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# Determination of molar heats of absorption of enantiomers into thin chiral coatings by combined IC-calorimetric and microgravimetric (QMB) measurements
## II. Thermodynamics of enantioselectivity in modified cyclodextrins

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**Abstract**

A combination of microgravimetric and microcalorimetric measurements was developed for the investigation of enantioselective gas–surface interaction. The sorption behaviour of the two enantiomers of methyl-2-chloropropionate was investigated at polydimethylsiloxane (PDMS) as an achiral receptor and octakis (3-*O*-butanoyl-2,6-di-*O*-*n*-pentyl)-γ-cyclodextrin (Lipodex E®) as a chiral receptor. The microgravimetric and microcalorimetric results are described by a suitable thermodynamic model providing the thermodynamic data of the absorption process. These data are discussed in terms of the mechanism of chiral recognition and compared to literature data derived from gas chromatographic results by the van't Hoff method.


*Keywords:* IC-calorimetry; Quartz crystal microbalance; Enantiomer separation; Thermodynamics; Cyclodextrines

## 1. Introduction

Chirality and chiral recognition are vital features of nature and of essential importance for the understanding of numerous processes in life sciences as well as chemistry. For the scientific understanding of the mechanism of chiral recognition and separation processes, detailed structural as well as thermodynamic knowledge, especially enthalpic and entropic contributions to the driving force, is required. Thermodynamic data quantifying the different interactions of the enantiomers with a chiral receptor, necessary for chiral separation processes, have been mostly determined indirectly by means of temperature dependent chromatographic or spectroscopic experiments and applying the van't Hoff analysis [1–3]. However, data resulting from a van't Hoff procedure are subject of current disputation because these data may be incorrect or misleading in some cases due to kinetic problems or change of mechanism in the temperature interval [4–6].

In order to overcome this principle problem, we recently suggest the combination of gas absorption IC-calorimetry and quartz crystal microgravimetry (QCM) for direct evaluation of thermodynamic data of chiral interactions [7]. The first paper of this series [7] presented the design and properties of a refined IC-calorimetric instrument capable of measuring the small differences in the heats of absorption of enantiomers into thin chiral coatings. The current contribution focuses on the applied microgravimetric method and on the thermodynamic data evaluation from calorimetric and microgravimetric results demonstrated by the absorption of the enantiomers of methyl-2-chloropropionate into octakis (3-*O*-butanoyl-2,6-di-*O*-*n*-pentyl)-γ-cyclodextrin (Lipodex E®) and poly-

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dimethylsiloxane (PDMS). Lipodex E® is widely used as a chiral stationary phase in gas chromatographic enantiomer separation [8]. The methyl-2-chloropropionate/Lipodex E® system has already been studied by gas chromatography [1] and QCM-microgravimetry [9] allowing a comparison of the results. Bodenhoefer et al. [10] also proposed a thermodynamic model for the description of QCM absorption experiments based on two contributions: Langmuir-type absorption for specific interaction and Henry-type absorption for non-specific interaction. It will be shown that a refinement of this concept leads to a model capable of describing both microgravimetric and calorimetric results consistently. The molar thermodynamic quantities $\Delta G$, $\Delta H$ and $\Delta S$ of the specific (chiral) and non-specific (achiral) interaction can easily be extracted from the model parameters.

## 2. Experimental

### 2.1. Chemicals

The enantiomers of methyl-2-chloropropionate were purchased from Aldrich (Steinheim, Germany) and used without further purification. Sample gas stock mixtures of methyl-2-chloropropionate were homemade by evaporation of a weighed amount of liquid into a compressed gas bottle and subsequent addition of synthetic air (Air Liquide, Germany) up to a pressure corresponding to the desired normal pressure concentration.

Polydimethylsiloxane (PDMS, ABCR GmbH Karlsruhe, Germany) was used as achiral receptor and octakis(3-*O*-butanoyl-2,6-di-*O*-*n*-pentyl)-γ-cyclodextrin (Lipodex E®, synthesized by the group of König, University of Hamburg, Germany) was used as chiral receptor. In order to obtain reproducible absorbing layers on the chip calorimeter with a defined mass, small quantities of the receptor dissolved in dichloromethane were dropped onto the chip surface using a microliter syringe.

### 2.2. The twin chip calorimetric device

The chip calorimeter was described in detail in the first part of the publication [7].

### 2.3. The quartz crystal microbalance device

The applied quartz crystal microbalance is homemade and a scheme of the instrument is shown in Fig. 1.

The experimental setup consists of two 10 MHz standard electronic quartzes with gold electrodes (FOQ Piezo Technik, Germany). One of them is uncoated and used as reference; the other one is coated with the receptor. Both quartzes are located in a thermostated metal block (controlled to 25 °C by a water thermostat) also containing a heat exchanger for the inflowing gas. The computer-controlled gas-mixing unit

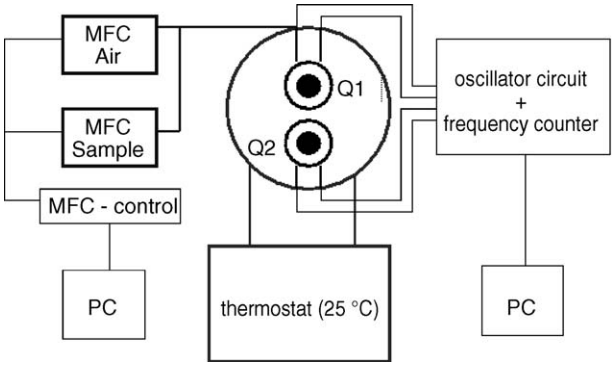


Fig. 1. Schematic representation of the QCM instrument.

consists of two mass flow controllers (MFC, MKS instruments) supplying sample gas stock mixture and synthetic air in the appropriate flow ratio. The measurements are carried out with a constant total flow rate of 20 mL/min. The resonance frequencies of the quartzes are measured by a multichannel frequency counter (HKR sensor systems Munich, Germany) with a resolution of 1 Hz. The frequency data can be read by the computer via a serial interface. The coating of the quartzes was performed by means of the electrospray method in collaboration with the Institute of Micro- and Sensor Systems at the University of Magdeburg, Germany. The receptor mass on the quartz was calculated using the Sauerbrey equation [11]:

$$\Delta f = -\frac{2f_0^2}{\rho_q c_q A}\Delta m = -C_f \Delta m,$$

where $f_0$ denotes the intrinsic resonance frequency, $A$, the area of the electrodes, $\rho_q$ and $c_q$ are the density of quartz and the speed of sound in quartz, respectively. For the quartzes used, $C_f$ is approximately 1.54 Hz ng$^{-1}$. The receptor mass was adjusted to approximately 4 μg which guarantees a comparable layer thickness to the IC-calorimeter. The validity of the Sauerbrey equation (viscoelastic contributions to the frequency shift must be negligible) for the coatings has been verified by impedance measurements according to a criterion proposed by Lucklum et al. [12] demanding a ratio of $\Delta R/\Delta f < 0.4$ ($\Delta R$, motional resistance derived from attenuation) for the gravimetric regime.

## 3. Results and discussion

The absorption of the two enantiomers of methyl-2-chloropropionate from the gas phase into thin layers of the chiral receptor Lipodex E® and the achiral receptor PDMS as a function of the enantiomer concentration has been investigated by means of the IC-calorimetric and microgravimetric method at 25 °C and similar experimental conditions. The results obtained with both methods are summarized in Figs. 2 and 3. In addition, Fig. 4 illustrates the typical output of a QCM experiment — the frequency shifts resulting from

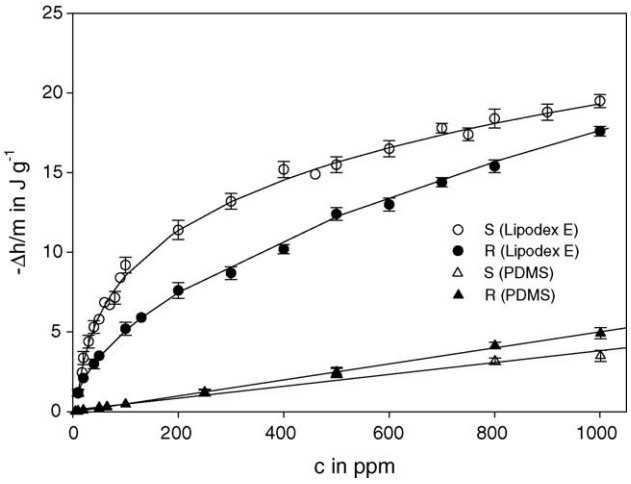


Fig. 2. Enthalpies of absorption (symbols) of S- and R-methyl-2-chloropropionate in Joule per gram of receptor (2.5 μg Lipodex E®, 100 μg PDMS) at 25 °C. Lines illustrate the fit of the model (Eq. (6)).

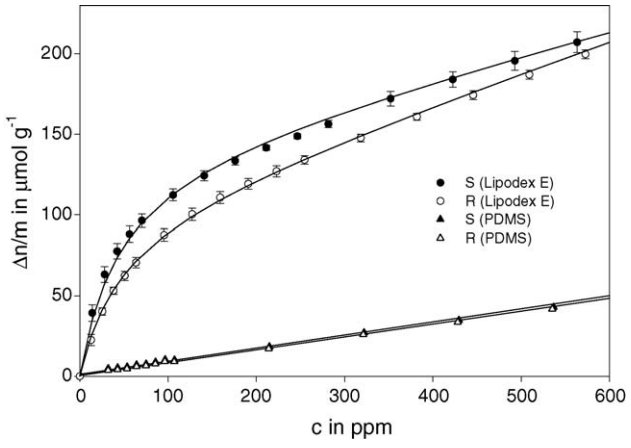


Fig. 3. Absorbed amounts (symbols) of S- and R-methyl-2-chloropropionate in μmol per gram of receptor (4.16 μg Lipodex E®, 4.32 μg PDMS) at 25 °C. Lines illustrate the fit of the model (Eq. (4)).

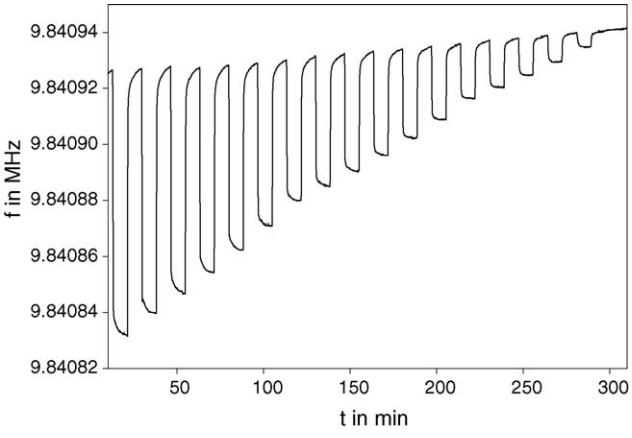


Fig. 4. Typical recording of frequency steps due to absorption–desorption cycles (S-enantiomer/Lipodex E®).

subsequent absorption–desorption cycles with varying enantiomer concentrations. The frequency shifts caused by the absorption are converted to mass by the Sauerbrey equation, thus, the microgravimetric experiments provide the absorbed amount (mole) of enantiomer per gram of receptor in dependence on the concentration (absorption isotherm, Fig. 3).

The results demonstrate that both experimental methods are capable of measuring the absorption effects in thin receptor films with high sensitivity as well as precision and are able to distinguish between the two enantiomers using a chiral receptor like Lipodex E®. It is clearly shown that the absorption behaviour is very different between a chiral and an achiral receptor. The non-linear concentration dependence and the comparatively large absorption effects in the chiral Lipodex E® layer, visible in both the calorimetric and microgravimetric results, indicate specific enantiomer–receptor interactions. The preferred absorption of the S-enantiomer, which is also reported from gas chromatographic separation experiments [1], is marked by significantly higher absorption effects in both methods, especially at low enantiomer concentrations (Figs. 2 and 3). Unlike the chiral receptor, the amount absorbed as well as the enthalpies of absorption into the achiral PDMS layer show a linear concentration dependence. In addition, the absorption effects are much smaller in magnitude and also the difference between the enantiomers is very small indicating a very weak chiral discrimination ability of PDMS. This behaviour is typical for a non-specific interaction like physical solution and should be expected for an achiral receptor.

Generally, it should be pointed out that both experimental methods provide qualitatively similar results making a combined thermodynamic analysis promising. The goal of this analysis is the reliable direct determination of molar thermodynamic quantities ($\Delta G$, $K$, $\Delta H$, $\Delta S$) of absorption required for a better understanding and discussion of chiral recognition processes. The starting point for that analysis should be a thermodynamic model capable of describing the experimental results based on absorption equilibria with equilibrium constants and absorption enthalpies as parameters. A promising approach successfully applied for the description of QCM results was suggested by Bodenhoefer et al. [10]. Inspired by this concept and in order to meet our requirements the model was refined in the following way. The total absorbed amount per mass of receptor $(n/m_r)_{total}$ at constant temperature consists of a term describing the specifically absorbed fraction $(n/m_r)_{chiral}$ and a term for the non-specifically absorbed fraction $(n/m_r)_{achiral}$:

$$\left(\frac{n}{m_r}\right)_{total} = \left(\frac{n}{m_r}\right)_{chiral} + \left(\frac{n}{m_r}\right)_{achiral}. \quad (1)$$

The contribution of the specific absorption is described by a Langmuir-type equation:

$$\left(\frac{n}{m_r}\right)_{chiral} = \Theta\frac{K_1 p_i}{(1 + K_1 p_i)}, \quad (2)$$

where $\Theta$ denotes the maximum occupation in mol kg$^{-1}$, $K_1$, the equilibrium constant for the specific absorption and $p_i$ is the partial pressure of the enantiomer in bar.

For the achiral contribution an equation according to Henry's law is used:

$$\left(\frac{n}{m_r}\right)_{\text{achiral}} = K_2 p_i, \tag{3}$$

where $K_2$ denotes the equilibrium constant for non-specific absorption.

Combining of Eqs. (1)–(3) results in the following equation for the absorption isotherm:

$$\left(\frac{n}{m_r}\right)_{\text{total}} = \Theta\frac{K_1 p_i}{(1+K_1 p_i)} + K_2 p_i. \tag{4}$$

Extending this approach for modelling calorimetric results, the following formulation can be assumed:

$$\left(\frac{\Delta h}{m_r}\right)_{\text{total}} = \Delta H_1\left(\frac{n}{m_r}\right)_{\text{chiral}} + \Delta H_2\left(\frac{n}{m_r}\right)_{\text{achiral}}, \tag{5}$$

where $\Delta H_1$ and $\Delta H_2$ denote the molar enthalpies of specific and non-specific absorption, respectively. Furthermore, if it is accepted that similar conditions in calorimetric and microgravimetric experiments lead to similar parameters, Eqs. (2), (3) and (5) can be combined to Eq. (6):

$$\left(\frac{\Delta h}{m_r}\right)_{\text{total}} = \Delta H_1\Theta\left(\frac{K_1 p_i}{(1+K_1 p_i)}\right) + \Delta H_2(K_2 p_i), \tag{6}$$

which describes the absorption enthalpies measured calorimetrically.

The fits of Eqs. (4) and (6) to the experimental results are shown in Figs. 3 and 2, respectively. For fitting the experimental data the partial pressure was used according to Eqs. (4) and (6) instead of the concentration value in ppm. The relation between concentration and partial pressure is represented by the following equation:

$$p_i[\text{bar}] = c[\text{ppm}] \times 10^{-6}\, RT \times 10^{-5}. \tag{7}$$

Excellent curve fitting has been obtained for all experimental data, particularly taking into account that for fitting the calorimetric data the parameters $\Theta$, $K_1$ and $K_2$ were adopted from the fit of the QCM data.

A complete summary of the fit parameters and derived thermodynamic data is made up in Table 1. The quantities $\Delta G^\circ$ and $\Delta S^\circ$ were calculated using the well-known relations:

$$\Delta G^\circ = -RT\ln K \quad \text{and} \quad \Delta S^\circ = \frac{\Delta H^\circ - \Delta G^\circ}{T}. \tag{8}$$

The calculated data also reflect the fundamental difference of specific and non-specific interaction. For the achiral PDMS receptor layer only the parameters of the second term, $K_2$ and $\Delta H_2$, are necessary to describe the linear isotherms. The absorption enthalpies are in the order of magnitude of heats of condensation and the difference between the Gibbs free energies of absorption of the enantiomers is not significant. In contrast to the non-specific absorption in PDMS, the description of the specific absorption into the chiral Lipodex E® layer requires the first (Langmuir) term. It is also obvious that the differences between the enantiomers are mainly reflected by the parameters of the chiral term. The enthalpy of the preferably absorbed S-enantiomer is −90 kJ/mol and that of the R-enantiomer −72 kJ/mol indicating a relatively strong binding in the range of a chemisorption as well as a considerable large difference between the enantiomers. On the other hand, large negative entropy contributions to the driving force are observed leading to a remarkable enthalpy–entropy-compensation effect [13]. Consequently, the Gibbs free energies of the specific interaction are much smaller than the enthalpies and also the difference between the values of the

Table 1
Thermodynamic data derived from the fits of Eqs. (4) and (6)

| | Lipodex E® | | PDMS | |
|---|---|---|---|---|
| | (R)-Methyl-2-chloro-propionate | (S)-Methyl-2-chloro-propionate | (R)-Methyl-2-chloro-propionate | (S)-Methyl-2-chloro-propionate |
| $\Theta$ (mol kg$^{-1}$) | 0.11 ± 0.01 | 0.12 ± 0.01 | | |
| $K_1$ (bar$^{-1}10^5$) | 8.1 ± 0.4 | 12.2 ± 0.2 | | |
| $\Delta H_1^\circ$ (kJ/mol) | −72 ± 1 | −90 ± 1 | Not significant | Not significant |
| $\Delta G_1^\circ$ (kJ/mol) | −33.7 ± 0.1 | −34.8 ± 0.1 | | |
| $\Delta S_1^\circ$ (J/(mol K)) | −126 ± 9 | −186 ± 7 | | |
| $\Delta_{R,S}(\Delta G)_1^\circ$ (kJ/mol) | −1.1 ± 0.2 | | | |
| $\Delta_{R,S}(\Delta H)_1^\circ$ (kJ/mol) | −18 ± 2 | | | |
| $\Delta_{R,S}(\Delta S)_1^\circ$ (J/(mol K)) | −59 ± 17 | | | |
| $K_2$ (mol kg$^{-1}$ bar$^{-1}$) | 7246 ± 158 | 6328 ± 65 | 3350 ± 370 | 3250 ± 20 |
| $\Delta H_2^\circ$ (kJ/mol) | −52 ± 5 | −45 ± 10 | −33.0 ± 0.1 | −27.7 ± 0.3 |
| $\Delta G_2^\circ$ (kJ/mol) | −22.03 ± 0.05 | −21.72 ± 0.02 | −20.11 ± 0.25 | −20.04 ± 0.01 |
| $\Delta S_2^\circ$ (J/mol K) | −102 ± 19 | −79 ± 36 | −43 ± 1 | −25 ± 1 |
| $\Delta_{R,S}(\Delta G)_2^\circ$ (kJ/mol) | 0.31 ± 0.07 | | 0.07 ± 0.26 | |
| $\Delta_{R,S}(\Delta H)_2^\circ$ (kJ/mol) | 7 ± 16 | | 5.3 ± 0.4 | |
| $\Delta_{R,S}(\Delta S)_2^\circ$ (J/(mol K)) | 23 ± 55 | | 17 ± 2 | |

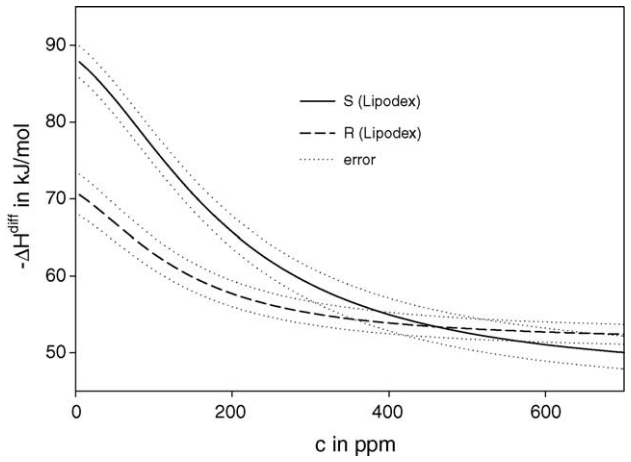


Fig. 5. Differential molar enthalpies of absorption plotted vs. the enantiomer concentration for the chiral receptor Lipodex E®.

enantiomers is reduced to 1.1 kJ/mol but the S-enantiomer is still favoured. It is also worth mentioning that the maximum specific site occupation $\Theta$ is equal for both enantiomers. Considering the important role of the absorption enthalpies for chiral discrimination in this case, it should be interesting to analyse closer the concentration dependence of the differential molar absorption enthalpies which my be defined as

$$\Delta H^{\mathrm{diff}} = \frac{\mathrm{d}(\Delta h/m_{\mathrm{r}})}{\mathrm{d}(n/m_{\mathrm{r}})}. \tag{9}$$

The results of applying Eq. (9) to the absorption into the chiral Lipodex E® receptor using the appropriate data from Table 1 and Eqs. (4) and (6) are presented in Fig. 5.

It can be deduced from Fig. 5 that a significant larger heat of absorption for the S-enantiomer only exists at low concentrations below 300 ppm. With increasing concentrations the difference between the differential molar heats of absorption of the enantiomers becomes smaller and disappears above 400 ppm. Both $\Delta H^{\mathrm{diff}}$ values approach a constant value of about −50 kJ/mol, the value of $\Delta H_2$. Consequently, the chiral separation efficiency should increase with decreasing enantiomer concentration, which in fact has been found in separation studies [2,10,14].

The thermodynamic data for the methyl-2-chloropropionate/Lipodex E® system determined by our direct method are compared to literature data [5] derived from gas chromatographic measurements by the van't Hoff method in Table 2.

Table 2
Comparison of directly determined thermodynamic data (this work) and gas chromatographic results from literature

| | This work (chiral term only) (25 °C) | Gas chromatography [5] (50–110 °C) |
|---|---|---|
| $\Delta H^\circ$ (S-enantiomer) (kJ/mol) | −90 ± 1 | −75.30 ± 0.9 |
| $\Delta_{R,S}(\Delta H)^\circ$ (kJ/mol) | −18 ± 2 | −13.73 ± 0.13 |
| $\Delta_{R,S}(\Delta G)^\circ$ (kJ/mol) | −1.1 ± 0.2 | −3.61 |
| $\Delta_{R,S}(\Delta S)^\circ$ (J/(mol K)) | −59 ± 17 | −32.67 ± 0.36 |

Generally, taking into account the different temperatures range and data evaluation methods, e.g. the enantiomer concentrations in the GC column are not known, the agreement of the data is remarkable and confirms the reliability of the new combination of experimental and data evaluation methods. However, the reported errors of our thermodynamic data seem to be much higher than those of the chromatographic method. For discussion it has to be considered that these errors result from several independent measurements and the combination of data of two independent experimental methods by using error propagation. The errors of the chromatographic data result only from the statistical uncertainty of the fit parameters of the linear van't Hoff plot (which is not really linear for the methyl-2-chloropropionate/Lipodex E® system as shown in [5]) without possible systematic errors.

The most significant advantage of the new method combination making it superior to the GC method is the access to the absorption isotherms. The knowledge of the concentration dependence allows the quantitative estimation of thermodynamic data for enantiospecific and non-specific contributions to the enantiomer absorption, whereas the GC method usually provides average values. For illustration, the $\Delta H$ value for the S-enantiomer from GC measurements is between the $\Delta H$ value of the chiral term and the achiral term (see Tables 1 and 2). Furthermore, our method combination is also able to measure at different temperatures but do not need the assumption of temperature independent $\Delta H$ and $\Delta S$ values.

## 4. Conclusions

The simultaneous measurement of heats of absorption and amounts absorbed into thin chiral receptor layers by IC-calorimetry and quartz crystal microgravimetry have been proved a reliable and innovative combination of methods for studying chiral recognition thermodynamics with considerable advantages over the established gas chromatographic method. Both the IC-calorimetric and QCM methods take effect of the fast mass and heat transfer inside thin films and short time constants of the detectors.

The isothermal mode of measurement avoids the known problems of the van't Hoff method based on temperature dependent GC experiments, especially non-linear separation factor-1/$T$-plots or changes of interaction mechanism in the temperature interval. The concentration dependent measurements provide significant new insights into the mechanism of chiral discrimination, especially the opportunity to distinguish between specific and non-specific contributions by analyzing the isotherms. Furthermore, time consuming and expensive measurements with references and different columns [14] can be eluded. In the future measurements at different temperatures are planned in order to contribute to a better understanding of temperature effects on chiral separation. In summary, the combination of IC-calorimetry and QCM measurements is a promising choice for sophisticated

thermodynamic studies of interactions with thin receptor layers.

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