.; Roos, E. E. *Chem. Ber.* **1955**, *88*, 1390-1395.
23. Cramer, F.; Mackensen, G.; Sensse, K. *Chem. Ber.* **1968**, *102*, 494-508.
24. Xu, W.; Wang, Y.; Shen, S.; Li, Y.; Xia, S.; Zhang, Y. *Chin. J. Polym. Sic.* **1989**, *7*, 16-22.
25. Timmermann, P.; Nierop, K. G. A.; Brinks, E. A.; Verboom, W.; Vanveggel, F. C. J. M.; Vanhoorn, W. P.; Reinhoudt, D. N. *Angew. Chem. Int. Ed*. **1995**, *34*, 132-143.
26. Fathallah, M.; Fotiadu, F.; Jaime, C. *J. Org. Chem.* **1994**, *59*, 1288-1293.
27. Perez, F.; Jaime, C.; Sanchez-Ruiz, X. *J. Org. Chem.* **1995**, *60*, 3840-3845.
28. Linert, W.; Margl, P.; Renz, F. *Chemical Physics* **1992**, *161*, 327-338.
29. Bekers, O.; Kettenes-van den Bosch, J. J.; van Helden, S. P.; Seijkens, D.; Beijnen, J. H.; Bult, A.; Underberg, W. J. M. *J. Inclusion Phenom. Mol. Recogn.* **1991**, *11*, 185-193.